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SPECIAL TOPIC: Gut microbiome and metabolism

REVIEW

When smoke meets gut: deciphering the interactions between tobacco smoking and gut microbiota in disease development

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Tobacco smoking is a prevalent and detrimental habit practiced worldwide, increasing the risk of various diseases, including chronic obstructive pulmonary disease (COPD), cardiovascular disease, liver disease, and cancer. Although previous research has explored the detrimental health effects of tobacco smoking, recent studies suggest that gut microbiota dysbiosis may play a critical role in these outcomes. Numerous tobacco smoke components, such as nicotine, are found in the gastrointestinal tract and interact with gut microbiota, leading to lasting impacts on host health and diseases. This review delves into the ways tobacco smoking and its various constituents influence gut microbiota composition and functionality. We also summarize recent advancements in understanding how tobacco smoking-induced gut microbiota dysbiosis affects host health. Furthermore, this review introduces a novel perspective on how changes in gut microbiota following smoking cessation may contribute to withdrawal syndrome and the degree of health improvements in smokers.

tobacco smoking | gut microbiota dysbiosis | nicotine | smoking cessation

Introduction

According to the World Health Organization, there are around 1.1 billion smokers worldwide, with over 8 million smoking-related deaths occurring each year. Tobacco smoking is the leading cause of preventable death globally, with smokers typically living roughly 10 years less than nonsmokers (Fouad et al., 2021; Warren et al., 2009). While cigarette smoking prevalence is declining in developed countries, it is increasing in many developing countries, particularly in Asia (Rom et al., 2013). Tobacco smoke contains toxic components that are thought to be a substantial contributor to serious disease, and the underlying pathogenic mechanisms have been thoroughly studied (Hoffmann et al., 2001; Smith et al., 2002). About half of smokers develop serious tobacco smoking-related diseases, such as chronic obstructive pulmonary disease (COPD) (Lai et al., 2022), cardiovascular disease (Duncan et al., 2022), liver disease (Marti-Aguado et al., 2022), and cancer (Hecht and Hatsukami, 2022). In addition, passive smoke exposure increases the risk of pathogenic infections and contributes to the exacerbation of other lung diseases including asthma (Thomson et al., 2022). Despite public awareness of the detrimental effects of smoking, there is still a large number of smokers globally (Rigotti et al., 2022).

In the past, there has been substantial research into how to lessen the hazards of smoking (Institute of Medicine, 2001), but there is still a lack of more effective approaches to accomplish beyond smoking cessation at the individual level. Tobacco smoking is an extremely tough addiction to break. Nicotine's highly addictive characteristics are the primary reason why smokers continue to use tobacco (Fiore et al., 1999). Weight gain and, presumably, insulin resistance after quitting are key causes of failure to stop for a long time or relapse (Siahpush et al., 2014), particularly in women (Kim et al., 2017). According to a recent study, changes in gut flora underlie the metabolic consequences of obesity linked with smoking cessation (Fluhr et al., 2021). To summarize, the benefits of smoking quitting outweigh the drawbacks, and future cessation programs and medicines should focus on minimizing post-cessation weight gain by modifying metabolically unfavorable gut flora (Harris et al., 2016).

The gut microbiota refers to a variety of microbial communities that symbiotically live in the host intestine to maintain microecological homeostasis, and there are approximately 10 trillion bacteria in the human intestine, mainly composed of Bacteroidetes, Firmicutes, Actinomycetes, and Aspergillus, most of which belong to intestinal commensal bacteria (Pushpanathan et al., 2019). They collaborate to create a complex organism that contributes to various physiological processes, including the fermentation of indigestible dietary fiber, the anaerobic metabolism of peptides and proteins, the protective activity against pathogens, and even the regulation of the immune system (Cai et al., 2022). Some research has begun to attempt to develop a database that includes drugs, microbes, and common diseases interactions (Wu et al., 2023), and some have even proposed that

gut microecology is a second "brain" for people (Zeng et al., 2023). Starting from childbirth, many factors affect the composition and metabolic functions of the gut microecology, which could further act on the distal host organs through gut microbiota-derived metabolites. In addition, dysbiosis of the gut microbiome is associated with the development of several metabolic disorders such as obesity (Wu et al., 2021b), hyperlipidemia (Jin et al., 2021), fatty liver disease (Wu et al., 2021a), polycystic ovary syndrome (Qi et al., 2019), and diabetes (Sun et al., 2018).

Interest in the gut microbiome has risen rapidly as sequencing technologies have evolved from 16S rRNA amplicon sequencing to shotgun metagenomics (Liu et al., 2022). Specific bacterial taxa, strains, pathways, and metabolites that may be associated with the development and progression of human disease have been identified through the application of shotgun metagenomics in conjunction with metabolomics and proteomics approaches (de Vos et al., 2022; Lynch and Pedersen, 2016; Tuganbaev et al., 2022). However, it remains unclear whether these microbial alterations contribute to disease or just result from disease conditions, which will be an important challenge in the future. Thus, the potential mechanisms and causal relationships between tobacco smoking, smoking-related health hazards, smoking cessation prognosis, and microbial dysbiosis found in humans and rodents exposed to tobacco smoke, as well as knowledge of how detrimental substances from the tobacco smoking process and smoking cessation interact with the gut microbiota to affect host health, warrant further research.

In this review, we summarize the major chemicals released during tobacco combustion, and highlight recent advances in understanding how tobacco smoking and smoking cessation affect the composition and metabolic processes of the gut microbiota. In addition, we discuss the possible impact of the ensuing microbial dysbiosis on tobacco smoking-related diseases.

Tobacco smoking remodels gut microbiota

Numerous microbiotas, particularly intestinal bacteria, inhabit the human gut, interacting with the host to create a stable intestinal microecology. However, the makeup of the gut microbiota varies with each person and is susceptible to variations in the host and environmental variables. The makeup of the gut microbiome in both humans and rodents is significantly altered by tobacco smoking (Figure 1) (Gui et al., 2021). Smoking causes changes in the gut microenvironment that may help some bacteria grow and lead to dysbiosis of the gut microbiota (Tomoda et al., 2011).

Among smokers, significant changes in fecal microbiome composition were observed compared with the nonsmoking group (Antinozzi et al., 2022; Kobayashi and Fujiwara, 2013; Nolan-Kenney et al., 2020; Opstelten et al., 2016; Stewart et al., 2018). Overall, fecal abundance of Prevotella, Veillonella, Bacteroides, Acidaminococcus and Oscillospira was increased in abundance (Lee et al., 2018; Lin et al., 2020), and Firmicutes and Proteobacteria were reduced in smokers (Lee et al., 2018). Also, several studies have shown that the Shannon index was significantly lower in the smoking population (Lee et al., 2018; Stewartet al., 2018). Yoon et al. (2021) investigated the effects of tobacco smoking on the composition of the microbiota in healthy males. A high abundance of Actinobacteria and a low abundance of *Bacteroides* spp. were the main features of the gut microbiota,

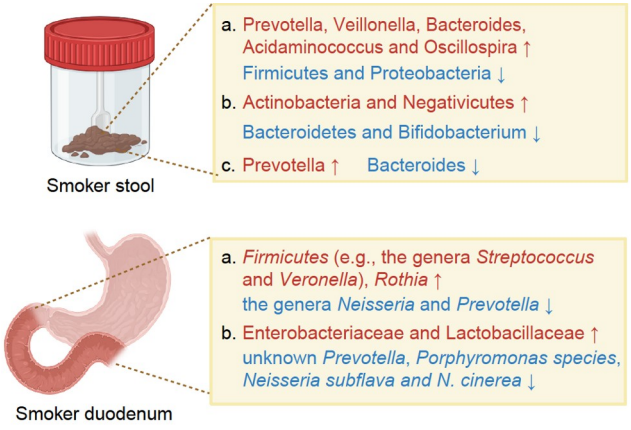

Figure 1. A schematic summary of changed microbiota in the mucosal duodenum and stool after smoking (Created using BioRender.com).

and current smokers could be distinguished from current non-smokers by their lower abundance of Bifidobacteria and higher abundance of Negativicutes. Lin et al. (2020) found that cigarette smoking and alcohol consumption alter the composition of the gut microbiota in healthy males. The relative abundance of the Firmicutes, Bacteroides and more than 40 genera was altered with cigarette and alcohol consumption. In addition, the abundance of Bacteroides was positively correlated with the year of smoking. Stewart et al. (2018) found that using electronic cigarettes (EC) or cigarette smoking altered the gut microbiota compared with non-smoking controls. Tobacco smokers had a higher abundance of Prevotella and a lower abundance of Bacteroides in the gut and significantly lower Shannon diversity in stool samples. In contrast, no significant differences in alpha diversity, beta diversity, or taxonomic relative abundance were found between EC users and non-smoking groups.

Most studies have indirectly analyzed the composition of the gut microbiota by testing human stool samples, which differs from the authentic gut environment in the intestine. Shanahan et al. (2018) analyzed and tested the mucosal microbiome of the duodenum in humans undergoing upper gastrointestinal endoscopy and found that changes in the mucosal microbiome of smokers included a higher abundance of phylum Firmicutes (e.g., the genera *Streptococcus* and *Veronella*) and genus *Rothia*, and lower abundance of phyla Neisseria and Prevotella. Consistent with these findings, Leite et al. (2022) examined the duodenal luminal microbiome of smokers and found that smokers exhibited enrichment in Enterobacteriaceae and Lactobacillaceae and lower abundance of unknown *Prevotella*, *Porphyromonas* species, and *Neisseria subflava* and *N. cinerea*. In addition, smokers had lower diversity of gut microbiota.

To study the effects of tobacco smoking, researchers typically use rodents with cigarette smoke exposure to mimic the process of human smoking. 16S rRNA sequencing of fecal samples from mice exposed to cigarette smoke for three weeks by Fluhr et al. (2021) showed significant changes in the fecal bacteria of these mice; as determined by shotgun metagenomics sequencing, dysbiosis during smoke exposure had different taxonomic features and functional characteristics metagenomics features. Similarly, Tomoda et al. (2011) found that rats exposed to cigarette smoke for four weeks altered the levels of some organic acids in the cecum, with a significant decrease in the number of Bifidobacteria and a significant increase in the pH of cecum

contents. These results suggest that cigarette smoke may alter the intestinal environment of rats. Tam et al. (2020) found that chronic exposure to cigarette smoke resulted in significant changes in the cecum microbial community in male and female mice, with the microorganism *Alistipes* spp. being the most consistently altered in the cecum, and this bacteria decreased with chronic smoking. Berkowitz et al. (2019) used intragastric administration of cigarette smoke condensate (CSC) in mice and found that antimicrobial peptide production and bactericidal capacity were reduced. Exposure to CSC resulted in an imbalance in fecal bacterial populations, leading to an increase in Erysipellaceae (including *Allobaculum*) and a decrease in Rikenellaceae and Eisenbergiella and resulted in a higher susceptibility of mice to bacterial infection producing ileal damage. Allais et al. (2016) reported significant changes in bacterial activity and community structure in the colon after 24 weeks of smoke exposure in mice, characterized by an increase in the activity of *Lachnospiraceae* sp. in the proximal and distal colon of smoke-exposed mice, and changes in the expression of intestinal mucin and pro-inflammatory cytokines.

Cigarette smoke can be divided into mainstream and side stream smoke, and inhaled side stream cigarette smoke is approximately four times more toxic per gram of total particulate matter (TPM) than mainstream cigarette smoke (Schick and Glantz, 2005). Wang (2012) found that exposure of mice to side stream commercial cigarette smoke for six weeks resulted in significant changes in the intestinal microbiota of mice, with an increase in *Clostridium perfringens* in the cecum but a decrease in Firmicutes (*Lactococi* and *Ruminococcus*), Enterobacteriaceae, and segmented filamentous bacteria. Also, side stream smoke reduced the intestinal inflammatory response in mice, which was associated with increased expression of tight junction proteins. It is also worth mentioning that hypoxia affects the composition of gut bacteria, which may be implicated in the combined effect of smoking on the microbes in the gut (Pan et al., 2022).

In conclusion, investigations on humans and rodents have shown that exposure to smoking might cause dysbiosis of the gut microbiota. Additional causative investigations are necessary to determine how smoking-related intestinal bacterial dysbiosis develops or whether it affects disease progression.

Effects of major detrimental components of tobacco on gut microbiota

More than 80% of tobacco users in the United States use combustible products, primarily cigarettes, cigars, pipes, and hookahs (National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, 2014). Commercially sold cigarettes contain more than 7,000 chemicals, and their combustion produces potentially toxic substances in the mainstream smoke (MS), side stream smoke (SS), secondhand smoke (SHS), thirdhand smoke (THS), and discarded cigarette butts (CBs) (Talhout et al., 2011). These include nicotine, smoke tar, aldehydes, polycyclic aromatic hydrocarbons (PAHs), and heavy metals (Gui et al., 2021; Rigotti et al., 2022). These toxic compounds seriously affect human health, and cigarette smoke contains a complex variety of substances, many of which affect gut microbiota and have different mechanisms of action for different substances (Table 1) (Breton et al., 2013; Fluhr et al., 2021; Motta et al., 2015; Ribière et al., 2016; Rom et al., 2017).

Effect of nicotine on gut microbiota

Nicotine is the most abundant alkaloid in tobacco and the primary active ingredient with addictive characteristics (Darby et al., 1984). Cigarettes contain 1%–2% nicotine by mass, with the maximum bioavailability of nicotine being 90% when inhaled and roughly 60% when taken orally, as in smokeless tobacco. Nicotine may be taken into the body through the lips, skin, and gastrointestinal tract when smoking (Benowitz, 1988; Le Foll et al., 2022; Onor et al., 2017). Previous research has focused on the distribution of nicotine in the plasma, liver, kidney, heart, and brain (Lindell et al., 1996; Sobkowiak and Lesicki, 2013; Yamazaki et al., 2010). The initial concentration of nicotine from smoke inhalation and cigarette intake is highest in lung tissue and the mouth, but after one hour, nicotine concentration in the stomach is significantly higher than in other tissues (Lindell et al., 1996). More intuitively, nicotine was considerably enriched in the gut, liver, nasal mucosa, and salivary glands after 15 min after intramuscular injection by 14C-nicotine radioautography (Schmiterlöw and Hansson, 1962). These results demonstrate that nicotine from tobacco works not only in the brain and lungs, but also in the liver, kidney, and digestive system, indicating that nicotine accumulation plays a major role in modifying gut microecology.

Nicotine's influence on bacterial activity was investigated in two *in vitro* investigations. At a dosage of 2 g mL^{-1}, nicotine demonstrated antibacterial action against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Streptococcus faecalis* (Pavia et al., 2000). At a dosage of 10 g mL^{-1}, nicotine was efficient against *Listeria monocytogenes* and *Streptococcus viridans* (Pavia et al., 2000). High levels of nicotine were detectable in saliva during smoking (Lindell et al., 1996) and affected oral microbiota homeostasis. *Streptococcus mutans* biofilm formation and metabolic activity were increased in a nicotine-dependent manner, and nicotine enhanced *Streptococcus mutans* biofilm formation and biofilm metabolic activity, promoting the formation of *Streptococcus mutans* biofilm on the tooth surface, thereby increasing the occurrence of dental caries (Huang et al., 2012). Similarly, nicotine could affect the pathogenicity of *Streptococcus mutans* and lead to increased dental caries by producing more lactic acid and upregulating virulence genes (Li et al., 2016). The oral microbiota of smokers represents a significant enrichment of *Veillonella dispar*, *Leptotrichia* spp. and *Prevotella pleutitis* compared with nonsmokers. Functional analysis revealed that smokers exhibited enrichment in tricarbonate utilization and lactic acid racemization compared with nonsmokers (Al Bataineh et al., 2020). Nicotine-induced differences in microbiome composition and functional differences may provide important insights into how changes in the oral microbiota may predispose smokers to respiratory disease and relapse to smoking cessation.

Notably, Chen et al. (2022) found that high levels of nicotine (approximately 200 ng g^{-1} tissue) were detected in the ileal mucosal tissue of smokers, the ileum of mice from different nicotine exposure models, and their contents. This suggests that nicotine may reshape the homeostasis of the gut microbiota during cigarette smoking or nicotine exposure by directly influencing processes like colonization and growth through enrichment in the intestine. Chi et al. (2017b) analyzed how oral nicotine delivery for 13 weeks affects gut microbiota composition and its metabolic profile in C57BL/6 mice. The results showed that the effects of nicotine on gut microbiota exhibited sex

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Table 1. Summary of animal studies on the effects of detrimental components in tobacco smoke on gut microbiota

Smoke components	Administration	Treatment time	Concentration	Animals	Gut microbiota changes	References
Nicotine	Water drinking	13 weeks	60 mg L^{-1}	Male/female mouse	Female: Christensenellaceae ↓ Anaeroplasmataceae ↓ F16 ↓ Male: F16 ↑ Peptococcaceae ↑ Turicibacteraceae ↑ Dehalobacteriaceae ↓	(Chi et al., 2017b)
	Subcutaneous pump	28 d	6 mg kg^{-1} d^{-1}	Female rats	Actinobacteria ↑ Firmicutes ↓	(Zubcevic et al., 2022)
	Subcutaneous pump	14 d	6 mg kg^{-1} d^{-1}	Female rats	Firmicutes ↑ Proteobacteria ↑ Actinobacteria ↑ Bacteroidetes ↓	(Rodrigues et al., 2021)
	Water drinking	3 weeks	0.15 mg mL^{-1}	Male mice	NA	(Fluhr et al., 2021)
	Subcutaneous pump	4 weeks	1.5 mg kg^{-1} d^{-1}	Male mice	Actinobacteria ↑ Tenericutes ↓	(Fluhr et al., 2021)
Bap	Oral gavage	28 d	50 mg kg^{-1} d^{-1}	Mice	Bacteroidaceae ↑ Porphyromonadaceae ↑ Paraprevotellaceae ↑ Lactobacillaceae ↓ Verrucomicrobiaceae ↓	(Ribière et al., 2016)
NNK and Bap	Oral gavage	4 weeks	NNK 2 μmol plus Bap 2 μmol	Mice	Actinobacteria ↑ Bifidobacterium ↑ Intestinimonas ↑ Alistipes ↓ Odoribacter ↓ Acetatifactor ↓	(Qu et al., 2021)
NNK	Intraperitoneal injection	8 weeks	150 mg kg^{-1} per week	Mice	Firmicutes ↑ Bacteroidetes ↓	(Finnicum et al., 2022)
Formaldehyde	Water drinking	24 d	1 and 3 ng mL^{-1}	Mice	Proteobacteria ↑ Actinobacteria ↑ Cyanobacteria ↓	(Guo et al., 2018)
Acrolein	Water drinking	30 d	3 mg kg^{-1} d^{-1}	Mice	Firmicutes ↑ Bacteroidetes ↓	(Rom et al., 2017)
Benzene	Subcutaneous injection	30 d	6, 30, and 150 mg kg^{-1} d^{-1}	Male mice	Actinobacteria ↑	(Sun et al., 2020)
	Subcutaneous injection	30 d	25, 125, and 625 mg kg^{-1} per week	Male mice	*Bacteroides sartorii* ↑ *Anaerotruncus* sp.↓	(Zhang et al., 2021a)
Arsenic	Water drinking	13 weeks	0.1 mg kg^{-1}	Female mice	Verrucomicrobia ↑ Firmicutes ↓	(Chi et al., 2017a)
	Water drinking	4 weeks	10 mg kg^{-1}	Female mice	Firmicutes ↓	(Lu et al., 2014)
	Water drinking	4 weeks	0.5 and 5 mg kg^{-1}	Male/female mouse	Verrucomicrobia ↑ Firmicutes ↓	(Wu et al., 2022)
	Oral gavage	5 d	15, 22, and 31 mg kg^{-1} d^{-1}	Rats	Proteobacteria ↑	(Richardson et al., 2018)
Nickel	Oral gavage	5 d	77, 232, and 300 mg kg^{-1} d^{-1}	Rats	Proteobacteria ↑ Verrucomicrobia ↓	(Richardson et al., 2018)
	Oral gavage	35 d	40 mg kg^{-1} d^{-1}	Male mice	Bacteroidetes ↑ Proteobacteria ↑ Firmicutes ↓	(Yang et al., 2023)
Cadmium	Oral gavage	5 d	35, 54, and 85 mg kg^{-1} d^{-1}	Rats	Verrucomicrobia ↑	(Richardson et al., 2018)
Chromium	Oral gavage	5 d	44, 62, and 88 mg kg^{-1} d^{-1}	Rats	Proteobacteria ↑ Verrucomicrobia ↑	(Richardson et al., 2018)

differences: in nicotine-treated female mice, the abundance of Christensenellaceae, Anaeroplasmataceae, F16, an unknown family of Bacillariophyceae, and RF39 bacteria were significantly reduced, whereas in nicotine-treated male mice, the abundance of F16, Turicibacteraceae, and Peptococcaceae were greatly increased and Dehalobacteriaceae bacteria were reduced considerably. In addition, nicotine disrupted the carbohydrate metabolic pathways of the gut microbiota and specifically reduced body weight gain in male mice. According to Zubcevic et al. (2022), one month following subcutaneous nicotine pump treatment, the overall trend in female rats during gestation was a decrease in Firmicutes and an increase in Actinobacteria. During intrauterine development, it affected fetal exposure to circulating short chain fatty acids (SCFA) and leptin. There was a decrease in Bacteroidetes and an increase in Firmicutes, Proteobacteria, and Actinobacteria in the gut of offspring of maternal nicotine exposure (MNE) during nursing rats. It has been proposed that nicotine exposure through breast milk causes long-term dysbiosis of the gut microbiota (Rodrigues et al., 2021). In Leviel Fluhr's study, whether mice received nicotine water or nicotine

subcutaneous injection treatment for three weeks, the gut microbiota was altered compared with the control group, and neither was the same as during smoke exposure (Fluhr et al., 2021). This suggests that additional cigarette smoke constituents are also involved in changing the gut microbiome of mice. At the moment, the only information available on the effects of nicotine on the gut microbiota is observational. As a result, extensive study is required to investigate the processes by which nicotine induces dysbiosis of the gut microbiota.

Recently, there has been a growing focus on the nicotine-metabolizing microbiome, which had potent for treating nicotine-related diseases. In sunbirds (*Cinnyris osea*) that ingested nicotine, administration of antibiotics that disrupted the intestinal bacterial community reduced the rate of nicotine degradation in their feces (Gunasekaran et al., 2021), suggesting that the gut microbiota may be involved in the metabolism of nicotine. In a recent study by Chen et al. (2022), higher levels of nicotine were detected in the gut of germ-free mice compared with SPF mice after nicotine drinking, suggesting that the gut microbiota can metabolize nicotine. Further, they identified that human intestinal commensal bacteria, *Bacteroides xylanisolvens*, could efficiently degrade intestinal nicotine and identified a novel nicotine metabolizing enzyme, NicX, and its metabolite, 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB). Administration of *B. xylanisolvens* intestinal colonization to SPF mice reduced nicotine levels in the gut, which in turn ameliorated the nicotine-accelerated nonalcoholic steatohepatitis (NASH) process. Thus, the pathway by which gut microbes utilize nicotine and other tobacco-related chemicals may offer a new potential possibility for the treatment of smoking-related metabolic diseases.

Effect of other substances in tobacco smoke on gut microbiota

The full or incomplete burning of tobacco and distillation at various temperatures result in the production of tobacco smoke, a process that is extremely complicated in terms of the materials used and the reactions that take place. In general, each inhalation of tobacco smoke has a varied composition of smoke, which might even differ greatly. In addition to nicotine, tobacco smoke typically contains additional hazardous components such as polycyclic aromatic hydrocarbons, aza-arenes, N-nitrosamines, aromatic amines, aldehydes, and other organic and inorganic compounds (Talhout et al., 2011).

PAHs

Many PAHs have been found to cause cancer in animals or humans in previous studies, but their effects on the gut microbiota have received more attention only in recent years. Benzo[a]pyrene (Bap) is the most representative component of tobacco PAHs and appears to have a relatively strong effect on gut microbes from lower to higher organisms. In a variety of aquatic organisms, Bap has been found to alter the diversity and composition of the gut microbiota, causing dysbiosis of the gut microbiota (Li et al., 2021; Quintanilla-Mena et al., 2021; Zhao et al., 2019). In mammals, Bap is absorbed and inhaled from the oral cavity, but BaP is also transported from the lungs to the digestive system via a mucosal ciliary clearance mechanism (Semmler-Behnke et al., 2007). This feature may lead to an essential role of Bap in the animal and human gut, especially for the gut microbiota exerting an important influence.

Although there was no substantial change in alpha diversity, it was discovered that the relative abundances of 15 families and 18 genera were severely altered. Among dominant taxa, the abundances of Verrucomicrobia were decreased, while Bacteroidetes were increased, respectively. Bacteroides, Parabacteroides and Paraprevotella showed significant increase at the end of the Bap treatment, whereas the relative abundances of *Lactobacillus* and Verrucomicrobiaceae (a family exclusively represented by *Akkermansia muciniphila*) were decreased. Following the modifications in these organisms, there was a considerable rise in the relative abundance of Lactobacillaceae in ileal and colonic mucosal inflammation, as well as enhanced ileal permeability in mice models (Ribière et al., 2016). However, in studies based on human infants, the relative abundance of *Akkermansia muciniphila*, a bacterium generally considered to be beneficial, was increased in infants exposed to Bap (Zhang et al., 2021b). These results suggest that Bap may be able to exert anti-inflammatory effects in the short term after exposure. After extended Bap exposure, gut microorganisms were disturbed, resulting in detrimental physiological consequences. Interestingly, microorganisms can respond to Bap exposure by regulating host xenobiotic metabolism following Bap exposure, in addition to the effects of Bap on gut microbiota (Garcia et al., 2022). It implies that the metabolism of many xenobiotics *in vivo* in mammals and gut microbes' co-interaction and evolution of metabolic processes are more complex and interesting than we previously knew.

Aza-arenes

Aza-arenes are organic components that are relatively abundant in tobacco, including quinoline, dibenz (a, h) acridine, 7H-dibenzo (c, g) carbazole (Snook et al., 1981). Such substances may be present in high concentrations in bile after ingestion (Mukherjee and Banerjee, 1947), and biliary excretion, which is considered one of the major excretion routes of quinoline. Thus, although not directly reported, it is reasonable to believe that aza-arenes ingested by tobacco smoking can have appreciable concentrations in the intestine. Many bacteria have been found to produce some quinoline derivatives as quorum-sensing molecules (Saalim et al., 2020). So although it is not clear how aza-arenes affect the gut microbiota, there is reason to believe that aza-arenes, at least the quinoline in them, can have a significant effect on the gut microbiota.

N-nitrosamines

Tobacco-specific N-nitrosamines, including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone or nicotine-derived nitrosamine ketone (NNK), N-nitrosonornicotine (NNN), nitrosaminoaldehyde (NNAL), N-nitrosoanatabine (NAT), N-nitrosoanabasine (NAB), iso-NNAL, and iso-N-nitrosamino acids (iso-NNAC), are present in tobacco smoke and proved pro-carcinogenic (Yalcin and de la Monte, 2016). NNK has been implicated in various cancers, and some recent studies suggest that NNK may affect cancer by influencing intestinal bacteria. For example, in a lung cancer mouse model, exposure to NNK plus Bap altered fecal bacterial composition, resulting in increased levels of Actinobacteria, Bifidobacterium and Intestinimonas and decreased levels of Alistipes, Odoribacter and Acetatifactor, ultimately affecting

several bacterial metabolite production, including purine metabolism, phenylalanine metabolism, primary bile acid biosynthesis, steroid hormone biosynthesis, biosynthesis of unsaturated fatty acids, linoleic acid metabolism, and others (Qu et al., 2021). A gradual increase in Firmicutes and a decrease in Bacteroidetes was also observed at different time points after the NNK treatment of mice. At the genus level, a progressive increase in the tumor-promoting *Helicobacter* and a decrease in *Lactobacillus*, *Akkermansia*, and *Ruminococcus*, which are considered beneficial bacteria, were found. Correspondingly, significant reductions in the levels of intestinal and circulating SCFAs (propionic acid and butyric acid) were also observed in NNK-treated mice, all of which suggest that NNK can significantly affect the composition and function of intestinal bacteria (Finnicum et al., 2022).

Aromatic amines

Although the intestine has been detected to contain a variety of aromatic amines that can affect intestinal bacteria and hosts, tobacco is also rich in aromatic amines. The aromatic amines in tobacco smoke are mainly 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, o-toluidine, and o-anisidine, as opposed to the typical intestinal aromatic amines (Ji and Jin, 2022). Whether these aromatic amines have a profound effect on intestinal bacteria is still unknown.

Aldehydes

Aldehydes are common toxic pollutants, with formaldehyde, acetaldehyde, and acrolein predominating in tobacco smoke. In one study, an increase in the relative abundance of Proteobacteria and Actinobacteria and a decrease in the relative abundance of Cyanobacteria were observed at the phylum level after Formaldehyde exposure was given to mice. At genus level, a significant increase in the abundance of 13 genera and a decrease in the abundance of 4 genera were found. Among the genera with increased relative abundance, *Prevotella* was one of the major genera (Guo et al., 2018).

Acetaldehyde is one of the most important components of aldehydes in tobacco smoke. Since its effects on intestinal bacteria have been mostly mentioned in ethanol-related studies in the past (Pohl et al., 2021), it is difficult to confirm what effects acetaldehyde can have on gut microbiota independently. Found in mitochondrial aldehyde dehydrogenase 2 (ALDH2) mutant mice, higher acetaldehyde concentrations may lead to decreased abundance of Actinobacteria and an increase in Deferribacteres (Yang et al., 2021b).

In addition, acrolein-fed mice also showed significant changes in gut microbiota composition, including phylum-level alterations with an increase in Firmicutes and a decrease in Bacteroidetes and family-level alterations with an increase in Ruminococcaceae and Lachnospiraceae. At genus level, *Coprococcus* significantly and positively correlated with lipid levels and peroxidation in serum, aorta, and macrophages (Rom et al., 2017).

Miscellaneous organic compounds

Benzene in tobacco smoke also causes dysbiosis and metabolic disturbances in the intestinal microbiota of mice. A study using three different concentrations of benzene to treat mice found significant changes in the composition of the gut microbiota in both cecum and feces, and it appeared that higher concentrations of benzene caused more drastic changes in the composition of the gut microbiota. Significant enrichments of Actinobacteria at the phylum level and *Helicobacter* at the genus level were observed in benzene-exposed mice (Sun et al., 2020). Another study found that increased Family_XIII_AD3011_group at the genus level and decreased *Anaerotruncus_sp* at the species level in the benzene-exposed group. In this study, mice were also treated with a similar dose of benzene as in the previous study, but no significant relationship was observed between the composition of gut microbiota and benzene concentration, which may be related to the different sexes of the two mouse models. Differences in the gut microbiota changes between genders were also observed in the effects of nicotine on the gut microbiota, and these phenomena may suggest that sex-specific factors, such as hormones, play an important role in the symbiosis between gut microbiota and their hosts (Zhang et al., 2021a).

Inorganic substances

Arsenic is a well-known environmental contaminant and a frequently detected inorganic component of tobacco (Iwai et al., 2016). The relative abundance of Muribaculaceae was significantly reduced in the arsenic-exposed mouse pups, while the relative abundance of *Akkermansia* and *Bacteroides* was significantly increased at the genus level. In both arsenic-exposed mouse models, profound remodeling of the gut microbiota appears to occur, indicating impaired intestinal barrier function and mucosal inflammation (Chi et al., 2017a; Lu et al., 2014; Wu et al., 2022).

Nickel is also common in tobacco as a common heavy metal contaminant. A decrease in *Lactobacillus* and *Blautia* and an increase in inflammation-promoting bacteria such as *Alistipes* and Mycoplasma were observed in both nickel-exposed humans and rats (Yang et al., 2023). More specifically, one study found that nickel exposure almost completely eliminated the very common Bacteroidetes S24-7, while the abundance of non-S24-7 Bacteroidetes was relatively increased (Richardson et al., 2018).

In addition to nickel, chromium exposure also significantly affected gut microbiota composition in mice, decreasing the diversity of the microbiome composition (Mu et al., 2022; Richardson et al., 2018), while cadmium also altered the abundance of specific strains of intestinal bacteria, decreased the abundance of *Prevotella* and *Lachnoclostridium* but increased *Escherichia coli_Shigella* (Yang et al., 2021a).

The types and levels of heavy metals contained in tobacco vary depending on the environment in which the crop is grown, and the more common ones include Plumbum, Polonium and other heavy metals. Due to the way tobacco is smoked, these heavy metals can often reach the digestive tract and may have a corresponding effect on the gut microbiota. Corresponding changes in gut microbiota are often observed in the presence of heavy metal exposure, but more detailed proof of the causality behind these correlated changes is still lacking.

Smoking affects disease through gut microbiota dysbiosis

Many substances in tobacco smoke may change the gut

microbiota, and differences in these bacteria may have a variety of impacts on various diseases. The function of gut microbiota in a number of diseases is well documented, and tobacco smoking has a variety of effects on the makeup of gut microbiota.

Analysis of changes in the composition and metabolism of gut microbiota can often suggest that changes in gut microbiota may be involved in different disease processes, but this association is often indirect and unsupported. A very good recent example is, which clearly demonstrates that the gut microbiota affected after smoke exposure is essential for smoking-cessation-induced weight gain in mice (Fluhr et al., 2021). This study clearly demonstrated the indispensable effect of smoke exposure on smoking-cessation-induced weight gain, and further analyzed the metabolites of bacterial origin and performed small-scale population validation. In another study, Bai et al. (2022) demonstrated that smoke-induced dysbiosis of the gut microbiota alters intestinal metabolites and impairs intestinal barrier function, thereby promoting colorectal cancer. This study also provides direct evidence that tobacco smoking affects disease by influencing gut microbiota.

Gut microbiota can affect cancer (Gagliani et al., 2014), IBD (Neurath, 2020), diabetes (Cani, 2019), nonalcoholic fatty liver disease (NAFLD) (Caussy and Loomba, 2018), and cardiovascular disease (Chakaroun et al., 2023) through changes in the metabolism of SCFAs, metabolism of bile acids, effects on intestinal permeability, increased LPS, decreased choline availability, and trimethylamine production (Figure 2).

In cancer, increased deoxycholic acid (DCA) caused by alterations in Clostridium Cluster IX promotes the development of obesity-associated liver cancer by promoting the senescence-associated secretory phenotype (SASP) (Yoshimoto et al., 2013). Genetic operations on *E. coli* NC101 revealed that colitis could promote tumorigenesis by altering microbial composition and inducing the expansion of microorganisms with genotoxic capabilities (Arthur et al., 2012). Additionally, clinical investigations have demonstrated that gut microbiota can influence the clinical outcomes of CAR-T cell cancer immunotherapy (Stein-Thoeringer et al., 2023) as well as the toxicity of combination CTLA-4 and PD-1 inhibition (Andrews et al., 2021).

The two types of IBD are ulcerative colitis and Crohn's disease, and intriguingly, smoking appears to have the exact opposite effect on both of these conditions (Lindberg et al., 1992; Russel et al., 1998). The increased frequency of IBD in developed nations and its sharp rise in recently industrialized nations both imply that the onset of IBD may be linked to various lifestyle choices (Kaplan and Ng, 2017). Both disorders have been linked to significant alterations in gut microbiota as compared with healthy people (Ananthakrishnan, 2015). Additionally, it is believed that several of the genes linked to IBD susceptibility that have been discovered by genome-wide association studies are also involved in modulating the host's response to the gut microbiota (Liu et al., 2015). It was found that the spore-forming component of indigenous intestinal microbiota, particularly clusters IV and XIVa of the genus *Clostridium*, promoted T(reg) cell accumulation and resulted in resistance to colitis (Atarashi et al., 2011). This suggests that components or metabolites of the gut microbiota could be directly involved in the inflammatory response of the gut as well as in the disease process. Overall, IBD is the result of a combination of genetic susceptibility, gut microbiota dysbiosis, and environment, each of which interacts in a complex way to cause IBD. These facts suggest that gut microbiota may also play an important role in the pathogenesis of IBD.

Indeed, the involvement of gut microbiota in the development of metabolic diseases has been reported abundantly. A study discovered that the metabolite of gut microbiota imidazole propionate, which activates mTORC1 signaling in the host liver, can disrupt insulin signaling (Koh et al., 2018). This shows that the development of diabetes mellitus is directly influenced by gut microbiota. Additionally, it has been discovered that metformin helps to improve metabolism by preventing the growth of *Bacteroides fragilis*, decreasing the action of this bacterium's bile salt hydrolase, raising GUDCA levels, and blocking intestinal FXR signaling (Sun et al., 2018). Clinical research has also discovered an association between some metabolic syndrome symptoms and certain gut microbiota, particularly *Ruminococcus gnavus* (Grahnemo et al., 2022).

Numerous NAFLD investigations have discovered that the gut microbiota promotes NAFLD through the intestine-hepatic axis and that the characteristics of the gut microbiota may also operate as diagnostic indicators (Aron-Wisnewsky et al., 2020).

After adjusting for the effects of lifestyle choices and medication as potential confounding factors, research on populations with ischemic heart disease (IHD) has revealed that middle-aged adults at various stages of the cardiometabolic disease spectrum, from metabolic disorders (obesity/diabetes) to ischemic heart disease, are characterized by corresponding changes in the microbiota and metabolome of the disease process (Fromentin et al., 2022). When it comes to acute coronary syndrome (ACS), metabolic abnormalities linked to nutrition and the gut microbiota may already exist at an early level, long before the onset of the condition (Talmor-Barkan et al., 2022). Trimethylamine oxide (TMAO), a metabolite produced by gut microbiota, has even been linked to the onset and progression of many kinds of cardiovascular disorders, including atherosclerosis (Wang et al., 2015), myocardial infarction (Wang et al., 2015), heart failure (Suzuki et al., 2019), and abdominal aortic aneurysms (AAA) (Benson et al., 2023).

It is obvious from the abundance of evidence that gut microbiota plays a role in the emergence of many diseases, but it is still unclear whether smoking can also influence these diseases by influencing gut microbiota. In other words, tobacco smoking has a significant impact on the gut and thus may influence the development and progression of many diseases through a variety of gut microbiota, although more direct causation studies are now needed to establish this.

Effects of smoking cessation on gut microbiota

It has been widely reported that tobacco smoking has a very important effect on gut microbiota, but the effect of smoking cessation on gut microbiota has received little attention. Cessation, as the most effective way to reduce the harms of tobacco smoking, can minimize the harm caused by smoking among the common methods of avoiding tobacco harm (Visseren et al., 2021). Nevertheless, several studies have found that the risk of developing a variety of smoking-related diseases after quitting does not decrease to the same extent as in non-smokers. In the Health Professionals Follow-up Study (HPFS), the incidence of peripheral artery disease in smokers who quit did not return to the level of non-smokers (Joosten et al., 2012). Epidemiology shows that the incidence of peripheral artery

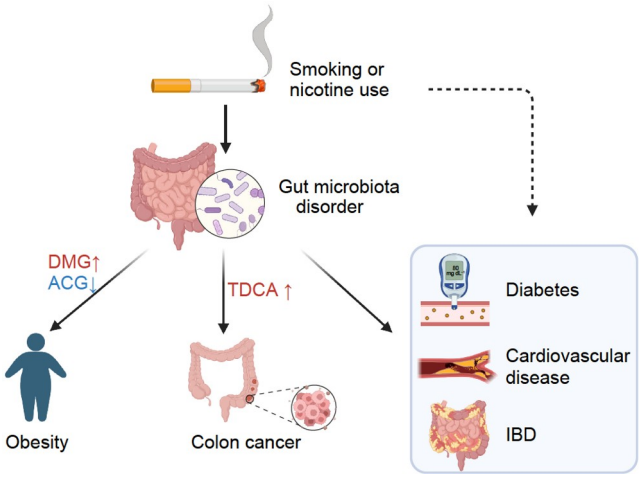

Figure 2. Smoking affects disease through gut microbiota dysbiosis. Solid arrow: direct evidence, dashed arrow: indirect hints (Created using BioRender.com).

disease is higher in low-income and middle-income countries, even among former smokers than among current smokers (Fowkes et al., 2017). In both Crohn's disease and Ulcerative colitis, former smokers who have quit smoking have a higher incidence of the disease compared with non-smokers. Former smokers also had a higher incidence of hepatocellular carcinoma (Abdel-Rahman et al., 2017). The incidence of type 2 diabetes was similar in former and current smokers (InterAct et al., 2014). All of these phenomena suggest that quitting smoking after experiencing smoking status does not readily restore the biological effects of tobacco smoking. Smoking exposure has been shown to have profound effects on host epigenetic information (Joehanes et al., 2016), which may account for the incomplete elimination of the harms of tobacco smoking after quitting.

Tobacco smoking has been shown to largely affect gut microbiota, but the alteration of gut microbiota by smoking cessation is relatively poorly understood. Studies based on 16S rRNA sequencing found significant changes in microbial composition after smoking cessation, with increases in Firmicutes and Actinobacteria and decreases in the proportions of Bacteroidetes and Proteobacteria at the phylum level. The microbial diversity increased after smoking cessation as opposed to a general decrease in microbial diversity after smoking cessation (Biedermann et al., 2013). A fluorescence *in situ* hybridization (FISH) based study also found that intestinal microbiota composition was substantially altered after smoking cessation as characterized by an increase in key representatives from the phyla of Firmicutes and Actinobacteria as well as a decrease in Bacteroidetes and Proteobacteria (Biedermann et al., 2014). A more detailed study evaluating cigarette smoking markers and the effect of smoking cessation on the gut microbiota of current quitters found that 12 weeks of smoking cessation resulted in only small changes in the gut microbiota, with Bacteroidetes increased and Firmicutes decreased observed at the phylum level (Sublette et al., 2020). A population-based cross-sectional study found that the gut microbiota composition of former smokers who had quit smoking for an average of up to 6 years was largely intermediate between current smokers and non-smokers, but former and current smokers showed taxa abundance differences only at the phylum level (Lee et al., 2018). Due to the complex composition and mechanisms associated with cigarettes and the complexity of gut microbiota ecology, the phenomena found in these studies of changes in gut microbiota after smoking cessation are not entirely consistent. However, functional changes in the gut microbiota after smoking cessation have been found through the transplantation of gut microbiota and have been shown to be involved in weight gain after discontinued smoke exposure (Fluhr et al., 2021). This finding suggests that intestinal bacteria may play a very important role in the physiological effects of smoking cessation. In general, our knowledge of the changes and functions of the gut microbiota after smoking cessation is still very poor. It is apparent that a gut microbiota viewpoint on the long-lasting effects of smoke exposure is novel and has a great deal of promise to offer new insights and actions to address improvements in the retention of the health concerns related to tobacco smoking over the long term.

Conclusion and perspectives

A bidirectional relationship between tobacco smoking and gut microbiota in smokers has been established, demonstrating that tobacco smoking affects gut microbiota, and gut microbiota, in turn, impact tobacco smoking effects. These interactions may contribute to the onset and progression of various diseases in the host. Studies have consistently found significant changes in gut microbiota in both experimental animals and humans following tobacco smoking exposure, as tobacco smoke consists of numerous components known to alter gut microbiota. Direct links between cigarette smoking and gut microbiota-promoted host diseases have been shown in colorectal cancer (CRC) (Bai et al., 2022) and smoking-cessation-induced weight gain (SCWG) (Fluhr et al., 2021). However, direct evidence of causality for many other disorders remains scarce. Furthermore, the influence of gut microbiota on smoking has been revealed, such as nicotine-degrading gut microbiota that can attenuate nicotine-induced liver damage (Chen et al., 2022). It is also noteworthy that the long-lasting effects of smoking and cessation on gut microbiota composition and functionality, future research should focus on understanding the underlying mechanisms and identifying potential therapeutic targets. Exploring probiotics or prebiotics as potential interventions to restore gut microbiota balance and mitigate the adverse health effects associated with smoking and cessation may pave the way for innovative treatment approaches. Additionally, personalized microbiota-based therapies could be developed to promote successful smoking cessation and optimize long-term health outcomes for former smokers. Each individual's tobacco damage varies. It is challenging to comprehend that there might be factors besides individual differences that affect how each person reacts to tobacco smoke based on prior knowledge. These groundbreaking studies imply that gut microbiota may play a significant role in the interactions between the host and tobacco components. Discovering and explaining the mechanism of connections between gut microbiota, tobacco components, and the host will be extremely relevant for understanding the development of various diseases and may lead to novel targets for treatments and therapeutic methods based on this new understanding. In conclusion, although still in its early stages, the pursuit of novel strategies to mitigate the detrimental effects of smoking or enhance the health benefits of smoking cessation through gut microbiota therapies holds tremendous potential and appeal.

Compliance and ethics

The author(s) declare that they have no conflict of interest.

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