The Effects of Recreational and Pharmaceutical Substance Use on Oral Microbiomes and Health

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Abstract: Oral health remains one of the most taken for granted parts of human body health, even though poor oral health has now been linked to various diseases, such as cancers, diabetes, autoimmune complications, neurological disorders, and cardiovascular disease, just to name a few. As we review in this paper, substance use or abuse, including alcohol, smoking, recreational drugs, and pharmaceutical drugs can have significant implications on oral health, which in turn can lead to more systemic diseases. In this paper, we show that oral microbiome dysbiosis and inflammatory cytokine pathways are two of the most significant mechanisms contributing to oral health complications from substance use. When substance use decreases beneficial oral species and increases periodontopathogenic strains, a subsequent cascade of oncogenic and inflammatory cytokines is triggered. In this review, we explore these mechanisms and others to determine the consequences of substance use on oral health. The findings are of significance clinically and in research fields as the substance-use-induced deterioration of oral health significantly reduces quality of life and daily functions. Overall, the studies in this review may provide valuable information for future personalized medicine and safer alternatives to legal and pharmaceutical substances. Furthermore, they can lead towards better rehabilitation or preventative initiatives and policies, as it is critical for healthcare and addiction aid specialists to have proper tools at their disposal.

Keywords: alcohol use; microbiome; oral dysbiosis; pharmaceutical drugs; recreational drugs

1. Introduction

Oral health and wellness is often greatly underestimated in connection to serious medical diseases, despite overwhelming evidence of oral associations with cardiovascular disease, pneumonia, osteoarthrosis, rheumatic disease, Crohn’s disease, kidney and liver disease, metabolic syndromes, cancer, Alzheimer’s, autoimmune disorders, adverse pregnancy outcomes, and various other illnesses [1–3]. The compositional diversity and functional homeostasis of the microbiome found on teeth and gums can greatly contribute to that oral health and wellness, which thus impacts the above listed concomitant ailments. The second largest and most varied microbiome after the gut is the oral microbiome, which includes about 700 species of bacteria, fungi, viruses, and protozoa [4]. The relationship between oral health and ailments in other parts of the body seems to be related to the dysbiosis of the human oral microbiome, as well as systemic spread of the oral microbiome inhabitants [5]. Substance use or abuse can significantly influence this dysbiosis leading to subsequent health complications [6–9].

The oral microbiome includes microbial colonization of saliva, oral mucosa, and teeth, with microbes that include protozoa, bacteria, viruses, and fungi [2]. In the oral cavity, bacteria can colonize two surfaces: the hard and soft tissues of the teeth, and the oral...
mucosa. Microorganisms can grow in the rich and ideal conditions provided by the teeth, tongue, cheeks, gingival sulcus, tonsils, hard palate, and soft palate [10]. *Streptococcus mutans* (*S. mutans*) is a major bacterium responsible for hard tissue infections of the teeth, leading to dental caries, which are the most prevalent chronic infectious disease in the oral cavity. In comparison with healthy individuals, dental caries are characterized by the increased complexity of microbial enzymes and decreased diversity of oral microbiota on their surfaces, which is probably as a result of the acidic environment [11]. This imbalance happens because of the bacterial metabolism of the glycoproteins present in the saliva and gingival crevicular fluid. The production of weak acid by the bacteria leads to tooth erosion [10,11]. As the main source of acid production that leads to dental caries is bacterial metabolism, the risk of developing dental caries is significantly influenced by the systemic host response to bacterial infections. The tooth structure can also be weakened due to factors such as genetics, medication side effects, other diseases, or environmental toxin exposure. Therefore, the likelihood of developing dental caries is determined by the bacterial composition, diet, and the host’s defense system [12].

In addition to dental caries of the hard tooth enamel, 20–50% of the global population are diagnosed with periodontal disease, which affects the soft gum tissue surrounding the teeth [13]. An imbalance in bacterial homeostasis of the oral microbiome can lead to the development of periodontal disease which initiates a host inflammatory response, resulting in damage of the soft and connective-tooth tissues. Moreover, the accumulation of microbial plaque and its enzymes on the teeth and gingiva triggers the human body’s defense response, which plays a significant role in the initiation of periodontal disease [14].

It has now been shown that various substances, such as alcohol, recreational drugs, and pharmaceutical drugs, can all impact the intricate connections described above with regards to the oral microbiome and the subsequent development of caries and periodontal diseases. Overall, the impact of medications on oral health is not a new concept. Even in 2008, a study of 529 participants in Turkey demonstrated that participants in the medication group (including anticholesterol, antidiabetes, cardiovascular drugs, and various other prescriptions) resulted in significantly higher rates of oral dryness, gingival bleeding, and alveolar bone resorption, leading to more missing teeth and prosthetic needs [15]. In this review, which prioritized peer-reviewed articles published within the past 5 years, mechanisms by which substance use and abuse lead to the development of oral health complications will be explored, as well as the significance towards potential remediation and treatment of those ailments. By examining the impact of both legal and illegal substances on oral health, we aim to demonstrate ways to better develop preventative strategies to minimize oral diseases and determine effective strategies to most effectively treat the complications that arise from these substances.

2. Dental Implications of Alcohol Use

Liver damage tends to be the first thought when exploring the implications of alcohol use on the body. Areas other than the liver, however, including the oral microbiome, have now been seen to also suffer great disruption from alcohol use, which can lead to a cascade of complications connected to oral health [1]. 16s rRNA gene sequencing has helped demonstrate strong correlations of specific tongue genera in alcohol use disorder, with a noticeable change in oral genera observed upon abstinence [16]. This microbial dysbiosis appears to have significant impacts on human health.

Alcohol consumption effects on the oral microbiome can have detrimental consequences through various pathways [17]. One mechanism observed is that the microbiome organisms produce alcohol dehydrogenase that then converts consumed alcohol into acetaldehyde, which is known to be carcinogenic [17]. Furthermore, alcohol intake hinders anti-oxidant pathways, such as glutathione (GSH), that protect against cancer consequences, and simultaneously increases detrimental chronic inflammation immune responses [17]. Thus alcohol abuse is not only associated with increased dental caries, but also with severe inflammation complications, such as necrotizing gingivitis, periodontitis, and stomati-
Bacteria 2024, 3

tis [18]. Ailments are further complicated and agitated by the various deficiencies and malnutrition that are also associated with alcohol abuse [18]. The host tends towards more severe medical outcomes in these situations due to the alcohol-induced damage to white blood cells, including neutrophils, macrophages, and T cells [18]. Alcohol use, and more importantly, abuse, also leads to consistent vomiting in many individuals, which then introduces gastric hydrochloric acid into the oral cavity, eroding dental tissues [19,20]. The highly acidic pH of many alcoholic beverages have also been found to contributes to the dental erosion, as well, which can then contribute to tooth fractures, pulpits, periodontitis, modification of the dimensions of bite, and temporomandibular joint damage [19,20]. It has been shown that damage in the oral cavity can also be further impacted by the significant environmental change that occurs when alcohol use leads to a dehydration cascade in which an antidiuretic hormone is secreted, salivary glands atrophy, and sialadenosis (gland inflammation) and xerostomia (dry mouth) are triggered [21,22].

With the various environmental changes in the oral cavity reported above in alcohol users, it is no surprise that the microbial organisms residing in the cavity change in abundance as alcohol use increases. Patients with alcohol dependency in one study demonstrated a drop in abundance of various oral genera that are highly abundant in healthy individuals (Moryella, Selenomonas, Bulleidia, and Catonella) and an increase in periodontitis-associated genera (Filifactor, Lactobacillus, and Dialister) [16]. Higher alcohol consumption has also been linked to oral enrichment of the genera Actinomyces, Leptotrichia, Cardio bacterium, and Neisseria [23]. This is of interest to the dental and medical community, as Neisseria is amongst the microbes known to produce the aforementioned carcinogen acetaldehyde at high rates from alcohol [23]. The increase in periodontopathogenic bacteria in the presence of alcohol use includes a higher association when genetic polymorphisms are present, such as ALDH2-deficient individuals. ALDH2-deficient individuals have a slower ethanol metabolism and thus these results demonstrate the impact of a more prolonged exposure to alcohol and alcohol metabolism [24]. The increased amount of periodontopathogenic bacteria was also associated with increased levels of salivary IL1β, which is a cytokine that increases inflammation and is linked to oncogenesis of oral squamous cell carcinoma via a mechanism of increased proliferation of cells and stimulation of other oncogenic cytokines [24].

Overall, not only is the increase in pathogenic or periodontic genera problematic, but a concurrent decrease in commensal normal flora is also observed, which then promotes further inflammation and detrimental consequences [23]. The decrease of commensal normal flora has even been shown to include microbes involved in the metabolic detoxification of the dangerous acetaldehyde into non-toxic or less toxic forms, which further leads to an accumulation of the acetaldehyde in alcoholics [23]. Alcohol type has also been shown to impact the consequences on the oral microbiome, with wine drinkers demonstrating a lower oral microbial alpha diversity and number of genera, whereas liquor and beer consumption were associated with increased alpha diversity and genera [23]. Wine drinking has been associated with a decrease in Peptococcus, beer drinking has been associated with decreased Porphyromonas, and liquor drinking has been associated with decreased Lachnospiraceae [23]. Beer drinking also appears to be associated with an increase in Pascardovia [23]. Differences in the impact observed with different alcohol types (such as beer versus liquor versus wine) can be attributed to various factors including the sugar content variations amongst types, as well as the difference in the percentage of alcohol actually present in each type of drink [16,23]. Additionally, the frequency of alcohol consumption also impacts the effects observed, as well as potential remediation [20]. When looking at data of dental caries and oral health, a higher frequency of drinking alcohol is associated with higher tooth wear in order of regular drinkers (42.5% drinkers with tooth wear), frequent drinkers (25%), occasional drinkers/non-drinkers (17.5%) (meaning a range of more than four days of drinking a week as regular drinkers down to zero days of drinks a week as non-drinkers) [22].

In addition, it should be noted that synergistic effects appear to exist, such as an increase in missing teeth or dental caries in alcoholic tobacco smokers compared to alcohol-
only users, but these connections need further experimentations [18,20,25]. It is believed that such connections are in part due to the observance of poorer oral hygiene in smokers or tobacco chewers, which further increases the number of caries and missing teeth [25]. Furthermore, smoking is known to have the same dehydrating effect mentioned already in regards to alcohol, which means smoking further enhances damaging inflammatory sialadenosis and xerostomia effects [21]. In one study, the difference in dental caries and tooth decay observed in alcohol-only users versus alcohol and drug use together was a 38% higher risk in the combined users [26]. Additionally, higher social status, white race, amount of alcohol consumed, and wine drinking all resulted in higher association with decay and number of fillings. It is explained that males of higher social status in the study drank wine and had great amounts of caries, whereas males of lower status tended to drink beer and thus has lower amounts of caries [26]. When individual layers of the plaque composition were analyzed, it was found that significant differences of both supragingival facultative aerobes and subgingival anaerobes exist in wine drinkers, with major decreases in microbial frequencies in both layers in wine users [27]. Interestingly, in that same study, it was also found that the same decrease was observed in coffee drinkers as well, which demonstrated that some of the decrease in the microbial oral composition of wine drinkers may be due in part to the polyphenol content contributing to an inhibition of adhesion or some other hindrance against microbes [27]. Polyphenols have been shown to block microbial adhesion via interactions with bacteria membrane proteins, and strongly inhibit bacterial glycosyltransferase and amylase, both of which participate in plaque formation [28–30].

The implications of alcohol use on oral health are highly interconnected as seen in Figure 1. The promising aspect, though, of these various studies looking into the impact of alcohol on oral health and hygiene is that many of the observed consequences have potential for remediation. For instance, in one study, within even just the first week of an alcohol-use dependency inpatient treatment program, a significant net increase of healthy genera and decrease of periodontitis-associated genera was observed, which is promising for remediation potential [16]. Data demonstrating improvement of dysbiosis consequences upon abstinence from alcohol and improved oral hygiene is promising as it demonstrates the reversibility of some of the microbial based damages to health [16].

Figure 1. A sample of the mechanisms by which alcohol consumption leads to various oral health issues (mechanisms are in blue; final disease states are in red; TMJ = Temporomandibular joint).
3. Dental Implications of Recreational Drug Use (Other than Alcohol)

Substance abuse is a growing public health issue and its interconnectedness with the oral cavity and the microbiome is becoming a main concern. The correlation specifically introduces the relationship between recreational drug users and their susceptibility to dental disease. Throughout the world, illegal substance abuse or recreational drug use has increased as a literature review from 2017 presents that illicit drugs affect around 27.8 million people in North America and will be more common in the coming years [31].

Common recreational drugs such as cocaine, heroin, methamphetamine, and cannabis have been widely recognized as contributors to the complications of dental hygiene [32]. Through a lack of hygienic habits when under the influence, increases in inflammatory cytokine pathways, a disruption of protective salivary fluids, and pH changes all modifying the composition and functional diversity of the oral microbiome, drug use can have significant impacts on oral health, including the development and progression of cancer [33,34].

3.1. Cannabis

Cannabis use has recently been on the rise, with recreational legalization occurring in 19 states as of August 2022, 49.6 million people reporting use in the past year, and 2.8 million initiating use during that period [35]. In the oral cavity, saliva stands as a key protection factor as it prevents the accumulation of harmful bacteria and aids in digestion [36]. Cannabis has been shown to significantly reduce the rate of salivary flow [37,38]. Saliva maintains oral hygiene by rinsing away microorganisms and enriching the environment in calcium and phosphate, allowing remineralization to occur and the hard tissues of the teeth to be protected [39,40].

The oral microbiome is heavily associated with and altered by cannabis use as there are fluctuations of several different bacterial species. A study done to uncover the change in the oral flora of cannabis users included the results that Actinomyces and Streptococcus had grown in a cannabis-containing environment [41]. In chronic cannabis smokers, the Actinomyces genus was more present as compared to tobacco smokers and was linked to increased CNS dysfunction or abnormalities [41]. Both Streptococcus and Actinomyces are considered “acid-tolerant”, hence their survival in the acidity of the saliva produced by cannabis [41]. Their ability to store extra sugars as intracellular polysaccharides after overproduction gives the non-mutans an energy source to produce acids when sugar is low, decreasing the pH and further demineralizing the enamel [42]. Although there is an increased risk with forming caries, cannabis has been seen to have anti-inflammatory properties in rats as it can inhibit the expression of RANK/RANKL that can ultimately lead to slowed progression of periodontitis [43]. RANKL is responsible for the balance between osteoblasts and osteoclasts, and the cannabinoids are linked to the decrease of production of inflammatory mediators [43]. Specifically, non-psychoactive CBD is responsible for this inhibition as the activation of CB2 receptors is seen to reduce osteoclastogenesis through the blockage of RANKL expression [43]. Therefore, cannabis can have both detrimental and advantageous aspects to the severity of dental disease.

3.2. Methamphetamine

Methamphetamine can be characterized as a powerful stimulant that increases physical activity by processing different neurotransmitters, including dopamine and serotonin [44,45]. In the ongoing drug abuse crisis, methamphetamine has become a dominant force, with its use increasing from 1.4 million people in 2016 to 2.0 million in 2019 in ages 12 or older within the United States [46]. This upward trend can be associated with the oral cavity as this pervasive substance abuse gives rise to certain conditions ultimately leading to increased cavity presence, usually on labial surfaces. Known as “meth mouth”, the frequent and direct use of methamphetamine can cause teeth to become “blackened” and “rotting” as the acidic nature of the drug can lead to conditions such as xerostomia [47]. Increased vulnerability to caries can be explained by meth’s ability to eliminate the buffering capacity of saliva, or its potential to neutralize acids [32]. It is active for about 8–12 h on average but
can be found in saliva for up to 24–28 h, therefore patients are unable to be treated after immediate use [48].

The relative abundance of certain bacterial species can be attributed to methamphetamine use, where the taxa that are known to cause dysbiosis are heavily prominent. The *Neisseria* genus had exhibited higher levels amongst abusers, which coincided with IL-17 abundance in saliva [49]. *Neisseria* produces extracellular polysaccharides and glycolytic sugars in the presence of sucrose, contributing to tooth decay as oral bacteria has the tendency to process sugars through the glycolytic pathways resulting in acids responsible for the degradation of enamel [49,50]. The increased presence of proinflammatory cytokine IL-17 is seen in patients suffering from periodontitis that induces the production of RANKL, causing this inflammatory response and ultimate osteoclastogenesis [51]. Moreover, *Peptostreptococcus* and *Gemella* increased while *Campylobacter* and *Aggregatibacter* reduced, affecting several oral microbiome pathways, such as the reduction of glutathione and porphyrin metabolism or the enhancement of the biosynthesis of steroids and the metabolism of tryptophan [52]. Specifically, tryptophan degradation is associated with the pathogenesis of oral cancer as it activates the kynurenine pathway [53]. Within this pathway, IDO enzymatic activity plays a role in the rate-limiting step and its contribution has been tied to the promotion and invasion of cancerous cells while its increase is attributed to proinflammatory cytokines [53].

3.3. Cocaine

Cocaine stands as one of the most common psychoactive drugs that stimulates a feeling of euphoria after altering brain chemistry. Although it is often consumed intranasally, addicts have tendencies to rub the drug on the gingival surface of teeth as to test the purity of the substance [54]. Cocaine has a pH of 4.5, making it capable of erosion of tooth enamel, which is an ideal environment for caries to thrive [55]. A low pH is able to produce an acidic environment where bacteria can flourish as well as causing demineralization to remain while the saliva’s defense mechanism is unable to function [39]. In a study conducted to reveal the status of the oral microbiome in cocaine users, saliva amongst these users showed significant enrichment in the *Streptococcus*–related species as compared to non-users, which can be attributed to the loss of buffering ability of saliva [56]. Cocaine was shown to induce increased plasma levels of a variety of monocyte activation markers, including monocyte chemotactic protein or macrophage inflammatory protein, that correlate to the presence of *Streptococcus* since monocytes are often elevated in the presence of chronic inflammation [56]. Cytokines are also often produced by cells with inflamed tissues and cocaine users exhibit an increased activity of specific neutrophils that can produce cytokines such as IL-17, which is heavily associated with osteoclastic bone resorption that is stimulated by the expression of RANKL42 [57]. In addition, cytokines that are produced by T helper 1 and T helper 2 cells are disturbed while metalloproteinase-9 is heavily involved with tissue degradation [57]. Monocytes often appear in inflamed gums and respond by producing pro-inflammatory cytokines, worsening inflammation and if left untreated, and can lead to the weakening of the body’s ability to fight back [58]. Notably, the enhancement of RANK-L expression from IL-17 is pronounced in gingiva of periodontitis patients and often promotes inflammation or bone destruction [58]. All factors that produce such imbalances potentially lead to dysbiosis and the overpowering of the body’s natural defenses [57].

In relation to caries, *Streptococcus* groups are the major contributors to erosion as they have the ability to adhere to enamel and produce extracellular polysaccharides along with the building up glycogen reserves, having a central role in the creation of an acidic environment [59]. The oral microbiome community is heavily disturbed with the increased usage of cocaine as the changing bacterial composition has a major impact on the regulation of caries.
3.4. Heroin

Heroin can be classified as a potent opioid that could be linked to several factors contributing to dental deterioration and vulnerability to caries. Common in heroin abusers, carious lesions tend to be rampant, appearing darker in color and covering labial or buccal surfaces in the oral cavity [60]. Heroin is able to mask dental pain as a result of the opioids’ pain-relieving qualities, causing patients to prolong any dental visits until there is severe pain present, increasing the prevalence of dental disease [61]. Additionally, heroin has the ability to lower salivary production, leading to xerostomia and increases in the craving for sweets, which can also lead to increased caries [62]. Users with a history of heroin abuse have been seen to develop mandibular osteomyelitis, chronic damage in the bone, which can be caused by *Candida albicans* [63]. *Candida* is often characterized as a trigger for infections, including periodontitis, where the species occupies the periodontal pocket, or in some instances, peri-implantitis—an inflammation of soft and hard gum tissue around implant sites—as it adheres to the implant surface [64,65]. *Neisseria subflava* have been found among decreased species in heroin users’ oral cavities, which occur in lower abundances of caries-infested oral environments [33]. *Neisseria* species are considered nitrate-reducing bacteria that have a role in regulation pH of the oral cavity and maintain homeostasis to slow the progression of caries, however this mechanism needs further study [66].

4. Dental Implications of Pharmaceutical Drugs

One of the most important factors that affect the microbial communities in the oral cavity is drug use. Both drug classes with intended and unintended antimicrobial actions impact the composition of the microbiome resulting in therapeutic activity or the development of diseases [67]. This imbalance of the oral microbiome is known as dysbiosis, which leads to interruption of the microecological balance between host and microorganisms, resulting in oral and systemic diseases. Generally, oral microorganisms maintain their balance through synergistic and antagonistic interactions among each other, keeping the detrimental microbes, such as *Veillonella, Scardovia, Lactobacillus*, and *Propionibacterium*, at low levels [68,69]. Antibiotics such as amoxicillin (AMX), metronidazole (MTZ), and spiramycin (SP) cause dysbiosis as they contribute to the reduction of microbial diversity and trigger metabolic changes. A study found that over six months, amoxicillin decreased the diversity and population of Actinobacteria and increased the population of Proteobacteria, which are antibiotic resistant strains. Imbalance caused by antibiotics leads to the outgrowth of resistant strains which negatively affects the overall health [70,71]. Another study revealed that Candida growth can be effectively controlled using antifungal medications, resulting in an immediate decrease in the symptoms of oral thrush. However, antifungals can also lead to dysbiosis through a reduction in fungal populations, which indirectly influence bacterial communities [72]. In addition, medications, such as thyroid hormones, statins, and proton pump inhibitors (PPIs), significantly influenced the oral microbiome. They either enriched or depleted populations of *Saprospiraceae* (uncultured), *Bacillus, Johnsonella, Actinobacillus, Stenotrophomonas*, and *Mycoplasma* [73].

Dental caries are a cavity in the form of a small lesion on the tooth surface that may lead to loss of tooth structure [74]. This disease emerges from the biofilm on the surface of the teeth, which is composed of polymicrobial communities formed by the oral microbiota [75,76]. Extracellular polysaccharides (EPS) are the main component of the caries biofilm that promotes the growth of cariogenic microorganisms by providing a pathological environment. Cariogenic microorganisms include the acid-producing bacteria, such as *Veillonella, Scardovia, Lactobacillus*, and *Propionibacterium*, that contribute to the progression of dental caries [77–79]. The development of dental caries is even worse when the dietary carbohydrates are fermented by the bacteria accumulated in the dental plaque for an extended period. The fermentation process leads to demineralization of the teeth if the produced acids cannot be neutralized by the buffering capacity of the salvia resulting in the formation of cavities [80].
Pharmaceutical drugs have the ability to influence dental caries through altering the oral environment, salivary flow, the composition’s pH levels, and the oral microbiota balance [81]. Saliva consists of water, calcium, and phosphate, which decreases the solubility of hydroxyapatite, the main component of teeth. Depending on the different types of buffering systems in the saliva, such as bicarbonate, phosphate, urea, and amino peptides, the saliva maintains a neutral oral cavity pH value up to 7.67 [82]. Reducing the solubility of hydroxyapatite leads to inhibition of tooth demineralization [83]. In addition, they further decrease the protective effects of the saliva by altering its composition and lowering the salivary pH. As a result, the susceptibility to oral pathologies rise due to the increased populations of \textit{S. mutans} and \textit{Lactobacillus acidophilus} [81,84]. A main cause of xerostomia is polypharmacy, which is the use of five or more medications and affects around 20\% of patients in the United States [85]. According to previous clinical studies, the risk of developing caries increases with decreased salivary flow. In spite of maintaining good oral hygiene, patients with xerostomia experience rapid onset and progression of carious lesions [86]. Drug-induced xerostomia occurs when medications inhibit the function of muscarinic receptors in the salivary glands, leading to a reduction in the flow of saliva.

Anticholinergic medications are known for significantly impairing the secretion of saliva and decreasing its protective functions, increasing the risk of dental caries [87]. More than 600 medications have anticholinergic properties that compromise the function of salivary glands. Antihistamines, antispasmodics, antidepressants, and antipsychotics are the most widely prescribed medications with anticholinergic side effects [85]. In addition, the use of inhaled corticosteroids, such as beta2-agonists for asthma treatment, reduce salivary flow and pH, which leads to a proliferation of harmful \textit{Lactobacilli} and \textit{Streptococcus mutans} in the mouth. Therefore, these medications raise the likelihood of oral problems, such as dental caries, dental erosion, tooth loss, periodontal disease, and oral candidiasis. Moreover, some dry powdered asthma medications consist of lactose monohydrate which is a fermentable sugar. These sugars play a significant role in increasing the risk of developing dental caries as they alter the composition of saliva [82]. Antibiotics can indirectly increase the risk of dental caries by causing an imbalance in the oral microbiome and proliferation of antibiotic resistant bacteria [88]. Despite this, antibiotics have been prescribed to treat bacterial infections and to prevent or treat dental caries. Over the recent years, the use of antibiotics gradually dropped due to the emergence of other antimicrobial agents that target oral bacteria responsible for oral disorders. Antimicrobial agents include fluoride, chlorhexidine, quaternary ammonium salts, and antimicrobial peptides (AMPs) [89]. Fluoride is among the most effective cavity prevention agents as it increases the remineralization of the tooth through the contact of fluoride ions with the minerals on the tooth surface. This prevents the acid-induced demineralization by cariogenic bacteria. Additionally, fluoride’s ability to inhibit the enzyme enolase in the glycolytic pathway, results in suppression of the growth and acid production of oral streptococci, including \textit{S. mutans} [90].

5. Conclusions

Substance use and abuse continues to be a growing problem worldwide, with many people underestimating the impact on oral health and instead focusing on consequences, such as liver disease or cardiovascular consequences [91–94]. Through our review, it became evident that a significant factor in the impact of substance use on oral health and consequently whole body health is that the oral cavity is comprised of a highly interconnected network of microorganisms susceptible to imbalance and destruction [95]. Of greatest concern is the significant link between oral dysbiosis and carcinogenesis [96]. Higher alcohol consumption has been linked to the enrichment of periodontopathogenic bacteria that produce acetaldehyde, while simultaneously decreasing the abundance of bacteria or anti-oxidants that would reduce this carcinogenic byproduct [17,23]. Acetaldehyde dehydrogenase activity is known to be reduced in the oral cavity, which further increases the harmful effects of this destructive byproduct [97]. The bacterial dysbiosis due to alcohol also leads to an increase in bacteria-releasing inflammatory cytokines and severe consequences.
on the immune system [24]. Interestingly, a similar pattern of increased inflammatory cytokines from oral microbiome shifts is also observed with methamphetamine and cocaine use as well [49,56]. Pharmaceutical use also appears to follow the same pattern of disrupting normal oral flora, leading to a decrease in beneficial microbes with a simultaneous increase in detrimental periodontopathogenic microbes [70–72]. *Fusobacterium nucleatum* and *Porphyromonas gingivalis* are two oral microbiome members highly associated with tumorigenesis development and progression through mechanisms of pro-inflammatory cytokines, immune suppression, and apoptosis inhibition [96]. Even though fusobacterium was previously associated with colorectal carcinoma, it has now been seen as an enriched periodontal pathogen associated with oral tongue squamous cell carcinoma [98]. Fusobacterium enrichment in tumor samples has been shown to be associated with increased programmed death-ligand 1 (PD-L1) mRNA expression and increased surface PD-L1 protein expression [98]. These oral microorganisms are also able to reduce the efficacy of chemotherapeutic agents, in addition to causing cancer complications. For example, *F. nucleatum* inhibits TLR4 and MyD88 immune mechanisms and activates autophagy, while also increasing chemokine production and inhibiting T cell function [96]. *P. gingivalis* has also been shown to reduce the efficacy of chemotherapeutics, including an increased resistance to Taxol and Paclitaxel via Notch1 activation [96]. Even commensal fungi of the oral mycobiome can become problematic instigators of carcinogenesis as opportunistic pathogens [97]. *C. albicans*, for instance, can generate carcinogenic products, such as nitrosamines or N-nitrosobenzylmethylamine, that can bind DNA and trigger cancerous progressions [97]. The great impact of oral microbiota dysbiosis in cancer development and progression is also made clear by the finding that localized infections of the upper respiratory tract negatively impact the outcome of oral cancer [99].

It has further been shown that the use of these substances in combination, such as someone partaking in alcohol use or medications and smoking, causes the effects to be even more deleterious as a synergistic impact appears [18,20,25]. It should be noted though, that it is difficult to obtain pure data on the true extent of individual alcohol and drug abuse towards dental complications, since there also exist many confounding factors as many of these patients tend to have simultaneous vices or poor hygiene habits, as well as poorer access to health care with varying social statuses.

Through this review it has become evident that recreational substances, including alcohol use, as well as pharmaceutical drug use can lead to significant consequences disrupting the oral microbiome and thus consequently impacting human health. This is of great significance clinically and in the research world, as these impacts on oral health in turn lead to a poor quality of life and can disrupt daily life functioning. Furthermore, exploring the impact of these substances on the oral microbiome and health can help in the development of personalized medicine, creation of safer alternatives of legal substances or pharmaceuticals, an increase in funding towards preventative programs or rehabilitations, and an overall increase in societal awareness initiatives for better public health and regulations. Specific microbial pathways or mechanisms can be targeted for therapeutic developments, such as the *Fusobacterium* or *Candida* mechanisms described in this review [96,98]. It also helps demonstrate the need to collect more extensive medical histories and lists of substance intake when treating or evaluating patients in dental practices, as ceasing problematic behaviors can prevent further visits to the dentist after the current damage is treated. Healthcare and addiction aid specialists should be made aware of these significant consequences and cascades in oral health. Additionally, studies demonstrate that substance use participants have lower oral microbiome diversity and an increase in negative periodontopathic strains. It is believed that the oral microbiome may be able to be used as a “risk or severity biological marker,” which can further enhance healthcare targeting of patients [100]. While dysbiosis and cancer emerge as major themes of consequences to oral disruption from substance use, it brings to light the question of how many other ailments may be linked to oral health that we have not yet found connections for. This will also hopefully encourage further study into the many other products that people use
daily that may activate similar mechanisms and dysbiosis, furthering the increases in oral cancers and related consequences.

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**References**


43. Napimoga, M.H.; Benatti, B.B.; Lima, F.O.; Alves, P.M.; Campos, A.C.; Pena-dos-Santos, D.R.; Severino, F.P.; Cunha, F.Q.; Guimarães, F.S. Cannabidiol Decreases Bone Resorption by Inhibiting RANK/RANKL Expression and pro-Inflammatory Cytokines during Experimental Periodontitis in Rats. *Int. Immunopharmacol.* 2009, 9, 216–222. [CrossRef]
68. Cicchinelli, S.; Rosa, F.; Manca, F.; Zanza, C.; Ojetti, V.; Covino, M.; Candelli, M.; Gasbarrini, A.; Franceschi, F.; Piccioni, A. The Impact of Smoking on Microbial Communities, Bacterial Growth, and Biofilm Formation. *Antibiotics* 2023, 12, 1433. [CrossRef] [PubMed]


91. Simon, T.G.; Roelstraete, B.; Alkhouri, N.; Hagström, H.; Sundström, J.; Ludvigsson, J.F. Cardiovascular Disease Risk in Paediatric and Young Adult Non-Alcoholic Fatty Liver Disease. *Gut* 2023, 72, 573–580. [CrossRef] [PubMed]


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