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Review

Cross Talk between Synthetic Food Colors (Azo Dyes), Oral Flora, and Cardiovascular Disorders

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Abstract: Synthetic food colors are important ingredients in the food industry. These synthetic food colorants are azo dyes, majorly acidic in nature such as Allura red and Tartrazine. They are present in sweets, carbonated drinks, meat products, and candies to attract the consumers. This review article is an attempt to explain the adverse effects of azo dyes and their association with oral cavities and cardiovascular disorders. These synthetic dyes (azo dyes) have staining effects on dentin. Poor dental care accelerates the bacterial accumulation on the dental crown (Gram-negative bacteria *P. gingivalis*, *T. denticola*, and *T. forsythia* and Gram-positive bacteria *Strep. Gordonii*), causing the washing of enamel, forming dental plaque. Bacterial pathogens *(P. ginigivalis* and *F. nacleatum)* release different chemicals (FadA and Fap2) that bind to protein on the cell by producing an inflammatory response through different line-host defenses, such as Gingival epithelial cells (ECs), Hemi-desmosomes, and desmosomes, which helps the bacterium migration from the cell–cell junction. This makes the junctions slightly open up and makes the whole vessel permeable, through which the bacterium enters into the blood stream line. This leads to different major arteries, such as the carotid artery, and causes the accumulation of plaque in major cardiac arteries, which causes different cardiovascular disorders. These bacterial species present in gums cause cardiovascular diseases, such as ischemic heart disease, coronary artery disease, heart attacks and strokes, and arrhythmias, which can lead to death.

Keywords: azo dyes; synthetic food colors; oral microbiome; periodontal disease; cardiovascular disorders

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1. Introduction

Food is the basic need of all humans; it is only beneficial or nutritive when it is present in fresh and pure form [1]. Synthetic food colors are considered to be the most important ingredient of industrial and commercial products to increase the taste, appearance, and flavors of products. These factors play an important role in the selection of products. The majority of consumers are trapped due to the attractive colors of food products [2].

Dyes are classified as cationic, anionic, and non-ionic. Dyes that are classified as anionic and non-ionic mostly contain anthraquinone or azo type chromophores. The major class of chemical compounds that are ubiquitous in plastics, textiles, food, pharmaceuticals, and cosmetic products are azo dyes (synthetic food colors). Azo dyes contain one or more R_1-N=N-R_2 bonds that are reduced into aromatic amines by enzymatic mechanisms. Several azo dyes, such as red azo dye (Allura red FD&C 40) and yellow azo dye (Tartrazine FD&C Yellow 5) are commonly used in beverages, puddings, icings, jellies, dairy products, spices, and in many baked goods, whereas yellow azo dye is used in dressings, yogurt, baked goods, snack foods, etc. [3]. The chemical structures of (a) Tartrazine and (b) Allura red are shown in Figure 1. Tartrazine causes adverse effects such as disorders of the gastrointestinal tract, respiratory tract, and central nervous system and different diseases involved with the skin, such as urticarial, angioedema, and eczema [4]. Allura red has claimed adverse effects on human health such as cancer, attention deficit hyperactivity disorders, brain damage, cardiac disease and asthma, multiple sclerosis, and food intolerance [5].

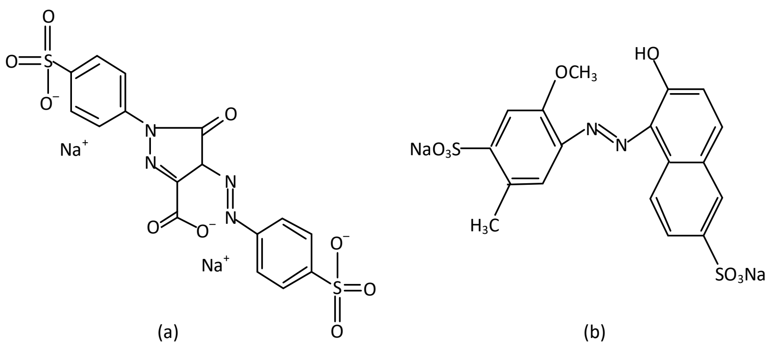

Figure 1. Chemical structures of (**a**) Tartrazine and (**b**) Allura red.

Recent research emphasized the toxicity and genotoxicity measures of both red and yellow dyes. Numerous studies have claimed the carcinogenicity of azo dyes [6]. The chemical composition of these azo dyes contains sodium chloride and sodium sulphate as principle uncolored components. Aromatic amines also play an important role in the chemistry of azo dyes; the aromatic amine phenylamine is very important on the industrial level, as it is used for the production of azo dyes. Basically, the aromatic amines are converted into diazonium salt, then the diazonium salt is combined with an aromatic compound such as phenol, resulting in the formation of azo dye. These azo dyes reduce azoreductases in human flora and release different aromatic amines and toxins [7].

There are thousands of azo dyes in the market, of which more than 500 exhibit potentially carcinogenic aromatic amines in the chemical formula. When these azo dyes enter the human body through food, skin contact, and injection, they are metabolized by azoreductases to aromatic amines in the oral cavity or in the gastrointestinal tract in the mammalian liver [8]. Four thousand azo dyes were examined in a survey, and almost 90% had LD50 values > 2000 mg/kg, with the highest toxicities being reported among diazo and basic dyes [9]. They are regarded as relatively persistent pollutants because of their ability to not degrade under aerobic conditions. There is more reduction in anaerobic conditions by oral and bacterial microbiome, having toxic, mutagenic, and carcinogenic effects on humans and animals. Azo dyes have also been identified in many tattoo colorants, including the derivatives of 3,3′-dichlorobenzidine, phthalocyanine derivatives, and azo-derivatives of 2-amino-4-nitrotoluene. Azo dyes used in food are reduced to aromatic amines by the azoreductase enzyme. The azoreductase enzyme is present in several bacteria as well as hepatic cells. In the liver, it is present in a less active state compared to the equivalent enzyme present in several bacteria. The activity of the bacterial azoreductase enzyme present in skin flora, gut flora, and oral flora has been studied thoroughly, such as *Neisseria flavescens*, *Staphylococcus hominis*, *Staphylococcus lentis* and *Lactobacillus* (oral bacteria) show azoreductase activity.

In this review, the presence of azo dyes (synthetic food colors) in food products and their association with periodontal and cardiovascular disease were addressed, such as their contribution to plaque buildup in the teeth and their reduction into aromatic amines through the azoreductase enzyme, released by the oral microbiome, causing different periodontal and gums disease, which contribute cardiovascular disorders.

2. Food Colors, Oral Flora and Cardiovascular Disorders

2.1. Food Colors

Food colors are considered to be the most important ingredient in any food, prepared at both the commercial and industrial level. Artificial food colors are pigments or dyes that produce color when they are added to beverages and drinks and many other food items. All synthetic food colors are chemical substances that are added to food materials to increase the sensory characteristics of the food product, which usually degrade during processing, and to retain the desired color appearance. A majority of consumers are trapped due to the attractive color of food products [2]. In recent years, the usage of synthetic food colorants has increased to substitute for natural food colors, to improve appearance, and to achieve certain characteristics, color uniformity, and high color intensity and stability [10,11]. All of these synthetic food colors are aromatic compounds and are coal tar derivative chemicals. Azo dyes are abundantly used in food, cosmetic, textile, pharmaceutical, and leather industries. Synthetic dyes are divided into triphenylmethane dyes, indigotin dyes, xanthene dyes, azo dyes, and quinoline dyes. Various beverages and food available in the market may contain non-permitted synthetic food colors. Various studies confirmed that intoxication is the most common cause of synthetic food colors and leads to many dangerous health problems in humans and animals. There are many synthetic food colors that have been extensively used in the past few decades but that are no longer permitted because of the evidence of their toxicity in the long-term and the higher frequency of potential health incidents [12,13]. To overcome this danger, the use of synthetic food colorants in the formation of food products leads to the need for the expansion of precise, selective, sensitive, and accurate analytical methods for their quantification and analysis [14].

The following are forms of synthetic food colors:

- Powder
- Granular
- FD&C (The United States Federal Food, Drug, and Cosmetic) colors
- D&C (Drugs and Cosmetics) colors
- Lake colors (Water-insoluble)

There are three type of synthetic food colors that are mentioned. The first one is primary food colors, which have serviceable value and are abundantly used in pharmaceuticals, food, cosmetics, and other industrial products. The composition of primary food colors are $(CH_2)_2CHNH_2$-COOH, $(CH_2)_2OH$, and $CH_2NHCOCH_3$, etc. [15]. The second is blended food colors. They are formed by mixing various primary and secondary colors with one another or independently. Blended food colors have unique color properties, and the chemical composition is CH_2OH-NH_2 [16]. The last type is lake food colors. They are used where dyes are not applicable because they are soluble in water, are consistently bright, and are used in many industries such as cosmetics, pharmaceuticals, and plastic food containers. The chemical composition of lake food is $C_{37}H_{36}AlN_2O_9S_3$ [17].

2.2. Effects of Food Colors on Human Health

Color pigments are an important part of food, which imparts the attractive appearance of the food product. The natural food shade tends to lessen during storage and processing, which is why synthetic food colors become a technological necessity. Most food-borne diseases result because of consuming non-permitted textile colors in direct and indirect ways, which are discharged as industrial effluents in the environment. The majority of food dyes tested in conventional toxicity experiments or parameters reported toxic effects at a very high level of consumption [18,19]. Several studies have reported that some synthetic food colors are cancer-causing and have adverse effects on the human body, as well as animals. Red 3 causes DNA damage (cancer) in animals, and there is other evidence showing that several other dyes are also carcinogenic. The consumption of Red No. 3 was reported with estrogen-like growth stimulatory properties and resulted in being genotoxic, and it had significant risk factors in human breast carcinogenesis [20]. Three dyes, Red 40, Yellow 5, and Yellow 6, have also been reported to be adulterate with other carcinogens or benzidine [21]. According to the Food

Additives Amendment of 1958, it is healthier to use the product that is naturally prepared than to utilize the product containing synthetic food colors, which is harmful to human health [22]. Artificial food colors also cause hypertension in children. Scientists at Southampton University discovered a genetic component that determines how food dyes influence a child. Studies claimed that there is a minor but notable association between hyperactivity in children and artificial food dyes [23,24]. Synthetic food colors also have some allergic effects on the human body. Several studies showed that tartrazine, which is also known as Yellow 5, causes hives and asthma symptoms. In a study conducted in people with chronic swelling and hives, 52% had an allergic reaction to most of the synthetic food colors; Red 40 and Yellow 5 and 6 are the most common synthetic food colors used in industrial and commercial levels, and they are the three most likely to cause or have allergic responses [17,25,26].

Different factors affect human health:

- The most evidential claim about azo dyes (synthetic food colors) is that they are carcinogenic.
- They cause different skin diseases, e.g., skin allergies, and cause hyperactivity in children.
- They produce different periodontal and gum disorders when azo dyes present in food are reduced to aromatic amines by the help of azoreductase enzyme. The break downing of azo compounds releases different carcinogenic amines in the oral cavity, which leads to many gum diseases, such as tartar or plaque formation.

Synthetic food colors have no nutritional benefits, which is why they have to be prohibited. Processed foods that are produced by the combination or addition of different additives have no nutritional value because the cleaved product present in azo dyes, such as benzidine, causes different human and animal tumors. Another azo dye component, p-phenylenediamine, causes allergic reactions. These are also the leading cause of hyperactivity in children, including ADHD, and behavioral and hormonal changes, such as the effect of Tartrazine and erythrosine on reproductive hormones and testicular genes in testis of male Wister rats. They also cause irritability and depression, hives, and asthma [27].

2.3. Oral Flora and Periodontal Disease

2.3.1. Oral Flora

The oral cavity is the second largest habitat in the human body where microbiota can colonize. The oral cavity exhibits both the epithelial surface of the mucosal membrane and the hard surface of teeth. The oral microbiota contains approximately 1000 subspecies. Because of the continuous exposure to saliva, oral microbiota obtain the features of avid adherence, which assures the colonization of oral bacteria and the resistance to the fluid flow force [28]. The oral microbiota contain complex polymicrobial communities that have convoluted interactions with the host's immunity and diet. The subjugated pathogenic resistance in oral microbiota is primarily promoted by the fluid phase, where the oral mucosa is disrupted due to poor oral hygiene, which leads to the settling of bacteria on the substrate. Under these conditions, the bacteria metabolize the substrate to produce acid, which decalcifies teeth. The improper treatment of this therapeutic invention leads to the promotion of the inactivation of bioactive molecules and causes serious oral disorders [29]. Oral pathogens exert the ability to trigger an immune response (pro-inflammatory response). Inflammation has been found to be an important driver in periodontal disease for the development of pathogenic microorganisms and inflammation, causing the damage of tissues, which provide nutrients to microbiomes [30,31].

2.3.2. Periodontal Disease

Periodontal disease is better known as a chronic inflammatory disease of periodontium, and its recent type is specified by periodontal ligament loss and damage of the surrounding alveolar bone [32]. It is considered to be one of the two major threats to oral health and is considered as a main cause of tooth loss. Almost 800 species of bacteria are recognized in the oral cavity [33], and it is hypothesized that the composite interaction of bacterial infections and the host response adapted by the behavioral factor can result in periodontal disease [34].

Periodontal diseases are considered a usual oral condition of the human population [35]. About 14–47% of the adult population had calculus deposits collate, with 36–63% of the adults being in developing countries, and a larger percentage of individuals had 4–5 mm of periodontal pockets, whereas older individuals exhibited 6 mm of periodontal pockets or above in both developed and developing countries [36]. Overall, 20–50% of the population around the world is affected by periodontal disease [37].

Digestive enzyme amylase is predominantly secreted by salivary glands and is also known as ptyalin. The principal function of amylase is to hydrolyze the glycosidic bonds in starch molecules and to help in breaking down the starch present in food into different simpler sugars (maltose and dextrin) [38]. Azo dyes contain higher staining properties, and because of the presence of the conjugate system, they are highly colored. The staining causes the formation of plaque, which promotes different microbes in oral flora such as *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Streptococcus gordonii*, and *Fusobacterium nacleatum* [39]. The chemistry of azo dyes contains different salts such as sodium sulphate, sodium chloride, potassium and calcium salts, and amines [40]. Different chemicals are released when food (sugar products, juices, and meat products) that contains azo dyes is grinded in the oral cavity. The most common bacterial species of oral flora that are involve in periodontal disorders are *P. gingivalis* and *Strep. Gordonii*; these species accelerate the process.

2.3.3. Role of Oral Flora in Periodontal Disease

Oral flora has a majopart in human health status and the human microbial community because it helps the human body against the invasion of an undesirable stimulation outside. An imbalance of microbial floras causes whole body and oral systematic diseases. There are different microbiomes present in the oral cavity, forming a bacterial community structure. Almost 1100 different types of taxa are recorded in the human oral flora [41]. About 20–50% of the world population are affected by periodontitis disease, which is caused by the three bacterial species *P. gingivalis*, *T. denticola*, and *T. forsythia*, and Gram-negative bacteria commonly involved in periodontitis disease are also nominated as a red complex group [42]. Recent studies revealed that *P. gingivalis* majorly contributed to causing periodontal disease because the bacterial species produces certain virulence factors and some extracellular proteases, such as gingipain, fimbria, and lipopolysaccharides, etc., which results in damaging the periodontal tissue. In the literature, there is almost six major phyla present in the human oral cavity, such as *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, *Spirochaetes*, and *Fusobacteria*, which contain about 96% of the taxa, as shown in Table 1.

Table 1. Five different Phyla of oral flora that contribute to the formation of different periodontal disorders in the human body [41,43,44].

Human Oral Flora				
Phyla	**Class**	**Order**	**Family**	**Genera**
Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Catonella*
	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*
	Clostridia	Clostridiales	Peptostreptococcacea	*Filifactor*
	Bacilli	Bacillales	staphylococcaceae	*Gemella*
	Bacilli	Lactobacillales	Carnobacteriaceae	*Granulicatella*
	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*
	Negativicutes	Vellionellales	Veillonellaceae	*Vellionella*
	Negativicutes	Selenomonadales	veillonellaceae	*Dialister*
	Negativicutes	Selenomonadales	Selenomonadaceae	*Selenomonas*
	Negativicutes	Selenomonadales	Veillonellaceae	*Megasphaera*
	Tissierellia	Tissierelliales	Peptoniphilaceae	*Parvimonas*

Table 1. *Cont.*

Human Oral Flora				
Phyla	**Class**	**Order**	**Family**	**Genera**
Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Aggregatibacter*
	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*
	Epsilonproteobacteria	Campylobacterales	Campylobacyeraceae	*Camplylobacter*
	Betaproteobacteria	Neisseriales	Neisseriaceae	*Kingella*
	Betaproteobacteria	Neisseriales	Nrisseriaceae	*Neisseria*
Bacteroidetes	Falvobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*
	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*
	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*
	Bacteroidetes	Bacteroidales	Porphyromonadaceae	*Tannerella*
Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*
	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	*Bifidobacterium*
	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Slackia*
Spirochaetes	Spirochaetia	Brachyspirales	Brachyspiraceae	*Brachyspira*
	Spirochaetia	Brevinematales	Brevinemataceae	*Brevinema andersonii*
	Spirochaetia	Leptospirales	Leptospiraceae	*Leptospira*
	Spirochaetia	Spirochaetales	Spirochaetaceae	*Spirochaeta*
Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*
	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leotothrichia*
	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*

The consumption of processed foods in daily life, such as sugar products, meat products, and carbonated and soft drinks containing synthetic food colorants contaminants, could pose a health risk [45]. These colors contain different azo dyes, which are acidic in nature. In dental health, these dyes cause a staining effect, which produces dental plaque. Dental plaque is commonly caused after the consumption of products that contain synthetic food colors (azo dyes), higher concentrations of citric acids and phosphoric rates, amino acids, and sodium concentration (especially sodium chloride). In addition to the six major phyla in Table 1, the remaining phyla contain *Chlamydia*, *Chloroflexi*, *SR1*, *Euryarchaeota*, *Synergistetes*, *Tenericutes*, and *TM7*, which makes up about 4% of taxa. All the bacterial phyla contribute to different and major oral disorders, such as periodontal disease, which is caused by releasing different chemicals and toxins. It causes gum disease by weakening the gum tissues [46]. Streptococcus mutans in the mouth thrives on sugar and produces acids, which eat the enamel [47,48], as shown in Figure 2. The basic principle of enamel is to protect the teeth from painful chemicals and temperature; it is the hard-protected layer that coats the crown (part of teeth). When the plaque is not treated in time, it is converted into tartar, which is considered to be the hardest layer (accumulated with different bacterial species). In addition to these bacterial species (*P. gingivalis*, *T. denticola*, *T. forsythia*, and *Strep. gordonii*) that contribute to periodontal disease [49], the Fusobacterium species also plays an important role in causing different diseases. The Gram-negative bacterium is implicated in periodontal disease. Fusobacterium is the most common bacteria, according to the literature survey. Fusobacterium is one of the first bacteria that was spotted in the accumulation of dental plaque biofilms. It is considered to be one of most common species isolated from extra-oral infections [50]. Oral microbiota not only cause cardiovascular disorders but are also involved in cancer and other systematic diseases. Increasing evidence supports an association between oral cancer and oral microbiomes, such as oral squamous cell carcinoma. A systematic understanding of such an association may originate from the ability of various microorganisms to alter the inflammatory microhabitat and to restrain host signalling pathways that control cell viability, proliferation, and differentiation. Peculiarly, the influence of the oral microbiome can expand beyond the oral cavity and can cause different diseases, such as coronary artery disease, the preterm delivery of low-birth weight neonates, and rheumatoid arthritis.

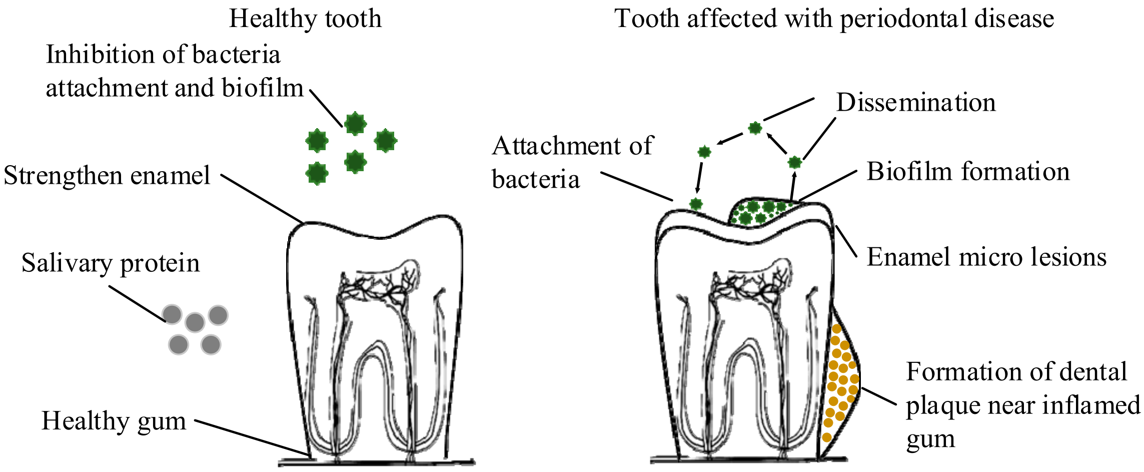

Figure 2. Difference between a healthy tooth and a tooth affected by periodontal disease.

3. Association between Periodontal and Cardiovascular Diseases

3.1. Cardiovascular Disorders

Cardiovascular diseases are a group of disorders related to the heart and blood vessels. They mainly include:

- Rheumatic heart disease (RHD)—muscle and valves of heart become damaged by rheumatic fever, resulting from to streptococcal bacteria.
- Coronary heart disease (CHD)—a disorder of blood vessels, which supply blood to heart muscles.
- Cerebrovascular disease (CD)—a disorder of blood vessels, which supply blood to the brain.

Cardiovascular disorders are the alarming cause of mortality and morbidity worldwide, including cerebrovascular disease, peripheral arterial disease, strokes, and heart attacks, which are usually acute conditions and are caused by a blockage that prevents the circulation of blood through the heart and brain. The most common cause of blockages of blood vessels is the deposition of fats, a build-up inside the inner corner of the blood vessel that regulates blood to the heart and brain, whereas bleeding from blood vessels in the brain or from blood clots causes strokes [51]. Particularly, empirical investigations of microbiota-dependent, downstream metabolites and microbiota transplantation have shown that oral microbiota may cause cardiovascular disorders (CVDs) and host metabolism through multiple or various meta-organism pathways.

3.2. Formation of Biofilms Leads to the Accumulation of Plaque in Major Arteries

Dental health plays an important role in the human body. Bad or poor dental health leads to different periodontitis disorders, such as dysbiosis flora. A higher prevalence of periodontal disorders is seen in adults and in older individuals, such as those of the ages 60–70. The consumption of unhealthy and non-hygienic food is the basic reason of periodontal disorders [52].

Biofilm is formed by the accumulation of bacterial pathogens, which move into blood vessels through cell–cell junction and cause the formation of plaque in major arteries. This would lead to different cardiovascular disorders through dental plaque formation, which produces a dental biofilm, a thick layer of bacteria [53]. The oral microbiomes such as *P. gingivalis*, *T. denticola*, *T. forsythia*, and *Strep. Gordonii* are considered to be the major pathogens causing periodontal diseases and also relate to cardiovascular disorders, as shown in Table 2. Recent studies revealed that *P. gingivalis* and *F. nucleatum* are related to cardiovascular disorders led by periodontal disease. Both of these bacterial species interact with the epithelial barriers with the help of Fusobacterial toxins such as FadA and Fap2 (a protein with one specific-function to open blood vessels). Basically they bind with the protein on the cells, which keep the endothelial cells joined together and produce a sustained inflammatory response, as shown in Figure 3 [54].

Table 2. Oral bacterial species and their relationship with cardiovascular disorders [44,55].

Oral Bacteria That Relates to Different Cardiovascular Disorders	
Oral bacterial species	Cardiovascular disorders
P. gingivalis (Gram-negative) *T. denticola (Gram-negative)* *T. forsythia (Gram-negative)* *Strep. gordonii (Gram-positive)* *F. nucleatum (Gram-negative)*	Causing periodontal disease, which leads to different chronic inflammations

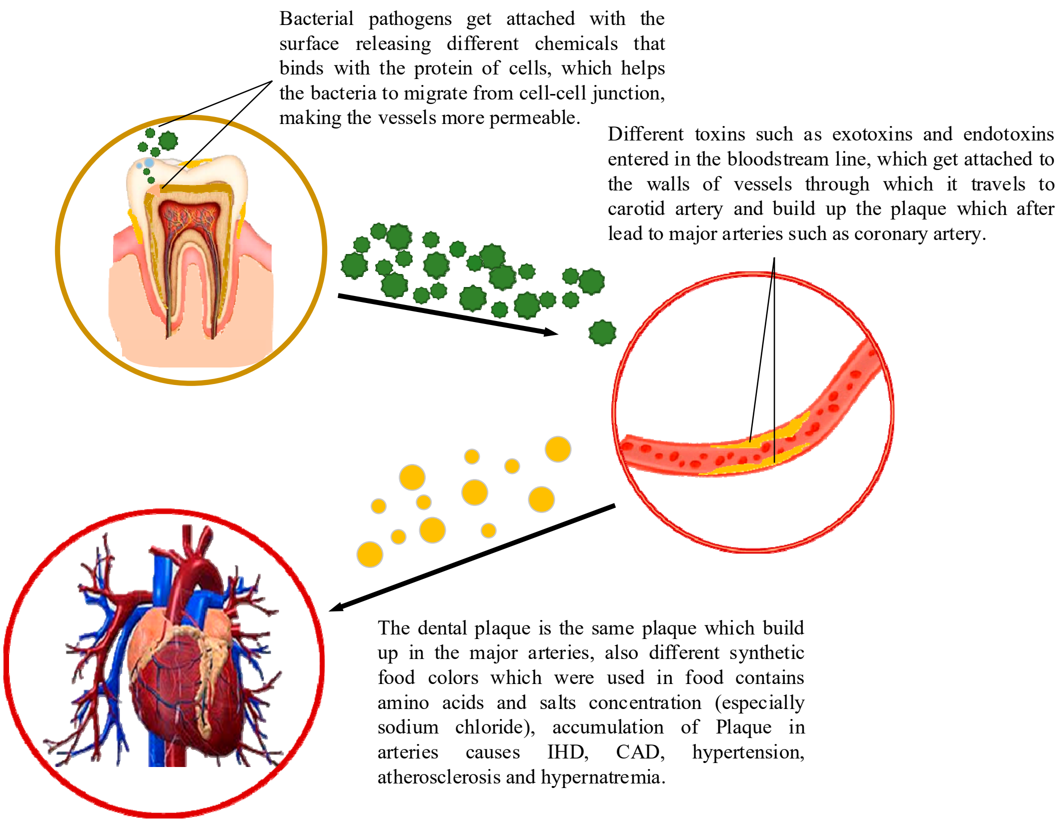

Figure 3. Formation of biofilms, which lead to the build-up of plaque in blood vessels and arteries, causing different cardiovascular disorders.

3.3. Different Line-Host Defense in between Bacterial Pathogens and Blood Vessels

There are different line-host defenses present between the bacterial pathogens and blood vessels. The first line-host defense is Gingival epithelial cells (ECs), which fight against the oral pathogens, and it is a multi-layered epithelium, which is affected by external pathogens at different levels. The Hemi-desmosomes (multi-protein complexes) and desmosomes (adhesive proteins) both are basic key factors of cell–cell junction. The innate immune response activation and invasion of virulence factors affect these basic structures, which leads to the break-down of epithelial barriers [56]. Through this, the bacterium migrates from the cell–cell junctions and makes the whole blood vessel more permeable. The dental calculus leads to the clogging of different vessels, which then migrates to major arteries. Different types of toxins are released from oral flora to the blood stream line during the breakdown of food. These toxins lead to the narrowing of cardiac vessels and many other blood vessels, as shown in Figure 4. A lot of research was conducted to see the interaction of the connection between two proteins (FadA and cadherin) and how they bind with each other. To see the interaction of the connection between two proteins, different types of binding tests were performed, such as a yeast-two-hybrid screen, basically a source of quick and dirty method to evaluate the interaction of the connection between two proteins [57]. They take out the proteins from the cell to test if they bind separately by sticking one protein (FadA) to a column, evaluating if it catches the other as it is washed through. After that, they put both the proteins back into the cells with colored markers attached to them to see if the proteins bind by the appearance of the colored marker in the same place. These results strongly suggest that both these proteins bind with each other [39,57].

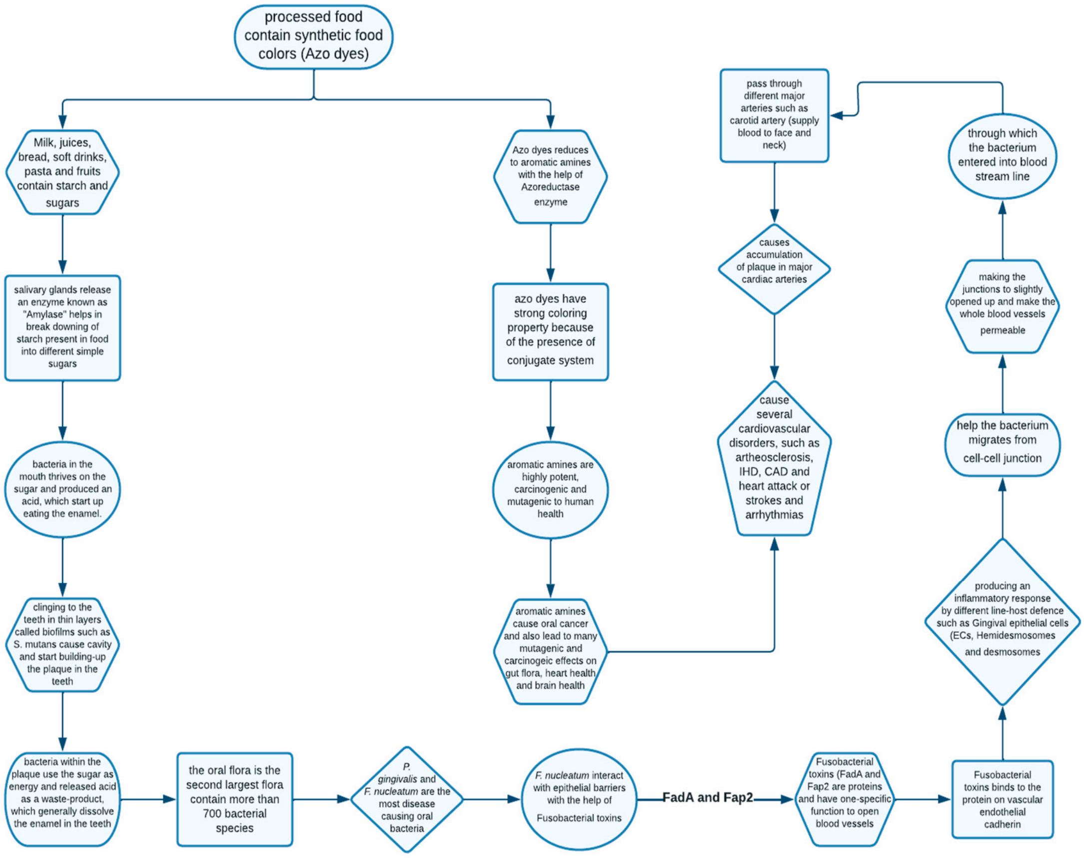

Figure 4. Flow chart explaining the mode of travel of oral microbiomes from the oral cavity to the blood stream, causing the narrowing of arteries, which leads to cardiovascular disorders [3,8,32,39,58].

4. Discussion

The application of food colors in bakery products, beverages, confections, dairy and ice cream, meat and savory foods, and seafood [59]. Among all of the synthetic food colors, tartrazine was the most commonly used azo dye (42.3%). According to the classification conducted by the International Union of Pure and Applied chemistry, azo dyes are derived from diazine HN=NH with the substitution of hydrogen by azobenzene, hydrocarbyl, or diphenyldiazene groups, and they also contain one or three azo bonds linked with phenyl and nephthyl rings, substituted by groups such as amino chloro, nitro, and hydroxyl. They are characterized by a strong coloration. When processed food is eaten by humans, the azo bonds (aromatic amines) present in these products are broken down by the enzymatic activity of the oral microbiome. Not only do they cause staining or plaque formation, but they also liberate many toxic chemicals into the blood stream line [60]. All these experimental data show that the oral microbiome travels through the bloodstream line and enters in different and major vessels and arteries, which lead to the heart. The external carotid artery is the artery that supplies blood to the face and neck [61]. It originates from the common carotid artery, and after that, it splits into the external and internal carotid artery [62]. The basic principle of this artery is to supply blood to the face and neck. In addition, most of the studies showed that sodium intake is associated with the carotid artery by producing tension in the artery walls [63]. The bacteria basically trigger the inflammation throughout the body, causing the narrowing of arteries. The carotid artery plays an important role in developing the link between the heart and face. The bacterial plaque starts developing in the external carotid artery, which produces the atherosclerotic plaque in the artery. This further promotes to the carotid artery and leads to the major arteries of heart [64,65], causing the narrowing of arteries, which leads to heart attacks and heart strokes. A majority of studies claim that the plaque that is produced on our teeth is the same plaque that builds up in the different major arteries, which lead to the heart, causing heart attacks.

The mild narrowing range of arteries lies between 15–49%. This blocking range also contributes to strokes, which lead to heart failure. Cardiovascular disorders are the most leading cause of death globally, with an estimated 17.9 million lives expired by CVDs globally in 2019, according to the WHO report released 11 June 2020. It included the top 10 diseases that lead to death in 2019, as shown in Figure 5 [66]. The most common cause of CVDs is diet, through which high blood pressure, obesity, and uncontrolled diabetes develop. Almost 85% of deaths are caused by heart attacks and strokes. The basic cause that leads to CVDs is food. Healthy eating will reduce the risk of physical health problems, which are considered to be the leading disease caused by the food consumption style in our daily basic life. The food we eat is full of salt contents (sodium chloride, etc.) that lead to hypertension and also cause hypernatremia and many other CVD disorders [67]. Rather than salt content, they were higher in amines [68], which cause the narrowing of major arteries. Basically, these chemicals cause the shrinking of vessels and arteries. Ischemic heart disease (IHD) is considered to be the most leading disease, through which approximately 9 million people died globally [58].

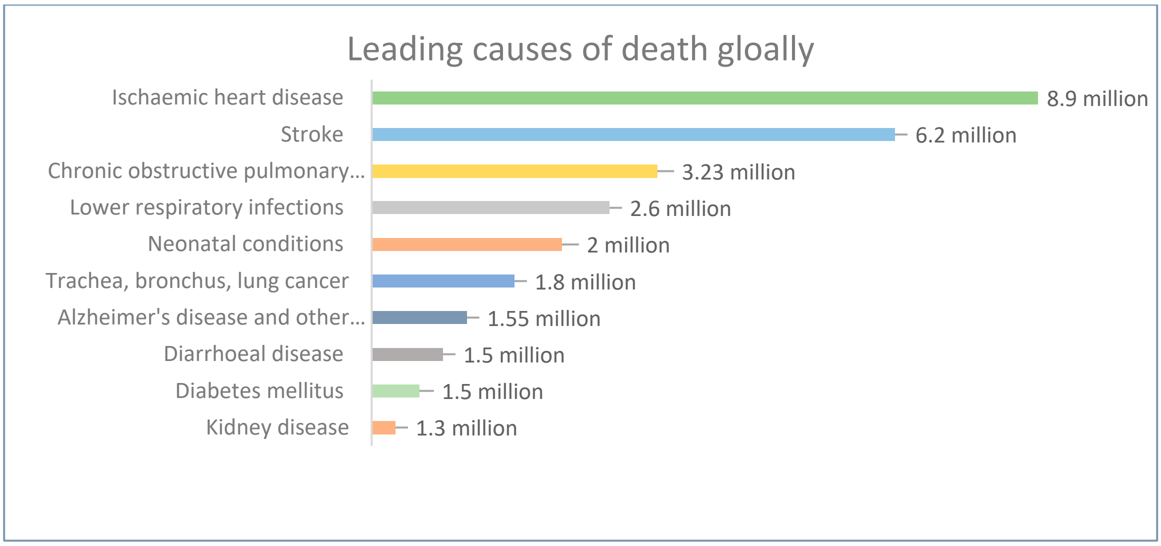

Figure 5. The top 10 causes of death and estimated disease rates in 2019, according to the WHO report [69].

5. Conclusions

Cardiovascular disorders are the leading cause of death globally. Being overweight, having an unhealthy diet, and smoking are considered to be the most common causes of

CVDs. Besides these dreadful things, human oral flora have bleak outcomes in causing cardiovascular disorders. The human mouth is considered to be the larger medium, it affiliates with microorganisms, and it has the ability to cause diseases. The oral cavity is considered to be the second biggest diverse microbiota, after the human gut microbiome, with the accumulation of more than 700 species. The oral cavity with various niches is considered to be the most suitable habitat for microbial accumulation. The basic source of acceleration of the oral microorganism is food. Food additives not only increase the appearance, taste, and self-lives of food, but they also increase the rate of toxicity levels of food. Food that contains azo dyes leads to many periodontal diseases caused by different oral bacterium (*P. gingivalis*, *T. denticola*, *T. forsythia*, *Strep. Gordonii*, and *F. nacleatum)*. Azo dyes release different aromatic amines when they come in contact with azoreductase enzymes, released by the oral microbiome, leading to the accumulation of plaque in the teeth. These oral microbiomes (*P. gingivalis* and *F. nacleatum*) interact with epithelial barriers, such as FadA and Fap2 (Fusobacterial toxins). These are proteins with one specific function: to open the blood vessels and accelerate the protein–protein interaction. Different types of toxins are released from oral flora to the blood stream line during the breakdown of food. These toxins lead to the narrowing of cardiac vessels and many other blood vessels. The accumulation of plaque in arteries causes IHD, CAD, hypertension, atherosclerosis, and hypernatremia. The basic principle of this critical review is to bring awareness to people to read the labels and ingredients of any product because the promises made by manufacturing industries are not trustworthy. Synthetic food colors, preservatives, and flavoring agents are all secondary ingredients, which are being consumed along with essential food content. Therefore, such unawareness may cause serious disorders and irreversible damage to the body.

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