Nusantara Sehat: Jurnal Kesehatan Indonesia
E-ISSN: 3110-2522
Website: https://publications.corejurnal.com/index.php/kesehatan

Food Additives in Ultra-Processed Foods: Mechanisms of Oxidative Stress and Endothelial Dysfunction

Dwi Widyawati[1], Ghea Farmaning Thias Putri[1*], Zaenudin[2]
[1]Faculty of Medicine and Health Sciences, Sultan Ageng Tirtayasa University, Serang, Banten, Indonesia
[2]Nursing Study Program, Al-Ikhlas *Nursing Academy*, Bogor, Jawa Barat, Indonesia
[*]*Corresponding email:* ghea.farmaning@untirta.ac.id

ABSTRACT

Introduction: Ultra-processed foods contain additives such as artificial sweeteners, emulsifiers, and preservatives that may contribute to oxidative stress and endothelial dysfunction, key mechanisms in cardiovascular disease.
Objective: This review evaluated the role of food additives in inducing oxidative stress and endothelial dysfunction and summarized their potential cardiovascular mechanisms.
Methods: A PRISMA-based literature search was conducted in PubMed, Scopus, ScienceDirect, SpringerLink, and Google Scholar for studies published between 2019 and 2026. Studies examining artificial sweeteners, emulsifiers, or preservatives in relation to oxidative stress, inflammation, endothelial dysfunction, or cardiovascular outcomes were included. Thirteen eligible studies were analyzed using narrative thematic synthesis.
Results: Food additives may increase reactive oxygen species production, mitochondrial dysfunction, gut dysbiosis, chronic inflammation, lipid peroxidation, and impaired antioxidant defenses. Artificial sweeteners were associated with reduced nitric oxide bioavailability, emulsifiers with intestinal dysbiosis and inflammation, and preservatives with oxidative and inflammatory activation. These alterations may promote endothelial dysfunction and increase cardiovascular risk.
Conclusion: Oxidative stress appears to be a central mechanism linking food additive exposure to endothelial dysfunction and adverse cardiovascular outcomes. However, direct human evidence remains limited, warranting further longitudinal and clinical studies.

Keywords: *endothelial dysfunction, food additives, oxidative stress, ultra-processed foods, vascular health*

Aditif Pangan dalam Makanan Ultra-Proses: Mekanisme Stres Oksidatif dan Disfungsi Endotel

ABSTRAK

Pendahuluan: *Pangan ultra-proses mengandung berbagai bahan tambahan pangan, seperti pemanis buatan, pengemulsi, dan pengawet, yang dapat berkontribusi terhadap stres oksidatif dan disfungsi endotel sebagai mekanisme penting dalam perkembangan penyakit kardiovaskular.*
Tujuan: *Tinjauan ini bertujuan mengevaluasi peran bahan tambahan pangan dalam memicu stres oksidatif dan disfungsi endotel serta merangkum mekanisme potensial yang mendasari dampaknya terhadap sistem kardiovaskular.*
Metode: *Penelusuran literatur berbasis PRISMA dilakukan melalui PubMed, Scopus, ScienceDirect, SpringerLink, dan Google Scholar terhadap artikel yang diterbitkan pada 2019–2026. Studi yang mengkaji pemanis buatan, pengemulsi, dan pengawet dalam kaitannya dengan stres oksidatif, inflamasi, disfungsi endotel, dan luaran kardiovaskular disertakan. Sebanyak 13 studi yang memenuhi kriteria dianalisis menggunakan sintesis tematik naratif.*
Hasil: *Bahan tambahan pangan dapat meningkatkan produksi spesies oksigen reaktif, disfungsi mitokondria, disbiosis usus, inflamasi kronis, peroksidasi lipid, dan gangguan pertahanan antioksidan. Pemanis buatan dikaitkan dengan penurunan bioavailabilitas nitrogen monoksida, pengemulsi dengan disbiosis usus dan inflamasi, serta pengawet dengan*

aktivasi oksidatif dan inflamasi. Perubahan tersebut dapat memicu disfungsi endotel dan meningkatkan risiko penyakit kardiovaskular.
Kesimpulan: *Stres oksidatif merupakan mekanisme utama yang menghubungkan paparan bahan tambahan pangan dengan disfungsi endotel dan luaran kardiovaskular yang merugikan. Namun, bukti langsung pada manusia masih terbatas sehingga diperlukan penelitian longitudinal dan klinis lebih lanjut.*

Kata kunci: *bahan tambahan pangan, disfungsi endotel, kesehatan vaskular, pangan ultra-proses, stres oksidatif*

INTRODUCTION

Ultra-processed foods (UPFs) have become an increasingly dominant component of contemporary dietary patterns worldwide. According to the NOVA classification system, UPFs are industrial formulations composed primarily of substances derived from foods and additives that are not commonly used in home cooking (Monteiro et al., 2019; Vadiveloo et al., 2025). The rapid expansion of the global food industry, coupled with the convenience, affordability, palatability, and extended shelf life of UPFs, has contributed to their increasing consumption across both developed and developing countries (Lu et al., 2025; Vadiveloo et al., 2025). Growing evidence indicates that high UPF intake is associated with adverse health outcomes, including obesity, hypertension, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease (Lu et al., 2025; Pant et al., 2024; Vadiveloo et al., 2025). As cardiovascular disease remains a leading cause of morbidity and mortality worldwide, understanding the biological mechanisms underlying the health effects of UPFs has become an important public health priority (Vadiveloo et al., 2025).

Food additives constitute one of the defining characteristics of UPFs (Rondinella et al., 2025; Seto et al., 2025). These substances are intentionally incorporated during food manufacturing to enhance texture, taste, appearance, stability, and shelf life. Common additives found in UPFs include artificial sweeteners, emulsifiers, preservatives, colorants, and flavor enhancers, many of which are rarely used in domestic food preparation (Gültekin, 2019; Rondinella et al., 2025). While regulatory agencies have established acceptable daily intake levels for most approved additives, concerns regarding their long-term biological effects have increased in recent years (Gültekin, 2019). Emerging evidence suggests that certain food additives may exert physiological effects beyond their technological functions by altering gut microbiota composition, disrupting intestinal homeostasis, and promoting inflammatory responses. Among these additives, artificial sweeteners, emulsifiers, and preservatives have attracted particular attention because of their potential involvement in pathways associated with oxidative stress and vascular dysfunction (Rondinella et al., 2025; Seto et al., 2025).

Oxidative stress has emerged as a key biological mechanism linking food additive exposure to chronic disease development. Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the capacity of endogenous antioxidant defense systems, resulting in disruption of cellular redox homeostasis and molecular damage (Abdelazim & Abomughaid, 2024). Increasing evidence suggests that several classes of food additives, including artificial sweeteners, emulsifiers, and preservatives, may contribute to excessive ROS generation either directly or indirectly through alterations in gut microbiota and metabolic pathways (Seto et al., 2025; Tkach et al., 2025).

Experimental studies have demonstrated that sucralose exposure may induce oxidative stress and microbiota disturbances, while commonly used

emulsifiers have been associated with metabolic dysregulation, intestinal dysbiosis, and inflammatory responses (Tkach et al., 2025). Likewise, chronic exposure to certain preservatives has been shown to promote lipid peroxidation, suppress antioxidant enzyme activity, and impair mitochondrial function (Çelik Atalay et al., 2025). Collectively, these findings indicate that food additives may act as potential pro-oxidant agents capable of initiating biological processes that contribute to cardiometabolic and vascular dysfunction (Abdelazim & Abomughaid, 2024; Çelik Atalay et al., 2025; Panyod et al., 2024; Tkach et al., 2025).

Endothelial dysfunction is increasingly recognized as a critical intermediary linking oxidative stress to cardiovascular disease (Wang & He, 2024). Under physiological conditions, endothelial cells maintain vascular homeostasis by regulating vascular tone, inflammation, thrombosis, and permeability through the production of vasoactive mediators, particularly nitric oxide (NO) (Kopych et al., 2025; Wang & He, 2024). However, excessive reactive oxygen species (ROS) can disrupt endothelial signaling pathways, reduce NO bioavailability, and impair endothelial nitric oxide synthase (eNOS) function, leading to endothelial dysfunction (Janaszak-Jasiecka et al., 2023; Negri et al., 2021). This condition is characterized by diminished vasodilatory capacity, increased vascular inflammation, enhanced leukocyte adhesion, and a pro-thrombotic vascular environment (Wang & He, 2024). Persistent endothelial dysfunction contributes to the initiation and progression of atherosclerosis and other cardiovascular disorders by promoting vascular injury and plaque development (Kopych et al., 2025). Given that several food additives have been associated with oxidative stress and metabolic disturbances, their potential role in endothelial dysfunction has emerged as an important area of investigation in cardiovascular research (Çelik Atalay et al., 2025; Panyod et al., 2024; Tkach et al., 2025).

Although increasing evidence links ultra-processed food consumption with adverse cardiometabolic outcomes, the underlying biological mechanisms remain incompletely understood (Gövez & Köksal, 2025; Vadiveloo et al., 2025). Recent evidence suggests that food additives and industrial processing methods may contribute to these effects beyond the nutritional composition of foods alone (Lalani et al., 2024; Vadiveloo et al., 2025). However, current findings are scattered across different additive classes and experimental models, making it difficult to establish a comprehensive understanding of their impact on endothelial function (Gövez & Köksal, 2025; Vadiveloo et al., 2025). Furthermore, major scientific organizations have highlighted the need for mechanistic research to clarify how specific food additives and processing-related components influence cardiometabolic health (Basson et al., 2021; Vadiveloo et al., 2025b). Therefore, this literature review aims to synthesize current evidence regarding the association between food additives and endothelial dysfunction, with a particular focus on the potential mechanisms linking additive exposure, oxidative stress, and vascular impairment.

METHOD

This study employed a literature review approach using a PRISMA-based search strategy to identify, screen, and synthesize relevant evidence regarding the role of food additives in ultra-processed foods in inducing oxidative stress and endothelial dysfunction. The review focused on studies discussing the biological mechanisms linking food additives, oxidative stress, vascular dysfunction, and cardiometabolic health outcomes.

Relevant literature was identified through searches of electronic databases and publisher platforms, including PubMed, Scopus, Google Scholar, SpringerLink, and ScienceDirect. The

literature search was conducted using combinations of the following keywords: “food additives,” “ultra-processed foods,” “oxidative stress,” “reactive oxygen species,” “endothelial dysfunction,” “vascular dysfunction,” “artificial sweeteners,” “emulsifiers,” and “preservatives.” Boolean operators such as AND and OR were used to refine the search strategy.

The inclusion criteria consisted of articles published in English between 2019 and 2026, available in full text, and discussing the association between food additives and oxidative stress, endothelial dysfunction, vascular impairment, or cardiometabolic health. Experimental studies, animal studies, observational studies, and relevant review articles were included. Articles were excluded if they were editorials, letters to the editor, conference abstracts, duplicate publications, non-English articles, or studies not relevant to the review objectives.

Article selection was performed through several stages, including identification, screening, eligibility assessment, and final inclusion based on the PRISMA framework. Titles and abstracts were initially screened according to the eligibility criteria, followed by a full-text evaluation of potentially relevant studies.

Data from the selected articles were extracted and analyzed using a narrative thematic synthesis approach. The extracted information included study characteristics, types of food additives, oxidative stress-related mechanisms, endothelial dysfunction findings, and reported cardiovascular implications. The findings were subsequently grouped into major themes to facilitate the interpretation and synthesis of the available evidence.

Ethical approval was not required because this study used publicly available published literature and did not involve human or animal participants.

RESULT

A total of 146 records were identified through searches of PubMed, Scopus, ScienceDirect, SpringerLink, and Google Scholar. After removing 31 duplicate records, 115 articles remained for title and abstract screening. Following the screening process, 82 records were excluded, and 33 full-text articles were assessed for eligibility. Twenty articles were subsequently excluded because they were not directly relevant to oxidative stress or endothelial dysfunction, focused on non-food additive applications, provided insufficient outcome data, or were published in languages other than English. Finally, 13 studies met the inclusion criteria and were included in the qualitative synthesis (Figure 1).

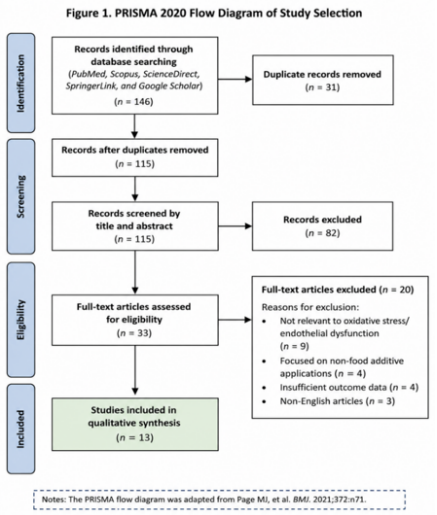

Figure 1. PRISMA flow diagram

A total of 13 studies were included in this literature review after screening and eligibility assessment based on the predefined inclusion and exclusion criteria. The selected studies employed various research designs, including three in vitro studies, three animal studies, two experimental studies, three prospective cohort studies, and two review articles. The studies were published between 2021 and 2026 and investigated the potential effects of food additives commonly found in ultra-processed foods on oxidative stress, inflammation, endothelial dysfunction, and cardiovascular health outcomes.

Based on the type of food additive investigated, the included studies were categorized into three major groups: artificial sweeteners, emulsifiers, and preservatives. Artificial sweeteners were represented by compounds such as aspartame and erythritol, while emulsifier-related studies primarily focused on carboxymethylcellulose and polysorbate 80. Preservative studies mainly investigated sodium benzoate, sodium nitrite, and mixed preservative exposures. The most frequently reported outcomes included increased reactive oxygen species (ROS) production, oxidative stress, impaired antioxidant defense systems, inflammation, endothelial dysfunction, insulin resistance, hypertension, and cardiovascular disease risk. A summary of the characteristics and main findings of the included studies is presented in Table 1.

Table 1. Characteristic of Studies Included in the Review

No	Author (Year)	Food Additive	Study Design	Main Findings
1	(Debras et al., 2022)	Artificial sweeteners	Prospective cohort	Higher artificial sweetener intake was associated with increased cardiovascular disease risk.
2	(Basson et al., 2021)	Artificial sweeteners	Review	Artificial sweeteners may alter gut microbiota and promote inflammatory responses.
3	(Griebsch et al., 2023)	Aspartame	In vitro	Increased ROS production, oxidative stress, mitochondrial dysfunction, and lipid alterations.
4	(Berry et al., 2025)	Erythritol	In vitro	Increased ROS, reduced nitric oxide bioavailability, and endothelial dysfunction.
5	(Bellanco et al., 2025)	CMC and Polysorbate-80	Experimental study	Altered gut microbiota composition and impaired intestinal barrier integrity.
6	(Rousta et al., 2021)	Carboxymethylcellulose	Animal study	Increased intestinal inflammation and pro-inflammatory cytokine expression.
7	(Sellem et al., 2025)	Carboxymethylcellulose (E466)	Prospective cohort	Associated with increased cardiovascular disease risk.
8	(Panyod et al., 2024)	Dietary emulsifiers	Animal study	Induced dysbiosis, hyperinsulinemia, and metabolic disturbances.
9	(He et al., 2025)	Polysorbate-80	Experimental study	Increased ROS generation, oxidative stress, and intestinal senescence.
10	(Sharma et al., 2026)	Sodium benzoate	In vitro	Increased ROS, lipid peroxidation, oxidative stress, and insulin resistance.

11	(Asejeje et al., 2025)	Sodium benzoate	Animal study	Increased oxidative stress, inflammation, and neuronal injury.
12	(Hasenböhler et al., 2026)	Preservatives	Prospective cohort	Preservative exposure was associated with higher incidence of hypertension and cardiovascular disease.
13	(Minari & Pisani, 2025)	Sodium benzoate and nitrites	Review	Preservatives may induce oxidative stress, mitochondrial dysfunction, and apoptosis.

As shown in Table 1, the majority of the included studies reported a positive association between food additive exposure and markers of oxidative stress. Experimental and in vitro studies consistently demonstrated increased reactive oxygen species production, lipid peroxidation, and impairment of antioxidant defense systems following exposure to artificial sweeteners, emulsifiers, and preservatives. In addition, several studies reported inflammation, metabolic disturbances, and endothelial dysfunction as downstream consequences of oxidative stress. Epidemiological evidence from prospective cohort studies further suggested associations between food additive consumption and increased risks of hypertension, cardiovascular disease, and other cardiometabolic disorders. These findings indicate that oxidative stress may represent a common mechanistic pathway linking different classes of food additives to adverse vascular and cardiovascular outcomes.

Artificial Sweeteners and Oxidative Stress

Artificial sweeteners were among the most frequently investigated food additives in relation to oxidative stress and vascular health (Basson et al., 2021). Evidence from experimental, epidemiological, and review studies suggested that artificial sweeteners may contribute to oxidative imbalance through increased reactive oxygen species (ROS) production, mitochondrial dysfunction, alterations in gut microbiota composition, and impaired endothelial function (Gültekin, 2019; Sharma et al., 2026).

Experimental evidence demonstrated that exposure to aspartame induced oxidative stress in cultured cells by increasing ROS generation and disrupting mitochondrial homeostasis. Aspartame exposure was also associated with lipid alterations and activation of cellular antioxidant responses, indicating the presence of oxidative damage and metabolic disturbances (Griebsch et al., 2023). Similarly, erythritol exposure was reported to adversely affect brain microvascular endothelial cells by increasing oxidative stress, reducing nitric oxide (NO) bioavailability, and impairing endothelial function (Berry et al., 2025). These findings suggest that certain artificial sweeteners may directly influence vascular homeostasis through ROS-mediated mechanisms.

In addition to direct cellular effects, several studies reported that artificial sweeteners may alter gut microbiota composition and promote low-grade inflammation (Basson et al., 2021). Such alterations have been proposed as indirect pathways contributing to oxidative stress and cardiometabolic dysfunction (Basson et al., 2021; Seto et al., 2025). Evidence from prospective cohort studies further indicated that higher consumption of artificial sweeteners was associated with an increased risk of cardiovascular disease, supporting the potential clinical relevance of these biological mechanisms (Debras et al., 2022).

Collectively, the available evidence suggests that artificial sweeteners may

contribute to oxidative stress through multiple interconnected pathways, including mitochondrial dysfunction, microbiota alterations, inflammation, and impaired endothelial nitric oxide signaling. These mechanisms may partly explain the observed associations between artificial sweetener consumption and adverse cardiovascular outcomes (Basson et al., 2021; Berry et al., 2025; Debras et al., 2022; Griebsch et al., 2023).

Emulsifiers and Oxidative Stress

Emulsifiers are widely used in ultra-processed foods to improve texture, stability, and shelf life. Recent evidence suggests that dietary emulsifiers may contribute to adverse health outcomes through mechanisms involving gut dysbiosis, inflammation, oxidative stress, and metabolic disturbances. Among the most frequently investigated emulsifiers are carboxymethylcellulose (CMC) and polysorbate 80 (P80), both of which have been associated with alterations in intestinal homeostasis (Bellanco et al., 2025; Panyod et al., 2024).

Experimental studies demonstrated that exposure to CMC and P80 altered gut microbiota composition and reduced intestinal barrier integrity (Bellanco et al., 2025). These changes were accompanied by increased intestinal permeability and a pro-inflammatory microbial profile, suggesting a potential role of emulsifiers in initiating chronic low-grade inflammation. Animal studies further showed that CMC exposure increased inflammatory responses and cytokine production, indicating that emulsifier-induced dysbiosis may trigger immune activation and intestinal injury (Rousta et al., 2021).

In addition to their effects on gut health, emulsifiers have been linked to oxidative stress and metabolic dysfunction. Recent evidence indicated that P80 exposure increased ROS generation and promoted oxidative damage, leading to intestinal senescence and impaired cellular homeostasis (He et al., 2025). Other studies demonstrated that dietary emulsifiers induced dysbiosis, hyperinsulinemia, and disturbances in glucose metabolism, which may further contribute to oxidative stress and cardiometabolic risk (Panyod et al., 2024).

Epidemiological evidence also supports the potential cardiovascular impact of emulsifiers. Data from a large prospective cohort study indicated that exposure to certain cellulose-based emulsifiers, particularly carboxymethylcellulose, was associated with an increased risk of cardiovascular disease (Sellem et al., 2025). Taken together, these findings suggest that emulsifiers may contribute to oxidative stress indirectly through gut microbiota alterations and inflammation, as well as directly through increased ROS production and metabolic impairment (Bellanco et al., 2025; He et al., 2025; Panyod et al., 2024; Rousta et al., 2021; Sellem et al., 2025).

Preservaties and Oxidative Stress

Preservatives are commonly added to ultra-processed foods to extend shelf life and prevent microbial spoilage (Çelik Atalay et al., 2025). Among the most frequently used preservatives are sodium benzoate, sodium nitrite, potassium sorbate, and sulfite-containing compounds. Recent studies have raised concerns regarding the potential adverse health effects of chronic exposure to these additives, particularly through mechanisms involving oxidative stress and inflammation (Hasenböhler et al., 2026).

Experimental evidence has demonstrated that sodium benzoate may induce oxidative stress by increasing reactive oxygen species (ROS) production and lipid peroxidation while simultaneously impairing endogenous antioxidant defense systems. In vitro studies reported elevated oxidative stress markers, reduced glutathione levels, and metabolic disturbances following sodium benzoate exposure (Sharma et al., 2026). Similarly, animal studies showed that

sodium benzoate exacerbated oxidative damage and inflammatory responses, as indicated by increased malondialdehyde levels, pro-inflammatory cytokine production, and depletion of antioxidant enzymes, including superoxide dismutase and catalase (Asejeje et al., 2025).

In addition to sodium benzoate, several preservative compounds have been associated with oxidative damage, mitochondrial dysfunction, and cellular injury (Çelik Atalay et al., 2025). Evidence summarized in recent reviews suggests that preservatives such as nitrites and sorbates may contribute to lipid peroxidation, oxidative imbalance, and apoptosis under certain exposure conditions. These biological alterations may promote metabolic dysfunction and increase susceptibility to chronic disease development.

Human evidence further supports the potential cardiovascular relevance of preservative exposure. Findings from the NutriNet-Santé cohort indicated that higher exposure to preservative food additives was associated with increased incidence of hypertension and cardiovascular disease (Hasenböhler et al., 2026). Notably, several preservative subclasses, including nitrites and sorbates, showed significant associations with cardiovascular outcomes, suggesting that long-term exposure to these additives may have implications beyond food preservation.

Overall, current evidence suggests that preservatives may contribute to oxidative stress through increased ROS generation, depletion of antioxidant defenses, and promotion of inflammatory responses. These mechanisms may facilitate metabolic and vascular disturbances that ultimately increase cardiovascular risk (Asejeje et al., 2025; Çelik Atalay et al., 2025; Hasenböhler et al., 2026; Sharma et al., 2026).

Mechanistic Pathways Linking Food Additives to Endothelial Dysfunction

Despite differences in chemical structure and biological function, artificial sweeteners, emulsifiers, and preservatives appear to share several common pathways that contribute to oxidative stress and vascular impairment (Basson et al., 2021). Evidence from the included studies suggests that these food additives may promote excessive reactive oxygen species (ROS) production either directly through cellular oxidative mechanisms or indirectly through gut microbiota alterations, chronic inflammation, and metabolic disturbances (Bellanco et al., 2025; Çelik Atalay et al., 2025).

Increased ROS generation was consistently associated with oxidative damage, mitochondrial dysfunction, lipid peroxidation, and depletion of endogenous antioxidant defenses. Experimental studies demonstrated that artificial sweeteners such as aspartame and erythritol increased oxidative stress and impaired cellular homeostasis, whereas emulsifiers including carboxymethylcellulose and polysorbate 80 promoted dysbiosis, intestinal inflammation, and ROS production (Berry et al., 2025; Griebsch et al., 2023). Similarly, preservative compounds such as sodium benzoate and nitrites were associated with oxidative imbalance and inflammatory activation (Asejeje et al., 2025; Çelik Atalay et al., 2025; Sharma et al., 2026).

Oxidative stress may subsequently affect vascular homeostasis through disruption of endothelial signaling pathways. Several studies reported reductions in nitric oxide (NO) bioavailability and impaired endothelial function following exposure to specific food additives. Reduced NO availability, together with persistent oxidative and inflammatory stimuli, may contribute to endothelial dysfunction, characterized by impaired vasodilation, vascular inflammation, and increased cardiovascular risk (Berry et al., 2025).

Collectively, the findings included in this review support a mechanistic framework in which food additive exposure contributes to oxidative stress through multiple interconnected pathways involving gut dysbiosis, inflammation, mitochondrial dysfunction, and ROS overproduction (Janaszak-Jasiecka et al., 2023; Wang & He, 2024). These alterations may ultimately promote endothelial dysfunction and increase susceptibility to hypertension, atherosclerosis, and cardiovascular disease (Berry et al., 2025; Debras et al., 2022; Hasenböhler et al., 2026; Sellem et al., 2025).

DISCUSSION

Oxidative Stress as a Central Mechanism

The findings of this review suggest that oxidative stress represents a central biological mechanism linking food additive exposure to adverse cardiovascular outcomes (Berry et al., 2025; Çelik Atalay et al., 2025; Griebsch et al., 2023; He et al., 2025; Sharma et al., 2026). Despite differences in chemical structure and intended technological functions, artificial sweeteners, emulsifiers, and preservatives consistently demonstrated the ability to induce oxidative imbalance through increased reactive oxygen species (ROS) production, impaired antioxidant defenses, mitochondrial dysfunction, or chronic inflammatory activation (Asejeje et al., 2025; Bellanco et al., 2025; Berry et al., 2025; Griebsch et al., 2023; Rousta et al., 2021; Sharma et al., 2026). These findings are in agreement with previous evidence indicating that excessive ROS generation disrupts cellular homeostasis and contributes to the development of chronic diseases (Backston et al., 2025; Negri et al., 2021; Wang & He, 2024).

Among artificial sweeteners, aspartame was shown to increase ROS generation and induce mitochondrial dysfunction, resulting in oxidative damage and alterations in cellular lipid metabolism (Griebsch et al., 2023). Similarly, erythritol exposure increased oxidative stress and impaired cellular homeostasis in endothelial cells (Berry et al., 2025). These findings suggest that artificial sweeteners may contribute to oxidative stress through direct cellular mechanisms that affect both metabolic and vascular functions (Berry et al., 2025; Griebsch et al., 2023).

Emulsifiers appear to induce oxidative stress through both direct and indirect mechanisms. Carboxymethylcellulose and polysorbate 80 have been shown to alter gut microbiota composition and disrupt intestinal barrier integrity, thereby promoting inflammatory responses (Bellanco et al., 2025). Chronic inflammation resulting from gut dysbiosis may subsequently increase systemic ROS production and oxidative imbalance (Panyod et al., 2024). Furthermore, polysorbate 80 was reported to directly increase ROS generation and promote cellular senescence, further supporting its role in oxidative stress-related pathology (He et al., 2025).

Importantly, the consistency between mechanistic studies and epidemiological findings strengthens the biological plausibility of these observations. Prospective cohort studies have reported associations of artificial sweetener consumption, emulsifier exposure, and preservative intake with increased risks of cardiovascular disease and hypertension (Debras et al., 2022; Hasenböhler et al., 2026; Sellem et al., 2025). Although causal relationships cannot be established from observational data alone, the convergence of evidence from cellular, animal, and population-based studies supports the hypothesis that oxidative stress represents a common mechanistic pathway linking food additives to adverse cardiovascular outcomes.

Gut-Vascular Axis and Endothelial Dysfunction

The results of this review suggest that endothelial dysfunction may represent a critical downstream consequence of food additive-induced oxidative stress.

Endothelial cells play a fundamental role in maintaining vascular homeostasis through the regulation of vascular tone, inflammatory responses, thrombosis, and permeability (Wang & He, 2024). Disruption of endothelial function is widely recognized as an early event in the development of atherosclerosis and other cardiovascular diseases (Kopych et al., 2025).

A growing body of evidence indicates that excessive reactive oxygen species (ROS) production can impair endothelial function by reducing nitric oxide (NO) bioavailability and disrupting endothelial nitric oxide synthase (eNOS) activity (Janaszak-Jasiecka et al., 2023). Under physiological conditions, NO acts as a major vasoprotective molecule that promotes vasodilation and inhibits inflammation, platelet aggregation, and leukocyte adhesion (Wang & He, 2024). However, excessive oxidative stress may accelerate NO degradation and contribute to endothelial dysfunction through ROS-mediated mechanisms (Negri et al., 2021).

Among the food additives evaluated in this review, erythritol provided the most direct evidence linking additive exposure to endothelial dysfunction. Berry et al. (2025) demonstrated that erythritol increased oxidative stress, reduced NO bioavailability, and impaired endothelial cell function. These findings suggest that oxidative stress induced by certain artificial sweeteners may directly compromise vascular homeostasis and endothelial integrity.

In addition to direct vascular effects, food additives may indirectly affect endothelial function through alterations in the gut microbiota. Emulsifiers such as carboxymethylcellulose and polysorbate 80 were shown to disrupt gut microbial composition and intestinal barrier integrity (Bellanco et al., 2025). Increased intestinal permeability may facilitate the translocation of microbial products and pro-inflammatory mediators into the systemic circulation, thereby promoting chronic inflammation and oxidative stress (Panyod et al., 2024). This process has been proposed as an important component of the gut-vascular axis linking intestinal dysbiosis to endothelial dysfunction and cardiovascular disease (Bellanco et al., 2025; Panyod et al., 2024).

Preservatives may also contribute to endothelial dysfunction through oxidative and inflammatory pathways. Experimental studies reported increased lipid peroxidation, depletion of antioxidant defenses, and elevated inflammatory cytokines following sodium benzoate exposure (Asejeje et al., 2025; Sharma et al., 2026). Although direct evidence regarding preservative-induced endothelial dysfunction remains limited, these biological alterations are recognized contributors to vascular injury and endothelial impairment (Çelik Atalay et al., 2025).

Collectively, the available evidence suggests that food additives may influence vascular health through both direct and indirect mechanisms. While some additives appear capable of directly inducing oxidative stress within endothelial cells, others may act through gut dysbiosis, inflammation, and metabolic disturbances that ultimately converge on endothelial dysfunction. These observations support the concept of a gut-vascular axis in which oxidative stress serves as a key mediator linking food additive exposure to cardiovascular disease development.

Cardiovascular implications of Food Additive Exposure

The evidence synthesized in this review suggests that the biological effects of food additives may extend beyond localized cellular and metabolic disturbances, potentially contributing to the development of cardiovascular disease. Although food additives are generally considered safe when consumed within regulatory limits, increasing consumption of ultra-processed foods has substantially increased cumulative exposure to multiple

additives in daily diets (Gövez & Köksal, 2025). This growing exposure has raised concerns regarding the long-term cardiovascular consequences of food additive consumption, particularly through mechanisms involving oxidative stress and endothelial dysfunction.

Endothelial dysfunction is widely recognized as an early and reversible stage in the pathogenesis of cardiovascular disease (Kopych et al., 2025). Persistent oxidative stress may impair endothelium-dependent vasodilation, promote vascular inflammation, and facilitate leukocyte adhesion to the vascular wall (Janaszak-Jasiecka et al., 2023). These alterations contribute to the initiation and progression of atherosclerosis, ultimately increasing the risk of coronary heart disease, cerebrovascular disease, and other cardiovascular complications (Wang & He, 2024).

Epidemiological evidence supports the potential clinical relevance of these biological mechanisms. In a large prospective cohort study, higher consumption of artificial sweeteners was associated with an increased risk of cardiovascular disease (Debras et al., 2022). Similarly, exposure to emulsifiers such as carboxymethylcellulose was associated with a higher incidence of cardiovascular disease in the NutriNet-Santé cohort (Sellem et al., 2025). More recently, preservative food additives were also linked to increased risks of hypertension and cardiovascular disease in a large population-based cohort study (Hasenböhler et al., 2026). Although these observational findings cannot establish causality, the consistency of associations across different additive classes strengthens concerns regarding their potential cardiovascular effects.

The findings of this review also highlight the importance of considering cumulative exposure rather than evaluating individual additives in isolation. Ultra-processed foods often contain multiple additives simultaneously, including sweeteners, emulsifiers, preservatives, colorants, and flavor enhancers (Gövez & Köksal, 2025). Consequently, additive interactions and long-term exposure patterns may contribute to biological effects that are not fully captured by traditional safety assessments focused on single compounds.

From a public health perspective, these observations support current recommendations encouraging reduced consumption of ultra-processed foods and greater adherence to dietary patterns emphasizing minimally processed foods. While further mechanistic and longitudinal studies are required to clarify causal relationships, the available evidence suggests that limiting excessive exposure to food additives may represent a potential strategy for reducing oxidative stress, preserving endothelial function, and promoting cardiovascular health.

Strenghs, Limitations, and Future Research Directions

This review provides a comprehensive overview of the potential role of food additives in ultra-processed foods in promoting oxidative stress and endothelial dysfunction. By integrating evidence from experimental, animal, epidemiological, and review articles, this review highlights oxidative stress as a common mechanistic pathway linking artificial sweeteners, emulsifiers, and preservatives to adverse cardiovascular outcomes. In addition, the findings support the potential involvement of the gut–vascular axis in mediating the effects of food additives on vascular health (Bellanco et al., 2025; Panyod et al., 2024; Wang & He, 2024).

Nevertheless, the available evidence remains heterogeneous in terms of study design, exposure assessment, and outcome measures. Most mechanistic findings were derived from in vitro and animal studies, while direct evidence of food additive-induced endothelial dysfunction in humans remains limited (Berry et al., 2025). Future studies should focus on longitudinal and

clinical investigations to clarify causal relationships, evaluate cumulative exposure to multiple food additives, and further elucidate the molecular pathways linking food additive consumption to cardiovascular disease risk.

CONCLUSION

This literature review highlights oxidative stress as the principal biological mechanism linking food additives in ultra-processed foods to endothelial dysfunction and increased cardiovascular risk. By integrating evidence from experimental, animal, and epidemiological studies, this review strengthens the current understanding that excessive exposure to artificial sweeteners, emulsifiers, and preservatives may adversely affect vascular health through interconnected pathways involving oxidative imbalance, inflammation, and gut–vascular interactions.

From a practical perspective, these findings support public health strategies aimed at reducing the consumption of ultra-processed foods and promoting dietary patterns based on minimally processed foods. Healthcare professionals should also emphasize limiting unnecessary exposure to food additives as part of cardiovascular disease prevention and nutrition education. Although current human evidence remains limited, future well-designed longitudinal and clinical studies are needed to establish causal relationships and provide stronger evidence for dietary guidelines and food policy development.

AUTHOR'S CONTRIBUTION STATEMENT

DW contributed to the conception and design of the study, literature search and screening, data extraction, data synthesis, manuscript drafting, and preparation of the final manuscript. GTP contributed to study supervision, interpretation of findings, critical revision of the manuscript, and served as the corresponding author. Z contributed to the interpretation of the literature, critical review of the manuscript, and improvement of the scientific content. All authors read, reviewed, and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

BIBLIOGRAPHY

Abdelazim, A. M., & Abomughaid, M. M. (2024). Oxidative stress: an overview of past research and future insights. In *All Life* (Vol. 17, Number 1). Taylor and Francis Ltd. https://doi.org/10.1080/26895293.2024.2316092

Asejeje, F. O., Abiola, M. A., Adeyemo, O. A., & Ogunro, O. B. (2025). Influence of high-dose sodium benzoate on lipopolysaccharide-induced neurobehavioral impairment, oxido-inflammatory brain damage, and cholinergic dysfunction in rats. *Toxicology Letters*, *410*, 121–129. https://doi.org/10.1016/j.toxlet.2025.06.008

Backston, K., Morgan, J., Patel, S., Koka, R., Hu, J., & Raina, R. (2025). Oxidative Stress and Endothelial Dysfunction: The Pathogenesis of Pediatric Hypertension. In *International Journal of Molecular Sciences* (Vol. 26, Number 11). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/ijms26115355

Basson, A. R., Rodriguez-Palacios, A., & Cominelli, F. (2021). Artificial Sweeteners: History and New Concepts on Inflammation. In *Frontiers in Nutrition* (Vol. 8). Frontiers Media S.A. https://doi.org/10.3389/fnut.2021.746247

Bellanco, A., Requena, T., & Martínez-Cuesta, M. C. (2025). Polysorbate 80

and carboxymethylcellulose: A different impact on epithelial integrity when interacting with the microbiome. *Food and Chemical Toxicology*, *196*. https://doi.org/10.1016/j.fct.2025.115236

Berry, A. R., Ruzzene, S. T., Ostrander, E. I., Wegerson, K. N., Orozco-Fersiva, N. C., Stone, M. F., Valenti, W. B., Izaias, J. E., Holzer, J. P., Greiner, J. J., Garcia, V. P., & DeSouza, C. A. (2025). The non-nutritive sweetener erythritol adversely affects brain microvascular endothelial cell function. *Journal of Applied Physiology*, *138*(6), 1571–1577. https://doi.org/10.1152/japplphysiol.00276.2025

Celik Atalay, E., Gulcin, A., Celep, S., Marotta, F., & Catanzaro, R. (2025). Oxidative stress induced by some preservatives and the protective effects of dietary bioactive compounds. *Bioactive Compounds in Health and Disease*, *8*(12), 585–601. https://doi.org/10.31989/bchd.8i12.1816

ÇELİK ATALAY, E., SAĞDIÇOĞLU CELEP, A. G., Marotta, F., & Catanzaro, R. (2025). Oxidative stress induced by some preservatives and the protective effects of dietary bioactive compounds. *Bioactive Compounds in Health and Disease - Online ISSN: 2574-0334; Print ISSN: 2769-2426*, *8*(12), 585–601. https://doi.org/10.31989/bchd.v8i12.1816

Debras, C., Chazelas, E., Sellem, L., Porcher, R., Druesne-Pecollo, N., Esseddik, Y., de Edelenyi, F. S., Agaësse, C., De Sa, A., Lutchia, R., Fezeu, L. K., Julia, C., Kesse-Guyot, E., Allès, B., Galan, P., Hercberg, S., Deschasaux-Tanguy, M., Huybrechts, I., Srour, B., & Touvier, M. (2022). Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort. *BMJ*, *378*. https://doi.org/10.1136/bmj-2022-071204

Gövez, N. E., & Köksal, E. (2025). Ultra-Processed Foods and Cardiometabolic Health: A Review of Current Evidence. *Current Nutrition Reports*, *14*(1), 110. https://doi.org/10.1007/s13668-025-00703-7

Griebsch, L. V., Theiss, E. L., Janitschke, D., Erhardt, V. K. J., Erhardt, T., Haas, E. C., Kuppler, K. N., Radermacher, J., Walzer, O., Lauer, A. A., Matschke, V., Hartmann, T., Grimm, M. O. W., & Grimm, H. S. (2023). Aspartame and Its Metabolites Cause Oxidative Stress and Mitochondrial and Lipid Alterations in SH-SY5Y Cells. *Nutrients*, *15*(6). https://doi.org/10.3390/nu15061467

Gültekin, F. (2019). Food Additives And Microbiota. *Northern Clinics of Istanbul*. https://doi.org/10.14744/nci.2019.92499

Hasenböhler, A., Javaux, G., Payen de la Garanderie, M., Szabo de Edelenyi, F., Yvroud-Hoyos, P., Agaësse, C., De Sa, A., Huybrechts, I., Pierre, F., Coumoul, X., Fezeu, L. K., Galan, P., Blacher, J., Julia, C., Allès, B., Hercberg, S., Chassaing, B., Deschasaux-Tanguy, M., Srour, B., & Touvier, M. (2026). Preservative food additives, hypertension, and cardiovascular diseases: the NutriNet-Santé study. *European Heart Journal*. https://doi.org/10.1093/eurheartj/ehag308

He, L., Zhang, L., Meng, F., Wei, J., Chen, F., Qin, S., Jin, G., & Cao, H. (2025). Dietary emulsifier Polysorbate 80-induced lipotoxicity promotes intestinal senescence. *Food Research International*, *209*.

https://doi.org/10.1016/j.foodres.2025.116165

Janaszak-Jasiecka, A., Płoska, A., Wierońska, J. M., Dobrucki, L. W., & Kalinowski, L. (2023). Endothelial dysfunction due to eNOS uncoupling: molecular mechanisms as potential therapeutic targets. *Cellular and Molecular Biology Letters*, *28*(1). https://doi.org/10.1186/s11658-023-00423-2

Kopych, V., Da Costa, A. D. S., & Park, K. (2025). Endothelial Dysfunction in Atherosclerosis: Experimental Models and Therapeutics. In *Biomaterials Research* (Vol. 29). American Association for the Advancement of Science. https://doi.org/10.34133/bmr.0252

Lalani, A. R., Rastegar-Pouyani, N., Askari, A., Tavajohi, S., Akbari, S., & Jafarzadeh, E. (2024). Food Additives, Benefits, and Side Effects: A Review Article. In *Journal of Chemical Health Risks* (Vol. 14, Number 1, pp. 1–10). Islamic Azad University. https://doi.org/10.22034/jchr.2023.1967340.1619

Lu, W., Ou, T., Song, Q., Shi, Z., Sun, Z., Shen, L., Ma, W., Mai, S., Wang, Z., & Zang, J. (2025). Ultra-Processed Food Consumption Is Associated with an Increased Risk of Abdominal Obesity in Adults: A Cross-Sectional Study in Shanghai. *Foods*, *14*(22). https://doi.org/10.3390/foods14223955

Minari, T. P., & Pisani, L. P. (2025). Exploring sodium nitrate supplementation in enhancing nitric oxide bioavailability and reducing oxidative stress: implications for blood pressure and endothelial dysfunction in hypertension. In *European Journal of Pharmacology* (Vol. 999). Elsevier B.V. https://doi.org/10.1016/j.ejphar.2025.177702

Monteiro, C. A., Cannon, G., Lawrence, M., Laura Da Costa Louzada, M., & Machado, P. P. (2019). *Ultra-processed foods, diet quality, and health using the NOVA classification system Prepared by*. FAO. http://www.wipo.int/amc/en/mediation/rules

Negri, S., Faris, P., & Moccia, F. (2021). Reactive oxygen species and endothelial ca2+ signaling: Brothers in arms or partners in crime? In *International Journal of Molecular Sciences* (Vol. 22, Number 18). MDPI. https://doi.org/10.3390/ijms22189821

Pant, A., Gribbin, S., Machado, P., Hodge, A., Wasfy, J. H., Moran, L., Marschner, S., Chow, C. K., & Zaman, S. (2024). Ultra-processed foods and incident cardiovascular disease and hypertension in middle-aged women. *European Journal of Nutrition*, *63*(3), 713–725. https://doi.org/10.1007/s00394-023-03297-4

Panyod, S., Wu, W. K., Chang, C. T., Wada, N., Ho, H. C., Lo, Y. L., Tsai, S. P., Chen, R. A., Huang, H. S., Liu, P. Y., Chen, Y. H., Chuang, H. L., Shen, T. C. D., Tang, S. L., Ho, C. T., Wu, M. S., & Sheen, L. Y. (2024). Common dietary emulsifiers promote metabolic disorders and intestinal microbiota dysbiosis in mice. *Communications Biology*, *7*(1). https://doi.org/10.1038/s42003-024-06224-3

Rondinella, D., Raoul, P. C., Valeriani, E., Venturini, I., Cintoni, M., Severino, A., Galli, F. S., Mora, V., Mele, M. C., Cammarota, G., Gasbarrini, A., Rinninella, E., & Ianiro, G. (2025). The Detrimental Impact of Ultra-Processed Foods on the Human Gut Microbiome and Gut Barrier. In *Nutrients* (Vol. 17, Number 5). Multidisciplinary Digital Publishing

Institute (MDPI). https://doi.org/10.3390/nu17050859

Rousta, E., Oka, A., Liu, B., Herzog, J., Bhatt, A. P., Wang, J., Habibi Najafi, M. B., & Sartor, R. B. (2021). The emulsifier carboxymethylcellulose induces more aggressive colitis in humanized mice with inflammatory bowel disease microbiota than polysorbate-80. *Nutrients*, *13*(10). https://doi.org/10.3390/nu13103565

Sellem, L., Srour, B., Javaux, G., Chazelas, E., Chassaing, B., Viennois, E., Debras, C., Salamé, C., Druesne-Pecollo, N., Esseddik, Y., de Edelenyi, F. S., Agaësse, C., De Sa, A., Lutchia, R., Louveau, E., Huybrechts, I., Pierre, F., Coumoul, X., Fezeu, L. K., … Touvier, M. (2025). Food additive emulsifiers and risk of cardiovascular disease in the NutriNet-Santé cohort: prospective cohort study. *BMJ*, *382*. https://doi.org/10.1136/bmj-2023-076058

Seto, T., Grondin, J. A., & Khan, W. I. (2025). Food Additives: Emerging Detrimental Roles on Gut Health. In *FASEB Journal* (Vol. 39, Number 13). John Wiley and Sons Inc. https://doi.org/10.1096/fj.202500737R

Sharma, O., Dua, A., Gupta, S., Injeti, E., & Mittal, A. (2026). Sodium benzoate, a common food preservative-induced Insulin resistance and atrophy in C2C12 myotubes. *Biochimie*, *241*, 56–71. https://doi.org/10.1016/j.biochi.2025.11.009

Tkach, V. V., Morozova, T. V., Gaivão, I. O. de M., Miranda, N. G. de, Ivanushko, Y. G., Martins, J. I. F. de P., & Barros, A. N. (2025). Sucralose: A Review of Environmental, Oxidative and Genomic Stress. In *Nutrients* (Vol. 17, Number 13). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/nu17132199

Vadiveloo, M. K., Gardner, C. D., Bleich, S. N., Khandpur, N., Lichtenstein, A. H., Otten, J. J., Rebholz, C. M., Singleton, C. R., Vos, M. B., & Wang, S. (2025a). Ultraprocessed Foods and Their Association With Cardiometabolic Health: Evidence, Gaps, and Opportunities: A Science Advisory From the American Heart Association. *Circulation*. https://doi.org/10.1161/CIR.0000000000001365

Vadiveloo, M. K., Gardner, C. D., Bleich, S. N., Khandpur, N., Lichtenstein, A. H., Otten, J. J., Rebholz, C. M., Singleton, C. R., Vos, M. B., & Wang, S. (2025b). Ultraprocessed Foods and Their Association With Cardiometabolic Health: Evidence, Gaps, and Opportunities: A Science Advisory From the American Heart Association. *Circulation*. https://doi.org/10.1161/CIR.0000000000001365

Wang, X., & He, B. (2024). Endothelial dysfunction: molecular mechanisms and clinical implications. In *MedComm* (Vol. 5, Number 8). John Wiley and Sons Inc. https://doi.org/10.1002/mco2.651