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Aspartame, saccharin, sucralose, and stevia: Oxidative stress pathways and functional food perspectives

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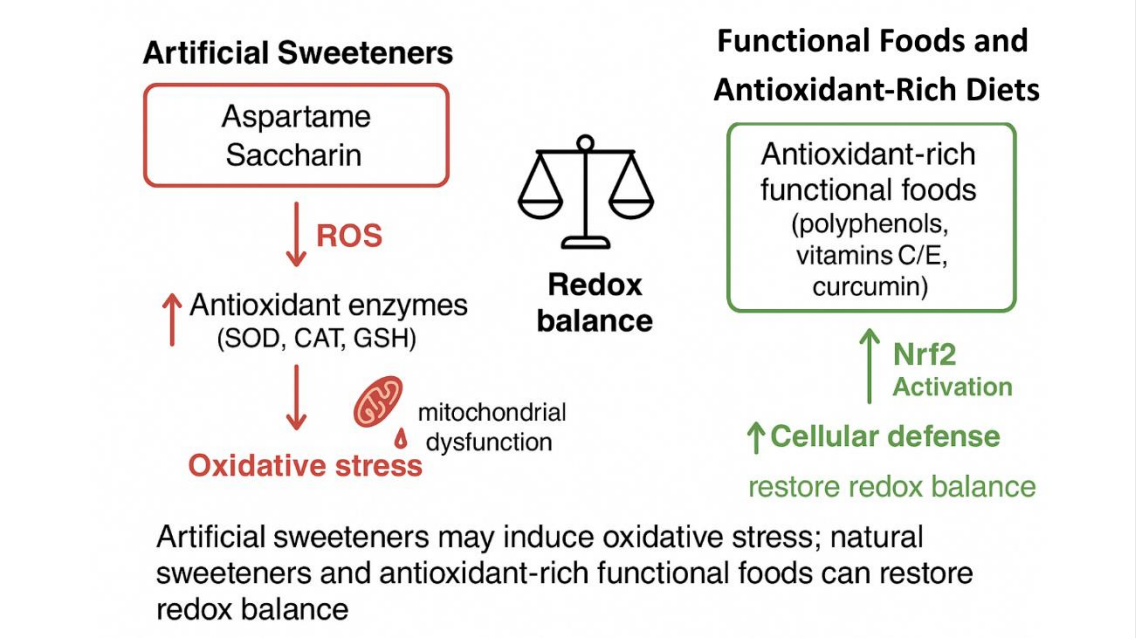
ABSTRACT

Background: The increasing consumption of non-caloric sweeteners has raised concerns regarding their potential effects on oxidative stress and related health outcomes. Emerging evidence suggests that artificial sweeteners, particularly aspartame and saccharin, may induce oxidative stress in a dose-, duration-, and tissue-dependent manner. In contrast, natural sweeteners, such as stevia, may offer protective effects.

This review synthesizes current findings on the oxidative and metabolic effects of non-caloric sweeteners, outlining key methodological limitations and the need for long-term clinical investigations. It further integrates mechanistic insights to distinguish the differential redox effects of artificial versus natural sweeteners and explores how antioxidant-rich functional foods might mitigate these impacts. This review comprehensively integrates mechanistic, experimental, and dietary evidence linking non-caloric sweeteners to oxidative stress while introducing functional food–based strategies to mitigate redox imbalance. It provides an updated synthesis relevant to evidence-based dietary guidance and regulatory evaluation.

Keywords: non-caloric sweeteners, aspartame, saccharin, stevia, antioxidants, oxidative stress, food additives, functional foods, bioactive compounds



Graphical Abstract: Aspartame, saccharin, sucralose, and stevia: Oxidative stress pathways and functional food perspectives.

INTRODUCTION

The widespread consumption of processed foods today has significantly increased the use of food additives, particularly low-calorie sweeteners. To reduce calorie intake and prevent health problems such as obesity, artificial sweeteners like aspartame, acesulfame K, saccharin, and sucralose are widely used in many processed foods, ranging from diet products to various foods and beverages [1, 2]. However, food processing conditions, such as heat treatment, may alter the stability and metabolic effects of these sweeteners. Recent experimental evidence demonstrated that thermal treatment of commercial sweetener solutions significantly modulated metabolic and oxidative responses in mice [3]. Although these products are often marketed as healthier alternatives to sugar, the effects of their long-term and intensive consumption on health have been increasingly debated and researched in recent years. Beyond their potential oxidative effects, non- and low-caloric sweeteners may also modulate substrate oxidation and energy metabolism. A recent systematic review of human trials reported that such sweeteners increased fat oxidation and decreased carbohydrate oxidation compared with caloric sugars, although evidence on total energy expenditure remains inconsistent [4].

However, despite extensive preclinical evidence, there remains a shortage of well-controlled human studies that directly evaluate whether consuming non-caloric sweeteners translates into clinically meaningful

oxidative stress-related outcomes. This gap complicates public health recommendations and underscores the need for translational research that links mechanistic findings to population-level risk.

Some studies have suggested that these sweeteners, particularly when used in high doses over long periods, may be associated with various health problems [5]. Preclinical and clinical studies have shown that these sweeteners may have dysbiotic effects on the gut microbiota. However, the inability to replicate these findings in some studies has made it difficult to reach a scientific consensus [6]. Furthermore, it has been claimed that sweeteners may alter taste perception and, by increasing sugar consumption, lead to undesirable outcomes; however, strong evidence supporting this hypothesis has yet to be obtained [7]. Notably, in 2023, the World Health Organization (WHO) released an updated hazard and risk assessment for aspartame, renewing scrutiny over its long-term safety and highlighting the need for further targeted research [8].

Acceptable Daily Intake (ADI) values for commonly used non-nutritive sweeteners (NNS), including aspartame, saccharin, and sucralose, are summarized in Table 1.

Table 1. Sweeteners and their ADIs

E number	Food Additive	Category	ADI (mg/kg bw/day)
E 955	Sucralose	Sweetener	0-15 [2]
E 954	Saccharin	Sweetener	0-5 [6]
E 951	Aspartame	Sweetener	0-40 [8]

Of particular concern, the consumption of artificial sweeteners may be associated with oxidative stress, a key factor in the pathophysiology of many chronic diseases. Oxidative stress is characterized by an increase in reactive oxygen species (ROS), which cause cellular damage and are a significant factor in the development of diseases such as diabetes mellitus, cardiovascular diseases, and neurodegenerative disorders. Recent studies have shown that non-caloric artificial sweeteners may increase oxidative stress, which could be linked to adverse health effects [9]. On the other hand, evidence suggests that stevia, a natural sweetener, may reduce oxidative stress through its antioxidant properties and may play a protective role [10-11]. Natural sweeteners, such as stevia, together with dietary antioxidants (including polyphenols, vitamins, minerals, and proper gut flora nutrition), may mitigate oxidative stress and provide protective effects; however, robust clinical evidence in humans remains limited [12-14].

This review synthesizes experimental, animal, and clinical studies to (1) evaluate evidence linking non-caloric sweeteners to oxidative stress, (2) examine putative mechanistic pathways, and (3) identify critical methodological limitations and research gaps. We place particular emphasis on the translational relevance of animal and in-vitro findings to human health and on potential dietary strategies — including functional foods rich in antioxidants — that could mitigate adverse redox effects. Additionally, understanding how these sweeteners interact with dietary bioactive compounds is crucial from a functional food perspective. Polyphenols, vitamins, and other plant-derived antioxidants may counteract sweetener-induced oxidative stress through mechanisms such as scavenging ROS, modulating redox-sensitive signaling (*e.g.*, Nuclear factor erythroid 2-related factor 2 (Nrf2), Nuclear Factor kappa B (NF-κB)), and supporting mitochondrial function [15-16]. Framing these interactions within the context of functional foods

allows translation of mechanistic insights into dietary strategies with potential clinical relevance. In our study, we aim to highlight gaps in the relevant literature and evaluate the possible health risks and mechanisms associated with these sweeteners, thereby informing future research.

Research strategy: A systematic literature search was conducted to identify relevant studies. We searched the following electronic databases: Web of Science, PubMed, EBSCO, Medline, Google Scholar, and the FFHDJ platform (www.FFHDJ.com). The search was limited to articles published from January 2010 to October 2025, with the final search conducted in November 2025. Search terms were used in Boolean combinations, including keywords such as: (aspartame OR acesulfame K OR sucralose OR saccharin OR stevia) AND (oxidative stress OR ROS). Peer-reviewed preclinical and clinical studies reporting oxidative stress–related or antioxidant outcomes were included. Non-original works (e.g., editorials, letters) and studies lacking redox-related endpoints were excluded. Screening and data extraction were conducted independently by two reviewers, with discrepancies resolved by consensus.

Non-caloric sweeteners and oxidative stress: Several pathways may explain how NCS influence redox biology. Aspartame and specific metabolites can increase ROS generation through mitochondrial dysfunction, impaired electron transport, and the activation of nitric oxide synthase isoforms (iNOS/nNOS), leading to lipid peroxidation and glutathione depletion [17]. Artificial sweeteners have also been reported to affect redox-sensitive signaling cascades (*e.g.*, NF-κB, mitogen-activated protein kinase (MAPK), which can enhance proinflammatory mediators and further exacerbate oxidative damage. Intestinal epithelial disruption and altered microbiota composition may provide an additional systemic route for the propagation of oxidative and inflammatory stress [18]. In particular, sucralose has been increasingly implicated in redox imbalance and oxidative damage. Recent evidence suggests that, beyond its metabolic inertness, sucralose may induce oxidative and genomic stress through mechanisms involving ROS generation and mitochondrial dysfunction [19]. Similarly, Nieto-Mazzocco et al. (2023) reported that thermally treated sucralose and steviol glycosides increased oxidative damage biomarkers, such as malondialdehyde and carbonylated proteins, in mice, underscoring that processing conditions can intensify the redox imbalance [3].

Consistent with this, recent evidence suggests that microbiome-mediated interactions represent a critical link between sweetener exposure and host metabolic responses. In a randomized human trial, NNS consumption modified gut microbial composition and plasma metabolites in a sweetener-specific manner, influencing glucose tolerance in a personalized fashion [20]. While personalised effects are observed in humans via the microbiome [20], the vast majority of mechanistic evidence regarding oxidative stress comes from animal and in vitro models focusing on aspartame and saccharin.

These studies generally focus on commonly consumed sweeteners, such as aspartame and saccharin, and assess their effects on oxidative balance across different tissues. Table 2 summarizes key findings from experimental models, providing an overview before discussing individual sweeteners in more detail.

Table 2. Animal studies investigate the relationship between sweeteners and oxidative stress.

Food additive(s)	Dosage and duration	Type of subject	Tissue	Findings
Aspartame [21]	50,500,1000 mg/kg 180 days	Male Wistar rats	Erythrocytes	↑ Serum total bilirubin, ↓erythrocyte GSH-Px and GR activities, ↓ GSH levels in 500 mg/kg and 1000 mg/kg of aspartame use
Aspartame [22]	75 mg/kg (Acute application)	Male Wistar rats	Brain	↑ lipid peroxidation, SOD, GSH-Px, and CAT activities, ↓ GSH and protein thiol levels
Aspartame [23]	40 mg/kg 90 days	Male Wistar rats	Brain	↑ expression of nNOS and iNOS levels
Aspartame [24]	240 mg/kg 2 months	Male Wistar rats	Liver	↑ MDA, ↓ SOD, CAT, GSH-Px, and GSH levels
Aspartame [25]	0.625, 1.875, or 5.625 mg/kg 2 weeks	Male Mice	Brain	5.625 of aspartame ↑ MDA and nitric oxide and ↓ GSH levels
Saccharin [26]	0.2% 35 days	Adult male mice	Sperm	↓ sperm motility and sperm count, ↑ ROS production and oxidative stress
Saccharin [27]	2.5, 5, and 10 mg/kg 120 days	Male Wistar rats	Liver	↑ CAT activity and 8-OHdG level treatment with 2.5 mg/kg saccharin. ↑ Oxidative status of the liver, isoprostane, uric acid, 8-OHdG, and CAT ↑

"↑" denotes increase; "↓" denotes decrease. Doses are reported as mg/kg unless otherwise specified. Abbreviations: GSH = glutathione; SOD = superoxide dismutase; CAT = catalase; MDA = malondialdehyde.

Aspartame is a widely used artificial sweetener and has been shown in several studies to increase oxidative stress [21-23, 28]. Recent evidence has led to its classification as possibly carcinogenic to humans [8]. The oxidative stress induced by aspartame is thought to result from methanol, a by-product released during its digestion, which is then metabolized into formaldehyde and formic acid [23]. Notably, the effects of aspartame on oxidative stress are dose-dependent and depend on exposure duration. For instance, a study reported that High-dose aspartame (1000 mg/kg, 180 days) significantly reduced erythrocyte GSH-Px and GR activities. Glutathione (GSH) levels also declined, indicating impaired antioxidant defense. While high doses (≥500 mg/kg) induced significant oxidative stress in rats, intake at the ADI level (40 mg/kg body weight/day) showed no measurable adverse effects [21]. This highlights a key discrepancy between experimental conditions and regulatory safety thresholds. Although most toxicological studies suggest that ADI-level consumption is unlikely to cause harm, a few experimental models report neuronal or reproductive effects even at lower or ADI-equivalent doses, underscoring the need for cautious interpretation [21, 23, 29].

Similarly, administering 75 mg/kg of aspartame for 14 days led to decreased glutathione S-transferase (GST) and catalase (CAT) activities in rats [30]. Acute exposure in Wistar albino rats elevated lipid peroxidation and antioxidant enzyme activities (SOD, GSH-Px, CAT), while depleting GSH and protein thiol levels 24 hours post-

administration, highlighting methanol-mediated oxidative stress [22].

Since experimental doses often exceed the human ADI by 10–20-fold, extrapolation of these findings to human risk is limited. Future studies should prioritize physiologically relevant dosing. Tissue-specific effects of aspartame have also been reported. Acute intraperitoneal administration (0.625–45 mg/kg) increased oxidative stress markers in the brain but not in the liver, suggesting selective organ sensitivity, though its clinical importance for human health remains uncertain [31]. Long-term intake at the human ADI level (40 mg/kg body weight) for 90 days increased the expression of neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS), indicating a stress response in neuronal tissues [23]. Moreover, exposure during pregnancy decreased manganese SOD expression in the placenta, potentially affecting placental development through oxidative stress pathways mediated by sweet taste receptors [29].

Furthermore, one study investigated the effects of artificial sweeteners, including aspartame, on the intestinal epithelial barrier. Disruption of the intestinal epithelial barrier, leading to increased permeability, is recognized as a contributing factor to systemic inflammatory disorders and multiple organ failure. Experimental studies using the Caco-2 cell line have explored the influence of widely consumed artificial sweeteners, including sucralose, aspartame, and saccharin, on epithelial integrity. At higher concentrations, aspartame and saccharin were shown to induce apoptosis and cell death. In contrast, lower concentrations of aspartame, when combined with sucralose, promoted barrier dysfunction, characterized by increased permeability and reduced claudin-3 expression at the cell surface. Notably, silencing of the T1R3 receptor attenuated these effects, supporting the notion that aspartame enhances ROS generation, thereby contributing to barrier impairment and claudin-3 internalization. This study highlights the adverse effects of artificial sweeteners on the intestinal epithelium, particularly through activation of the sweet taste receptor T1R3 [32].

In a related study, the prooxidative effects of aspartame on the antioxidant defense status of rats' erythrocytes were investigated. Rats administered aspartame (40 mg/kg body weight) daily for six weeks exhibited significant increases in serum glucose, cholesterol, and triglycerides. Additionally, the aspartame-treated group exhibited elevated concentrations of oxidative stress markers, including superoxide anion, hydrogen peroxide, and lipid peroxides, in their erythrocytes. These findings suggest that long-term consumption of aspartame may promote oxidative stress–related changes in glucose and lipid metabolism in animal models [33]. However, direct relevance to humans remains to be clarified.

Adding to this body of evidence, a recent study explored the effects of aspartame and its metabolites (aspartic acid, phenylalanine, and methanol) on oxidative stress and lipid homeostasis in human neuroblastoma SH-SY5Y cells. In this study, aspartame (271.7 µM) or its metabolites induced significant oxidative stress associated with mitochondrial damage. Reduced cardiolipin levels and increased expression of key markers of mitochondrial dysfunction, including SOD1, SOD2, PINK1, and FIS1, evidenced this damage. Moreover, increased fluorescence levels of 3'-(p-aminophenyl) fluorescein (APF) suggested elevated ROS levels [17]. In addition to oxidative damage, treatment of SH-SY5Y cells with aspartame and its metabolites altered lipid metabolism, leading to a significant increase in triacylglycerides and phospholipids, including phosphatidylcholines and phosphatidylethanolamines. Lipid droplets also accumulated in the neuronal cells, suggesting that aspartame may disrupt brain lipid homeostasis and contribute to neurodegenerative processes [17]. Given emerging evidence, the use of

aspartame as a sugar substitute, particularly regarding its potential neurotoxic effects and metabolic alterations, warrants further investigation. Findings from in vitro models, such as SH-SY5Y cells, underscore the need for in vivo studies to examine the broader implications of aspartame for brain metabolism and neurodegenerative diseases.

Moreover, a study investigated the mechanism of aspartame-induced reproductive toxicity in male mice following long-term consumption. Male mice received three doses of aspartame (40, 80, and 160 mg/kg body weight) daily for 90 days. The results revealed significant reductions in the gonadosomatic index, serum levels of pituitary-testicular axis hormones (FSH, LH, and testosterone), sperm parameters, and total antioxidant capacity. Additionally, there were increases in nitric oxide and malondialdehyde levels in testis tissue and sperm samples. Histomorphometric analyses showed a decrease in testicular indices and an increase in apoptosis rates, indicating that long-term consumption of aspartame results in male reproductive toxicity through induction of oxidative stress and apoptosis in the testis [34].

Overall, these findings suggest that aspartame can alter the oxidative balance across tissues. However, the magnitude and relevance of these changes depend strongly on dosage, exposure duration, and the experimental model used.

Saccharin, another widely used artificial sweetener, has been linked to oxidative stress in reproductive health. In a study on adult mice, the consumption of saccharin (0.2% in water) for 35 days significantly reduced sperm motility and count, likely due to increased production of ROS. The study also reported increased sperm DNA fragmentation and apoptosis in the saccharin-treated group [26].

Recent findings have extended similar concerns to sucralose, revealing its potential to induce oxidative and reproductive toxicity. Experimental data from both in vitro and in vivo models demonstrated that exposure to sucralose decreased Leydig and Sertoli cell viability, disrupted autophagy, and induced oxidative stress. Chronic exposure in male rats also impaired sperm viability and testicular morphology while downregulating steroidogenic activity, suggesting that sucralose may adversely affect male reproductive function through oxidative and autophagy-related mechanisms [35].

Natural sweeteners have been proposed as alternatives to artificial sweeteners. One study indicated that the natural sweetener stevioside and the prebiotic inulin exhibited protective effects against oxidative stress [36].

Overall, these studies suggest that while high doses of artificial sweeteners, such as aspartame and saccharin, can induce oxidative stress and affect various physiological parameters, the impact varies with dosage, duration, and tissue type. Importantly, these findings suggest that habitual consumption at doses exceeding the ADI may pose risks, whereas intake within regulatory limits appears to be less harmful.

A study aimed at investigating the effects of various commercially available NNS (aspartame, saccharin, sucralose, and cyclamate) on the antioxidant status in a rat model of Type 2 Diabetes (T2D) showed promising results. Ad libitum consumption of these sweeteners was found to reduce T2D-induced lipid peroxidation and to increase serum, hepatic, renal, cardiac, and pancreatic glutathione (GSH) levels. Moreover, the activity of key antioxidant enzymes, such as catalase, superoxide dismutase, and glutathione peroxidase, was enhanced in the serum and most organs, likely as an adaptive response to oxidative stress induced by diabetes. Interestingly, the study noted that aspartame-based sweeteners may not provide significant antioxidant benefits, whereas saccharin-based sweeteners demonstrate potent antioxidative properties in the context of T2D [9]. These contrasting findings suggest that saccharin may exert tissue- and context-dependent

effects, displaying pro-oxidative actions in reproductive models while demonstrating antioxidative responses under diabetic conditions. Similarly, evidence from recent human meta-analyses suggests that NNS may not have measurable effects on serum lipid parameters, indicating that their metabolic consequences are selective rather than universal across biomarkers [37].

While much of the current evidence is derived from small-scale animal studies, recent systematic reviews emphasize the need to contextualize these findings within broader human health outcomes [1, 38].

Replacing artificial sweeteners with natural alternatives, such as stevia, may represent a safer strategy for reducing potential oxidative stress–related adverse effects. However, this substitution should be interpreted with caution, since evidence from human clinical trials remains limited and further long-term studies are needed to establish clear recommendations.

These findings underscore the need for further clinical studies to validate the potential health benefits of NNS in diabetic populations [9]. While animal and *in vitro* studies provide mechanistic insights into oxidative stress pathways, translating these findings into human health outcomes remains uncertain. This gap highlights the importance of large-scale epidemiological and intervention studies.

A randomized, triple-blind clinical trial involving overweight subjects assessed the impact of adding stevia, sucralose, and sucrose (as a control) to maqui-citrus juices on antioxidant and inflammatory markers. Participants consumed test beverages (330 mL daily) for 60 days, during which various parameters were measured, including antioxidant status, lipid profile, and inflammatory biomarkers. The results showed a significant increase in homocysteine levels after consumption of sucralose (27%) and sucrose (40%), indicating potential adverse effects. Conversely, the stevia-sweetened beverage led to an increase in IL-10, an anti-inflammatory marker, and improved antioxidant status (21% increase in Oxygen radical absorbance capacity (ORAC) values) among those with initially low antioxidant levels. These findings suggest that while stevia may have protective effects, both sucralose and sucrose can induce oxidative stress and inflammatory responses [39]. Further studies are needed to clarify the health implications of these sweeteners at normal consumption levels.

Oxidative stress and antioxidants: Functional foods, defined here as whole foods or food ingredients with concentrated bioactive compounds (*e.g.*, polyphenol-rich fruits, certain seaweeds, and prebiotic fibers), may modulate the oxidative response to non-caloric sweeteners [40-41]. Controlled clinical trials suggest that dietary patterns rich in antioxidants and low in processed foods can modulate oxidative stress and improve related metabolic outcomes. Systematic reviews indicate that plant-based dietary patterns, particularly the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, are inversely associated with biomarkers of oxidative stress and inflammation. However, larger, high-quality randomized controlled trials are still needed to establish causality [38]. Such dietary patterns exemplify the principles of functional foods, in which nutrient-dense, bioactive compound–rich ingredients directly influence redox homeostasis [42-43]. In this context, functional foods not only serve as sources of antioxidants but also modulate endogenous defense pathways that can mitigate the pro-oxidant effects of chronic exposure to sweeteners. Integrating food technology with health science is now considered essential for developing next-generation functional foods that can counterbalance ROS and chronic inflammation in vivo [44, 45]. Conversely, diets high in processed foods, refined carbohydrates, saturated fats, or overall caloric intake can increase oxidative stress [46, 47]. Oxidative stress is proposed as a mechanistic link between obesity and its associated complications [48-50]. However,

dietary intake of antioxidant nutrients in a healthy diet can help reduce oxidative stress by neutralizing free radicals [46, 51-52]. Vegetables and fruits, nuts, oilseeds, spices, and herbs are rich in antioxidants [53-54]. Animal studies suggest that dietary intake of phenolic acids may improve metabolic syndrome and oxidative stress biomarkers induced by a high-fructose diet [54-55]. Several studies have reported an inverse association between the consumption of anthocyanin-rich fruits and markers of oxidative stress and inflammation [56-63]. Functional foods, especially those rich in polyphenols, vitamins, and prebiotic fibers, can enhance endogenous antioxidant defenses and may offset NCS-induced oxidative perturbations [64-65].

The mechanisms through which nutrients counteract oxidative stress are not yet fully elucidated. Nutrients with antioxidant properties may prevent oxidative damage by directly interacting with free radicals [49, 66-68]. Some nutrients can increase the production and activity of endogenous antioxidant enzymes. Specific nutrients are proposed to regulate cellular redox status by modulating key signaling pathways involved in ROS production and scavenging, such as the MAPK and NF-κB pathways [67]. In addition, many nutrients, such as folic acid, B12, and zinc, are involved in DNA synthesis and repair [68-71].

In some studies, antioxidant nutrients were combined with food additives, and the potential of antioxidants to mitigate oxidative stress induced by food additives was investigated. An overview of studies examining the combined effects of food additives and antioxidants is presented in Table 3.

Aspartame increased lipid peroxidation and decreased antioxidant enzyme levels. However, it has been demonstrated that various antioxidant compounds (*Sargassum vulgare*, acetylcysteine, carnitine) protect against oxidative damage caused by aspartame [24, 72, 74]. The use of antioxidants such as *Sargassum vulgare* and N-acetylcysteine reduced aspartame-induced oxidative damage and increased antioxidant enzyme activities.

Table 3. Studies in which food additives and various antioxidant components were applied together.

Supplement and dosage	Food Additives and Dosage	Type of animal model	Findings
150 mg/kg *Sargassum vulgare* 3 weeks Oral [72]	Aspartame 500 mg/kg 1 week Oral	Male Wistar rats	*Sargassum vulgare* has been shown to improve the effects of aspartame. ↑ SOD and CAT levels, ↓ TNF-α and IL-6 levels
150 mg/kg N-acetylcysteine 2 weeks Intraperitoneal [73]	Aspartame 40 mg/kg 6 weeks Oral	Male Wistar rats	N-acetylcysteine reduced oxidative damage in the brain induced by aspartame. ↑ SOD, GPx, GR activities, ↑ non-protein thiols, ↑ TRAP, CAT, and GST activities remained low; no change in glucose levels.
10 mg/kg l-carnitine 30 days Oral [74]	Aspartame 75-150 mg/kg 30 days Oral	Male rats	Aspartame → ↑ lipid peroxidation and ↓ GSH levels. L-carnitine → ↓ MDA levels and ↑ CAT, GSH-Px, SOD, and GSH levels

"↑" denotes increase; "↓" denotes decrease. Doses are reported as mg/kg unless otherwise specified. Abbreviations: GSH = glutathione; SOD = superoxide dismutase; CAT = catalase; MDA = malondialdehyde.

Additionally, L-carnitine reduced lipid peroxidation and increased the activity of antioxidant enzymes [72, 74]. L-carnitine can minimize hydrogen peroxide production, prevent lipid peroxidation, and mitigate oxidative damage [74]. These studies were conducted in animal models and used different doses and durations. More research is needed to draw direct conclusions in humans. However, these studies on the protective effects of antioxidants against the potential oxidative stress effects of aspartame may help guide future research and clinical trials.

CONCLUSION

Non-caloric sweeteners, particularly aspartame and saccharin, have been shown to influence oxidative stress in a dose-, duration-, and tissue-dependent manner. Preclinical studies indicate that high-dose or long-term consumption may induce oxidative damage in neuronal, reproductive, and intestinal tissues, while consumption within ADI limits appears less harmful. Saccharin, in particular, has demonstrated both pro-oxidative effects in reproductive tissues and potential antioxidative benefits in specific metabolic contexts, such as type 2 diabetes models.

Diets rich in fruits, vegetables, and other antioxidant sources, including Mediterranean and DASH dietary patterns, are consistently associated with lower oxidative stress and inflammation. The findings of this study, when linked to functional food science, may contribute to the development of applicable nutrition strategies [40, 75]. Including foods rich in bioactive components or appropriate supplements in the diet may be a practical approach to reducing the oxidative burden associated with high sweetener consumption. Incorporating polyphenol-rich functional foods that utilize modern microencapsulation technologies could further enhance antioxidant stability and bioavailability, supporting redox balance even under dietary stress conditions [76-78]. Understanding the potential synergistic mechanisms between NNS and antioxidant bioactive compounds is critical for developing personalized nutrition approaches and functional food-based interventions.

The findings of this review position NNS within the framework of Functional Food Science by linking their oxidative and redox-modulating effects to health outcomes. Understanding these compounds through bioactive and mechanistic pathways—particularly involving mitochondrial function, redox signaling (e.g., Nrf2, NF-κB), and inflammatory modulation supports their evaluation alongside antioxidant-rich functional foods. Integrating formulation, dosage, and dietary context can inform translational strategies for developing safe, evidence-based functional products. Recent publications within the FFHDJ ecosystem highlight the potential of polyphenol-, fiber-, and vitamin-enriched foods to restore oxidative balance, offering promising directions for product innovation and regulatory alignment [40–43, 61, 64, 76-78]. This highlights the critical role that nutritionists and dietitians have in promoting healthy eating habits and accurately communicating the potential effects of these compounds to individuals [79].

Large-scale, long-term human studies are needed to clarify the extent to which these protective effects can mitigate oxidative stress induced by artificial sweeteners.

Overall, while animal and *in vitro* studies provide mechanistic insights, translating these findings into human health outcomes remains uncertain. Future research should prioritize well-designed, long-term clinical trials to determine safe consumption levels of non-caloric sweeteners, clarify their tissue-specific effects, and evaluate the potential protective roles of natural sweeteners and antioxidants. Such studies are essential for guiding evidence-based dietary recommendations and for understanding the complex

interactions between sweetener consumption, oxidative stress, and metabolic health.

This review advances current understanding by integrating mechanistic, experimental, and dietary perspectives on NNS-induced oxidative stress. It highlights the dual role of artificial and natural sweeteners within oxidative pathways and proposes a framework for evaluating these compounds in conjunction with antioxidant-rich functional foods. The practical implications include providing evidence-based recommendations on sweetener consumption, identifying biomarkers for future clinical monitoring, and informing regulatory decisions on safe intake levels and product formulation.

Future research should prioritize well-powered human intervention studies that use physiologically relevant doses of NNS and include long-term follow-up to capture cumulative effects. Developing standardized panels of oxidative biomarkers (including lipid and protein oxidation markers, along with validated measures of total antioxidant capacity) will enable meaningful comparisons across studies. Combined dietary interventions examining whether functional foods rich in polyphenols or targeted antioxidant supplementation can attenuate oxidative changes induced by sweeteners are particularly needed. Moreover, mechanistic human studies employing tissue-relevant models, such as organoids and biopsy samples, are necessary to verify the involvement of mitochondrial and redox pathways. Finally, integrated microbiome–metabolome analyses should be expanded to clarify indirect systemic pathways linking sweetener exposure to oxidative and inflammatory responses. Addressing these priorities will be essential to translating preclinical evidence into clear, practical public health guidance.

Abbreviations: ADI: Acceptable Daily Intake; NNS: Non-nutritive sweeteners, T2D: Type 2 Diabetes; WHO: World Health Organization; MAPK: Mitogen-activated protein kinase; Nrf2: Nuclear factor erythroid 2-related factor 2, NF-κB: Nuclear Factor kappa B; GSH: Glutathione; SOD: Superoxide dismutase; CAT: Catalase; MDA: Malondialdehyde.

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REFERENCES

1. Debras C, Chazelas E, Srour B, Druesne-Pecollo N, Esseddik Y, Szabo de Edelenyi F, et al. Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. *PLoS Med.* 2022;19(3):e1003950. DOI: https://doi.org/10.1371/journal.pmed.1003950
2. Additives EPoF, Food NSat. Safety of the proposed extension of use of sucralose (E 955) in foods for special medical purposes in young children. *EFSA Journal*. 2016;14(1):4361. DOI: https://doi.org/10.2903/j.efsa.2016.4361
3. Nieto-Mazzocco E, Franco-Robles E, Saldaña-Robles A, Pacheco N, Ozuna C. Thermal Treatment of Commercial Sweetener Solutions Modulates the Metabolic Responses in C57BL/6 Mice during a 24-Week-Long Exposition. *Processes.* 2023;11(8):2445. DOI: https://doi.org/10.3390/pr11082445
4. Andersen SSH, Zhu R, Kjølbæk L, Raben A. Effect of Non- and Low-Caloric Sweeteners on Substrate Oxidation, Energy Expenditure, and Catecholamines in Humans—A Systematic Review. *Nutrients*. 2023;15(12):2711.

DOI: https://doi.org/10.3390/nu15122711

5. Khalilipanah S, Zamani K. Non-caloric artificial sweeteners: A mini-review of current perspectives on health benefits and potential risks. *Journal of Current Biomedical Reports*. 2024:82-86. DOI: https://doi.org/10.61882/jcbior.5.3.307
6. (FAF) EP on FA and F, Castle L, Andreassen M, Aquilina G, Bastos ML, Boon P, et al. Re-evaluation of saccharin and its sodium, potassium and calcium salts (E 954) as food additives. *EFSA J*. 2024:22(11):e9044.
DOI: https://doi.org/10.2903/j.efsa.2024.9044
7. Wilk K, Korytek W, Pelczyńska M, Moszak M, Bogdański P. The Effect of Artificial Sweeteners Use on Sweet Taste Perception and Weight Loss Efficacy: A Review. *Nutrients*. 2022;14(6).
DOI: https://doi.org/10.3390/nu14061261
8. World Health Organization. Aspartame hazard and risk assessment results released. 2023 [cited 2025 Jan 10]. Available from: https://www.who.int/news/item/14-07-2023-aspartame-hazard-and-risk-assessment-results-released.
9. McHunu N, Chukwuma CI, Ibrahim MA, Oyebode OA, Dlamini SN, Islam MS. Commercially available non-nutritive sweeteners modulate the antioxidant status of type 2 diabetic rats. *J Food Biochem*. 2019;43(3):e12775.
DOI: https://doi.org/10.1111/jfbc.12775
10. Wang L, Chang T, Zhu T, Hu W, Wang X, Dong C, et al. Stevia rebaudiana Bertoni as a sweet herbal medicine: traditional uses, potential applications, and future development. *Front Pharmacol*. 2025;16:1638147.
DOI: https://doi.org/10.3389/fphar.2025.1638147
11. El-Mesallamy AMD, Mahmoud SA, Elazab KM, Hussein SAM, Hussein AM. Attenuation of metabolic dysfunctions in the skeletal muscles of type 1 diabetic rats by Stevia rebaudiana extracts, via AMPK upregulation and antioxidant activities. *Acta Sci Pol Technol Aliment*. 2018;17(3):289-297.
DOI: https://doi.org/10.17306/j.Afs.0567
12. Li Z, Kanwal R, Yue X, Li M, Xie A. Polyphenols and intestinal microorganisms: A review of their interactions and effects on human health. *Food Bioscience*. 2024;62:105220.
DOI: https://doi.org/10.1016/j.fbio.2024.105220
13. Agulló V, García-Viguera C, Domínguez-Perles R. Use of alternative sweeteners (sucralose and stevia) in healthy soft-drink beverages enhances the bioavailability of polyphenols relative to classical caloric sucrose. *Food Chem*. 2022;370:131051.
DOI: https://doi.org/10.1016/j.foodchem.2021.131051
14. Riaz Rajoka MS, Thirumdas R, Mehwish HM, Umair M, Khurshid M, Hayat HF, et al. Role of Food Antioxidants in Modulating Gut Microbial Communities: Novel Understandings in Intestinal Oxidative Stress Damage and Their Impact on Host Health. *Antioxidants*. 2021;10(10):1563.
DOI: https://doi.org/10.3390/antiox10101563
15. Rudrapal M, Khairnar SJ, Khan J, Dukhyil AB, Ansari MA, Alomary MN, et al. Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights Into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action. *Front Pharmacol*. 2022;13:806470.
DOI: https://doi.org/10.3389/fphar.2022.806470
16. Attiya H. Protective effect of Spirulina against aspartame induced oxidative stress and molecular gene brain damage. *Journal of the Hellenic Veterinary Medical Society*. 2022;73(1):3689-3698.
DOI: https://doi.org/10.12681/jhvms.25509
17. Griebsch LV, Theiss EL, Janitschke D, Erhardt VKJ, Erhardt T, Haas EC, et al. Aspartame and Its Metabolites Cause Oxidative Stress and Mitochondrial and Lipid Alterations in SH-SY5Y Cells. *Nutrients*. 2023;15(6).
DOI: https://doi.org/10.3390/nu15061467
18. Basson AR, Rodriguez-Palacios A, Cominelli F. Artificial sweeteners: history and new concepts on inflammation. *Frontiers in Nutrition*. 2021;8:746247.
DOI: https://doi.org/10.3389/fnut.2021.746247
19. Tkach VV, Morozova TV, Gaivão IOM, Miranda NG, Ivanushko YG, Martins J, et al. Sucralose: A Review of Environmental, Oxidative and Genomic Stress. *Nutrients*. 2025;17(13).
DOI: https://doi.org/10.3390/nu17132199
20. Suez J, Cohen Y, Valdés-Mas R, Mor U, Dori-Bachash M, Federici S, et al. Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. *Cell*. 2022;185(18):3307-28.e19.
DOI: https://doi.org/10.1016/j.cell.2022.07.016
21. Abhilash M, Varghese MV, Paul MVS, Alex M, Nair RH. Effect of long-term intake of aspartame on serum biochemical parameters and erythrocyte oxidative stress biomarkers in rats. *Comparative Clinical Pathology*. 2015;24(4):927-933.
DOI: https://doi.org/10.1007/s00580-014-2013-8
22. Ashok I, Sheeladevi R, Wankhar D. Acute effect of aspartame-induced oxidative stress in Wistar albino rat brain. *Journal of Biomedical Research*. 2015;29(5):390.
DOI: https://doi.org/10.7555/JBR.28.20120118
23. Iyaswamy A, Kammella AK, Thavasimuthu C, Wankupar W, Dapkupar W, Shanmugam S, et al. Oxidative stress evoked damages leading to attenuated memory and inhibition of

NMDAR–CaMKII–ERK/CREB signalling on consumption of aspartame in rat model. *Journal of Food and Drug Analysis*. 2018;26(2):903-916.
DOI: https://doi.org/10.1016/j.jfda.2017.11.001

24. Lebda MA, Tohamy HG, El-Sayed YS. Long-term soft drink and aspartame intake induces hepatic damage via dysregulation of adipocytokines and alteration of the lipid profile and antioxidant status. *Nutr Res*. 2017;41:47-55.
DOI: https://doi.org/10.1016/j.nutres.2017.04.002
25. Abdel-Salam OM, Salem NA, Hussein JS. Effect of aspartame on oxidative stress and monoamine neurotransmitter levels in lipopolysaccharide-treated mice. *Neurotox Res*. 2012;21(3):245-255.
DOI: https://doi.org/10.1007/s12640-011-9264-9
26. Rahimipour M, Talebi AR, Anvari M, Sarcheshmeh AA, Omidi M. Saccharin consumption increases sperm DNA fragmentation and apoptosis in mice. *Iranian Journal of Reproductive Medicine*. 2014;12(5):307.
27. Azeez OH, Alkass SY, Persike DS. Long-Term Saccharin Consumption and Increased Risk of Obesity, Diabetes, Hepatic Dysfunction, and Renal Impairment in Rats. *Medicina (Kaunas).* 2019;55(10).
DOI: https://doi.org/10.3390/medicina55100681
28. Iyyaswamy A, Rathinasamy S. Effect of chronic exposure to aspartame on oxidative stress in brain discrete regions of albino rats. *Journal of Biosciences*. 2012;37:679-688.
DOI: https://doi.org/10.1007/s12038-012-9236-0
29. Huang SY, Sun R, Chen YC, Kang L, Wang CT, Chiu CF, et al. Aspartame consumption during pregnancy impairs placenta growth in mice through sweet taste receptor-reactive oxygen species-dependent pathway. *J Nutr Biochem*. 2023;113:109228.
DOI: https://doi.org/10.1016/j.jnutbio.2022.109228
30. Souto NS, Dassi M, Braga ACM, Rosa É VF, Fighera MR, Royes LFF, et al. Hepatic susceptibility to oxidative damage after repeated concomitant exposure to aspartame and aflatoxin B1 in rats. *Drug and Chemical Toxicology*. 2022;45(6):2780-2785.
DOI: https://doi.org/10.1080/01480545.2021.1991196
31. Abdel-Salam OM, Salem NA, El-Shamarka ME, Hussein JS, Ahmed NA, El-Nagar ME. Studies on the effects of aspartame on memory and oxidative stress in brain of mice. *Eur Rev Med Pharmacol Sci*. 2012;16(15):2092-2101.
32. Shil A, Olusanya O, Ghufoor Z, Forson B, Marks J, Chichger H. Artificial Sweeteners Disrupt Tight Junctions and Barrier Function in the Intestinal Epithelium through Activation of the Sweet Taste Receptor, T1R3. *Nutrients*. 2020;12(6).
DOI: https://doi.org/10.3390/nu12061862
33. Prokic MD, Paunovic MG, Matic MM, Djordjevic NZ, Ognjanovic BI, Stajn AS, et al. Prooxidative effects of aspartame on antioxidant defense status in erythrocytes of rats. *J Biosci*. 2014;39(5):859-866.
DOI: https://doi.org/10.1007/s12038-014-9487-z
34. Anbara H, Sheibani MT, Razi M, Kian M. Insight into the mechanism of aspartame-induced toxicity in male reproductive system following long-term consumption in mice model. *Environ Toxicol*. 2021;36(2):223-237.
DOI: https://doi.org/10.1002/tox.23028
35. Chiang Y-F, Chen Y-C, Huang K-C, Ali M, Hsia S-M. Exposure to Sucralose and Its Effects on Testicular Damage and Male Infertility: Insights into Oxidative Stress and Autophagy. *Environmental Health Perspectives*. 2025.
DOI: https://doi.org/10.1289/EHP15919
36. Stoyanova S, Geuns J, Hideg E, Van den Ende W. The food additives inulin and stevioside counteract oxidative stress. Int J Food Sci Nutr. 2011;62(3):207-214.
DOI: https://doi.org/10.3109/09637486.2010.523416
37. Najafi A, Moghtaderi F, Seyedjafari B, Rostampour K, Salehi-Abargouei A. The effects of non-nutritive sweeteners on lipid profile in adults: a systematic review and meta-analysis of randomized controlled clinical trials. *Scientific Reports*. 2025;15(1):21106.
DOI: https://doi.org/10.1038/s41598-025-00612-3
38. Aleksandrova K, Koelman L, Rodrigues CE. Dietary patterns and biomarkers of oxidative stress and inflammation: A systematic review of observational and intervention studies. *Redox Biology*. 2021;42:101869.
DOI: https://doi.org/10.1016/j.redox.2021.101869
39. Zafrilla P, Masoodi H, Cerdá B, García-Viguera C, Villaño D. Biological effects of stevia, sucralose and sucrose in citrus-maqui juices on overweight subjects. *Food Funct*. 2021;12(18):8535-8543.
DOI: https://doi.org/10.1039/d1fo01160j
40. Fekete M, Lehoczki A, Kryczyk-Poprawa A, Zábó V, Varga JT, Bálint M, et al. Functional Foods in Modern Nutrition Science: Mechanisms, Evidence, and Public Health Implications. *Nutrients.* 2025;17(13).
DOI: https://doi.org/10.3390/nu17132153
41. Martirosyan D, Lampert T, Ekblad M. Classification and regulation of functional food proposed by the Functional Food Center. *Functional Food Science*. 2022;2:25.
DOI: https://doi.org/10.31989/ffs.v2i2.890
42. Scuto M, Majzúnová M, Torcitto G, Antonuzzo S, Rampulla F, Di Fatta E, et al. Functional Food Nutrients, Redox Resilience

Signaling and Neurosteroids for Brain Health. *Int J Mol Sci*. 2024;25(22).
DOI: https://doi.org/10.3390/ijms252212155

43. Cuciniello R, Di Meo F, Filosa S, Crispi S, Bergamo P. The Antioxidant Effect of Dietary Bioactives Arises from the Interplay between the Physiology of the Host and the Gut Microbiota: Involvement of Short-Chain Fatty Acids. *Antioxidants*. 2023;12(5):1073.
DOI: https://doi.org/10.3390/antiox12051073
44. Granato D. Functional foods to counterbalance low-grade inflammation and oxidative stress in cardiovascular diseases: a multilayered strategy combining food and health sciences. *Current Opinion in Food Science*. 2022;47:100894.
DOI: https://doi.org/10.1016/j.cofs.2022.100894
45. Mohammadi N, Farrell M, O'Sullivan L, Langan A, Franchin M, Azevedo L, et al. Effectiveness of anthocyanin-containing foods and nutraceuticals in mitigating oxidative stress, inflammation, and cardiovascular health-related biomarkers: a systematic review of animal and human interventions. *Food Funct*. 2024;15(7):3274-3299.
DOI: https://doi.org/10.1039/d3fo04579j
46. Mehdi WT, Hadi MM. The Sensitivity of Male Rat Reproductive Organs to Sodium Benzoate. *Biochemical & Cellular Archives*. 2018;18(1):323-330.
47. Tan BL, Norhaizan ME. Effect of High-Fat Diets on Oxidative Stress, Cellular Inflammatory Response and Cognitive Function. *Nutrients*. 2019;11(11).
DOI: https://doi.org/10.3390/nu11112579
48. Patil BS, Patil JK, Chaudhari HS, Patil BS. Oxidative Stress, Inflammation, and Obesity: Insights into Mechanism and Therapeutic Targets. *Proceedings*. 2025;119(1):6.
DOI: https://doi.org/10.3390/proceedings2025119006
49. Moratilla-Rivera I, Pérez-Jiménez J, Ramos S, Portillo MP, Martín MÁ, et al. Hydroxytyrosol supplementation improves antioxidant and anti-inflammatory status in individuals with overweight and prediabetes: A randomized, double-blind, placebo-controlled trial. *Clin Nutr*. 2025;52:17–26.
DOI: https://doi.org/10.1016/j.clnu.2025.07.006
50. Olivares-Vicente M, Herranz-López M. The Interplay Between Oxidative Stress and Lipid Composition in Obesity-Induced Inflammation: Antioxidants as Therapeutic Agents in Metabolic Diseases. *Int J Mol Sci.* 2025;26(17):8544.
DOI: https://doi.org/10.3390/ijms26178544
51. Marotta F, Chui DH, Jain S, Polimeni A, Koike K, et al. Effect of a fermented nutraceutical on thioredoxin level and TNF-alpha signalling in cirrhotic patients. *J Biol Regul Homeost Agents*. 2011;25(1):37-45.
52. Cizmarova B, Hubkova B, Birkova A. Quercetin as an effective antioxidant against superoxide radical. *Functional Food Science*. 2023;3(3):15-25.
DOI: https://doi.org/10.31989/ffs.v3i3.1076
53. Fernandes AS, Ferreira-Pêgo C, Costa JG. Functional Foods for Health: The Antioxidant and Anti-Inflammatory Role of Fruits, Vegetables and Culinary Herbs. *Foods*. 2023;12(14):2742.
DOI: https://doi.org/10.3390/foods12142742
54. Ibitoye OB, Ajiboye TO. Dietary phenolic acids reverse insulin resistance, hyperglycaemia, dyslipidaemia, inflammation and oxidative stress in high-fructose diet-induced metabolic syndrome rats. *Arch Physiol Biochem*. 2018;124(5):410-417.
DOI: https://doi.org/10.1080/13813455.2017.1415938
55. Acikel-Elmas M, Algilani SA, Sahin B, Bingol Ozakpinar O, Gecim M, Koroglu K, et al. Apocynin Ameliorates Monosodium Glutamate Induced Testis Damage by Impaired Blood-Testis Barrier and Oxidative Stress Parameters. *Life (Basel)*. 2023;13(3). DOI: https://doi.org/10.3390/life13030822
56. Bloedon TK, Braithwaite RE, Carson IA, Klimis-Zacas D, Lehnhard RA. Impact of anthocyanin-rich whole fruit consumption on exercise-induced oxidative stress and inflammation: a systematic review and meta-analysis. *Nutrition Reviews*. 2019;77(9):630-645.
DOI: https://doi.org/10.1093/nutrit/nuz018
57. Cesar T, Oliveira MR, Sandrim V, Mendes A, Bruder R, et al. Citrus flavonoid supplement enhances glycemic and metabolic control in prediabetic patients on metformin: a randomized controlled trial. *Front Nutr.* 2025;12:1639901.
DOI: https://doi.org/10.3389/fnut.2025.1639901
58. Edirisinghe I, Banaszewski K, Cappozzo J, Sandhya K, Ellis CL, Tadapaneni R, et al. Strawberry anthocyanin and its association with postprandial inflammation and insulin. *Br J Nutr*. 2011;106(6):913-922.
DOI: https://doi.org/10.1017/s0007114511001176
59. Jokioja J, Linderborg KM, Kortesniemi M, Nuora A, Heinonen J, Sainio T, et al. Anthocyanin-rich extract from purple potatoes decreases postprandial glycemic response and affects inflammation markers in healthy men. *Food Chem*. 2020;310:125797.
DOI: https://doi.org/10.1016/j.foodchem.2019.125797
60. Kaspar KL, Park JS, Brown CR, Mathison BD, Navarre DA, Chew BP. Pigmented potato consumption alters oxidative stress and inflammatory damage in men. *J Nutr*. 2011;141(1):108-111.
DOI: https://doi.org/10.3945/jn.110.128074
61. Martins I, Maciel MG, do Nascimento JLM, Mafra D, Santos AF, Padilha CS. Anthocyanins-rich interventions on oxidative stress, inflammation and lipid profile in patients undergoing

hemodialysis: meta-analysis and meta-regression. *Eur J Clin Nutr*. 2023;77(3):316-324.
DOI: https://doi.org/10.1038/s41430-022-01175-6

62. Maqsood S, Basher NS, Arshad MT, Ikram A, Kalman DS, et al. Anthocyanins From Sweet Potatoes (Ipomoea batatas): Bioavailability, Mechanisms of Action, and Therapeutic Potential in Diabetes and Metabolic Disorders. *Food Sci Nutr*. 2025;13(9):e70895.
DOI: https://doi.org/10.1002/fsn3.70895
63. Zhang H, Xu Z, Zhao H, Wang X, Pang J, Li Q, et al. Anthocyanin supplementation improves anti-oxidative and anti-inflammatory capacity in a dose-response manner in subjects with dyslipidemia. *Redox Biol*. 2020;32:101474.
DOI: https://doi.org/10.1016/j.redox.2020.101474
64. Abd Elgadir M, Chigurupati S, Mariod AA. Selected potential pharmaceutical and medical benefits of phenolic compounds: Recent advances. *Functional Food Science-Online*. 2023;3(7):108-128.
DOI: https://doi.org/10.31989/ffs.v3i7.1118
65. Martirosyan D, Lampert DT, Lee MA. Comprehensive review on the role of food bioactive compounds in functional food science. *Functional Food Science*. 2022;3(2): 64-78.
DOI: https://doi.org/10.31989/ffs.v2i3.906
66. Chandimali N, Bak SG, Park EH, Lim H-J, Won Y-S, Kim E-K, et al. Free radicals and their impact on health and antioxidant defenses: a review. *Cell Death Discovery*. 2025;11(1):19.
DOI: https://doi.org/10.1038/s41420-024-02278-8
67. Kuchi Bhotla H, Meyyazhagan A, Pappusamy M, Park S, Arumugam VA, Pushparaj K, et al. Dietary nutrients and their control of the redox bioenergetic networks as therapeutics in redox dysfunctions sustained pathologies. *Pharmacological Research*. 2021;170:105709.
DOI: https://doi.org/10.1016/j.phrs.2021.105709
68. Bjørke-Monsen AL, Ueland PM. Folate - a scoping review for Nordic Nutrition Recommendations 2023. *Food Nutr Res*. 2023;67. DOI: https://doi.org/10.29219/fnr.v67.10258
69. Halczuk K, Kaźmierczak-Barańska J, Karwowski BT, Karmańska A, Cieślak M. Vitamin B12-Multifaceted In Vivo Functions and In Vitro Applications. *Nutrients*. 2023;15(12).
DOI: https://doi.org/10.3390/nu15122734
70. Ilari S, Proietti S, Milani F, Vitiello L, Muscoli C, Russo P, et al. Dietary Patterns, Oxidative Stress, and Early Inflammation: A Systematic Review and Meta-Analysis Comparing Mediterranean, Vegan, and Vegetarian Diets. *Nutrients*. 2025;17(3):548. DOI: https://doi.org/10.3390/nu17030548
71. Wong CP, Beaver LM, Ho E. Protective role of dietary zinc on DNA damage, oxidative stress, and metal toxicity. *Front Mol Biosci*. 2025;12:1618318.
DOI: https://doi.org/10.3389/fmolb.2025.1618318
72. Ibrahim RYM, Hammad HBI, Gaafar AA, Saber AA. The possible role of the seaweed Sargassum vulgare as a promising functional food ingredient minimizing aspartame-associated toxicity in rats. *Int J Environ Health Res*. 2022;32(4):752-771.
DOI: https://doi.org/10.1080/09603123.2020.1797642
73. Finamor IA, Ourique GM, Pês TS, Saccol EM, Bressan CA, Scheid T, et al. The protective effect of N-acetylcysteine on oxidative stress in the brain caused by the long-term intake of aspartame by rats. *Neurochem Res.* 2014;39(9):1681-1690.
DOI: https://doi.org/10.1007/s11064-014-1360-9
74. Hamza RZ, Al-Eisa RA, Mehana AE, El-Shenawy NS. Effect of l-carnitine on aspartame-induced oxidative stress, histopathological changes, and genotoxicity in liver of male rats. *J Basic Clin Physiol Pharmacol*. 2019;30(2):219-232.
DOI: https://doi.org/10.1515/jbcpp-2018-0064
75. Martirosyan D, Alvarado A. Functional foods regulation system: Proposed regulatory paradigm by functional food center. *Functional Food Science*. 2023;3(11):275-287.
DOI: https://doi.org/10.31989/ffs.v3i11.1265
76. Bińkowska W, Szpicer A, Stelmasiak A, Wojtasik-Kalinowska I, Półtorak A. Microencapsulation of Polyphenols and Their Application in Food Technology. *Applied Sciences*. 2024;14(24):11954.
DOI: https://doi.org/10.3390/app142411954
77. Ali Redha A, Kodikara C, Cozzolino D. Does Encapsulation Improve the Bioavailability of Polyphenols in Humans? A Concise Review Based on In Vivo Human Studies. *Nutrients*. 2024;16(21). DOI: https://doi.org/10.3390/nu16213625
78. Arshad Z, Shahid S, Hasnain A, Yaseen E, Rahimi M. Functional Foods Enriched with Bioactive Compounds: Therapeutic Potential and Technological Innovations. *Food Science & Nutrition*. 2025;13(10):e71024.
DOI: https://doi.org/10.1002/fsn3.71024
79. Atalay EÇ, Demirhan BE, Celep AGS. Low-Calorie Sweeteners and Reproductive Health: Evidence and Debates. *Curr Nutr Food Sci*. 2025;21(3):309–332.
DOI: https://doi.org/10.2174/0115734013315621240802055207