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Oxidative stress induced by some preservatives and the protective effects of dietary bioactive compounds

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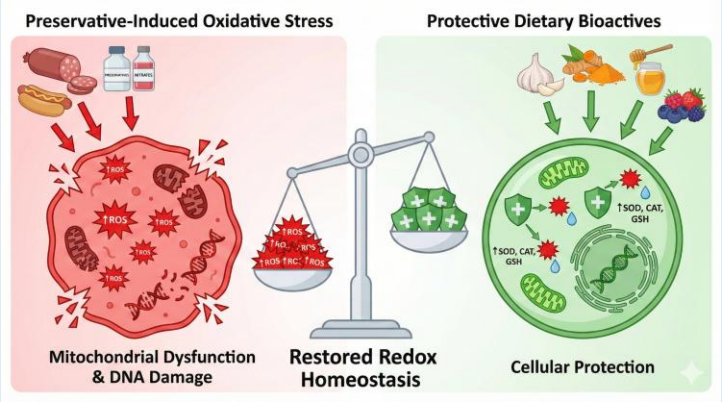
ABSTRACT

Food preservatives such as nitrites, nitrates, sodium benzoate, and synthetic phenolic antioxidants are widely used to enhance the safety, stability, and sensory properties of foods. Despite these benefits, increasing evidence indicates that chronic or high-dose exposure to preservatives may induce oxidative stress, which plays a central role in the pathogenesis of cancer, metabolic disorders, and reproductive dysfunction. This review summarizes findings from animal, in vitro, and human studies on the relationship between preservatives and oxidative stress, with a focus on nitrites in processed meats and sodium benzoate. Experimental data consistently demonstrate increased lipid peroxidation, suppression of endogenous antioxidant enzymes, mitochondrial dysfunction, and apoptosis following high-dose preservative exposure, although these doses often exceed typical human dietary intake. Epidemiological studies support the association between nitrite-derived N-nitroso compounds and colorectal carcinogenesis, aligning with the International Agency for Research on Cancer (IARC) classification of processed meats as Group 1 carcinogens. In contrast, dietary bioactive compounds such as garlic oil, honey, Nigella sativa, curcumin, berberine, omega-3 fatty acids, and polyphenols have shown protective effects by modulating oxidative pathways and restoring redox balance. However, most of these benefits are observed at pharmacological levels, raising concerns about their practical relevance in human diets. Unlike previous reviews that focus solely on the toxicity of preservatives, this study uniquely integrates the mechanistic

evidence of preservative-induced oxidative stress with the mitigating potential of functional food-based dietary strategies. Overall, preservatives may act as pro-oxidants under certain conditions, while antioxidant-rich dietary patterns may offer protective potential. Further human-based studies at realistic exposure levels are essential to strengthen risk assessment and guide public health recommendations.

Keywords: Preservatives; Oxidative Stress; Antioxidants; Bioactive Compounds; Nutrition.



Graphical Abstract: Oxidative stress induced by some preservatives and protective effects of dietary bioactive compounds

INTRODUCTION

Food additives are widely used to improve the shelf-life, safety, and sensory properties of foods [1]. However, concerns have been raised regarding the potential adverse health effects of additives commonly present in processed and packaged foods, particularly their capacity to induce oxidative stress, a key factor in the development of chronic diseases associated with unhealthy dietary patterns [2–4], especially when considering concurrent environmental exposure to mutagens [5].

Among different categories of additives, preservatives such as nitrites, nitrates, and sodium benzoate are frequently used and have been extensively studied for their impact on oxidative stress pathways. Although different classes of food additives, such as sweeteners, colorants, and flavor enhancers, have been associated with oxidative stress, this review primarily focuses on preservatives due to the relatively higher number of studies and widespread human exposure. Regulatory authorities, including the European Food Safety Authority (EFSA), have also set acceptable daily intakes (ADIs) for these compounds, which vary considerably: 5 mg/kg bw/day for sodium benzoate, and only 0.07 mg/kg bw/day for sodium nitrite, reflecting its higher potential risk [6–8].

Processed meat products (e.g., bacon, ham, sausages, deli meats) are a major dietary source of added nitrites and nitrates used for curing and preservation [9-10]. Epidemiological evidence has linked processed meat consumption to increased colorectal cancer risk, and nitrite-derived N-nitroso compounds are considered a plausible mechanistic pathway [11]. Some studies have shown that the intake of nitrites and nitrates from processed meat consumption can exceed the ADI values set by EFSA, particularly in individuals with high

consumption of such products [12–14]. Therefore, focusing on nitrites in the context of processed meat consumption is both timely and relevant for public health.

This review provides a unique perspective by integrating evidence on preservative-induced oxidative stress with the potential protective role of nutrition, highlighting not only mechanistic insights but also the importance of antioxidant-rich dietary patterns in mitigating these risks. Recent frameworks in functional food science emphasize the critical role of these bioactive compounds in managing chronic disease risks [15].

METHODOLOGY

A narrative literature review was conducted to synthesize evidence regarding the impact of food preservatives on oxidative stress and the protective potential of dietary bioactive compounds. A comprehensive search was performed in PubMed, Scopus, Web of Science, and Google Scholar databases covering the period up to December 2024. The search strategy utilized combinations of the following keywords: nitrite, nitrate, processed meat, sodium benzoate, preservatives, oxidative stress, lipid peroxidation, antioxidants, and bioactive compounds. The selection criteria were defined to include original research articles, encompassing in vivo animal studies, in vitro models, and human trials, that explicitly reported quantitative data on oxidative stress biomarkers (e.g., MDA, SOD, CAT, GSH) in response to preservative exposure, provided the articles were published in English. Conversely, conference abstracts, editorials, letters without full-text availability, duplicate publications across databases, and studies lacking specific data on redox parameters were excluded. Throughout the selection process, priority was given to studies that offered mechanistic insights into mitochondrial dysfunction and apoptosis, as well as those evaluating the remedial effects of functional food components.

Preservatives: Preservatives, which are widely used in the food industry, are a group of food additives whose effects on oxidative stress have been investigated. Table 1 summarizes numerous studies investigating the effects of preservatives on oxidative stress and related biomarkers. These studies highlight the impact of different preservatives, such as nitrites, nitrates, and sodium benzoate, on health parameters.

Table 1. Animal Studies Investigating the Relationship Between Preservatives and Oxidative Stress.

Sodium Nitrite Sodium Benzoate [16]	80 mg/kg 200 mg/kg 8 weeks	Male albino rats	Liver	Overproduction of p53 in the sodium nitrite group ↑ AST and ALT levels. ↓ antioxidants and ↑ MDA levels
Sodium Nitrite [17]	20, 40, 60, 75 mg/kg (Acute oral)	Male Wistar rats	Liver and kidney	↑ MDA, AST, and ALT levels ↓ SOD, CAT and GSH levels
Sodium Benzoate [18]	0.56, 1.125, and 2.25 mg/mLm 4 weeks	Male Swiss albino mice	Brain	↓ GSH levels
Sodium Benzoate [19]	0-1000 mg/day 90 days	Male Wistar rats	Reproductive organs	↓ antioxidant enzyme activity and GSH levels
Sodium Benzoate [20]	200, 400 and 700 mg/kg 30 days	Male Wistar rats	Liver	↓ hepatic antioxidant enzyme activity

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CAT: Catalase; GSH: Glutathione; MDA: Malondialdehyde; SOD: Superoxide Dismutase.

Nitrites and nitrates, naturally present in some vegetables and commonly used as preservatives in processed meat products, have been the focus of numerous studies. High exposure levels to these preservatives have been documented in both adults and children [21–24]. For instance, a study found an association between exposure to paraben derivatives and oxidative stress biomarkers such as 8-OHdG in children [22,25]. Similarly, research involving pregnant women observed a relationship between urinary paraben derivatives and increased oxidative stress in nucleic acids and lipids [21].

Nitrites and Processed Meats: The health effects of nitrates, nitrites, and their metabolism product, nitric oxide, remain a topic of ongoing discussion [26]. Nitrates and nitrites can be converted to the carcinogen nitrosamine, and these compounds are also associated with cancer risk [27] with potential time- and age-related cumulative effects [28]. Sodium nitrite has been shown to increase apoptosis, decrease uperoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities, and elevate intracellular calcium levels [29]. However, studies also suggest that nitric oxide may offer protective benefits against cardiovascular disease due to its roles in blood flow regulation, cell signaling, and energy production [30-31].

Multiple large epidemiological studies and pooled analyses report a positive association between processed meat intake and colorectal cancer incidence; the IARC Monograph concluded that processed meat is carcinogenic to humans (Group 1). Although causality cannot be established from observational data alone, formation of N-nitroso compounds from nitrites (and heme-mediated endogenous nitrosation) provides biologically plausible mechanisms linking processed meat consumption to colorectal carcinogenesis [32].

Further studies have demonstrated the negative impacts of sodium nitrite on fertility in female mice by increasing oxidative stress [33]. High sodium nitrite administration during pregnancy has been linked to fetal brain inflammation and mitochondrial damage [34].

It should be noted that many experimental studies administer nitrite doses that greatly exceed typical human dietary exposure. The European Food Safety Authority (EFSA) established an acceptable daily intake (ADI) for nitrite of 0.07 mg nitrite ion/kg body weight/day; direct comparison of animal dosing regimens to this ADI is essential when interpreting translational relevance.

Sodium Benzoate: Sodium benzoate, a preservative widely used in foods for its antimicrobial effects, is generally considered safe. However, excessive consumption of sodium benzoate may induce oxidative stress, raising concerns about its potential health impacts [35]. In a study investigating the hazardous effects of sodium nitrite and sodium benzoate, rats were administered sodium nitrite (80 mg/kg body weight) and sodium benzoate (200 mg/kg body weight) for 8 weeks. The study found that both sodium nitrite and sodium benzoate, as well as their mixture, caused a critical increase in serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Additionally, antioxidant chemicals (glutathione [GSH], CAT) decreased, while malondialdehyde (MDA) activity and tumour suppressor p53 protein levels increased in liver tissue. The mixture of sodium nitrite and sodium benzoate also led to changes in biochemical parameters and immune histopathology [16]. Another animal study reported that oxidative damage induced by sodium nitrite increased in a dose-dependent manner (20, 40, 60, and 75 mg/kg) in the liver and kidneys. The expression levels of caspase 3 and Bax were found to be increased, particularly at high doses [17]. Sodium benzoate

administered orally to mice at various doses (0.56, 1.125, and 2.25 mg/mL) for 4 weeks caused a decrease in GSH levels and an increase in MDA levels in the brains [18]. Similarly, prolonged exposure to sodium benzoate (0-1000 mg/kg body weight) for 90 days inhibited antioxidant enzyme activity and GSH levels while increasing oxidative stress, suggesting adverse effects on the reproductive system [19].

Considering the widespread use of sodium benzoate, these results are particularly relevant in terms of consumers' exposure. However, another study showed that administering sodium benzoate at various doses (70-700 mg/kg body weight) for 30 days in rats decreased GSH-Px, CAT, glutathione S-transferase (GST), glutathione reductase (GR), and SOD activities in liver tissue, but this effect was not seen at the higher dose of 70 mg/kg. The researchers emphasized the need for long-term studies to understand the effect of sodium benzoate at lower doses [36], also in light of its recently suggested beneficial potential in neuropsychiatric disorders [37].

In the study investigating the effects of different food additives on oxidative stress markers and liver enzymes, aspartame, sodium benzoate, sodium nitrite, and sodium sulphite were administered to thirty Wistar rats at a dose of 20 mg/kg body weight for 30 days. As a result, ALT increased significantly with sodium nitrite and sodium sulphite, and alkaline phosphatase (ALP) increased significantly ($p<0.05$) with sodium sulphite. CAT, a marker of oxidative stress, increased significantly with sodium benzoate and sodium sulphite. At doses of 20 mg/kg body weight, the toxicity of food additives was ranked as follows: Sodium Nitrite > Sodium Benzoate > Sodium Sulphite > Aspartame [16].

Synthetic Phenolic Antioxidants: Butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tertiary butyl hydroquinone (TBHQ) are used as preservatives in the food industry, particularly for the preservation of fatty foods [38–40], although recent studies have shown they may exert protective effects against experimental liver damage [41]. However, high levels of these compounds cause carcinogenicity, cytotoxicity, oxidative stress induction, and endocrine-disrupting effects [40,42]. However, some studies have suggested that BHA and BHT can reduce reactive oxygen species (ROS) levels and necrosis of cells. BHA has also been found to be able to act as a direct RIPK1 inhibitor to prevent tumor necrosis factor (TNF) cytotoxicity [43]. Therefore, the relationship between BHA, BHT, and oxidative stress is a complex issue and requires further research to be fully understood.

Oxidative Stress and Antioxidants: Diet may play an important role in regulating oxidative stress [44-45], aging *per sè* being a further limiting factor [46]. Dietary habits with high consumption of processed foods, refined carbohydrates, and saturated fats, high-calorie intake, or poor nutrition can lead to increased oxidative stress [47-48]. Oxidative stress is thought to be the mechanistic link between obesity and its associated complications [49]. However, dietary intake of antioxidant elements in a healthy diet can contribute to the reduction of oxidative stress by neutralizing free radicals [50]. Bioactive compounds are found in foods such as fruit, vegetables, whole grains, and legumes, and can modulate oxidative stress and inflammation pathways [51]. Vegetables and fruits, nuts, oilseeds, spices, and herbs are rich in antioxidants [15]. It has been shown in rats that dietary intake of phenolic acids can improve metabolic syndrome and oxidative stress biomarkers induced by a high-fructose diet [52-53]. Some studies have shown a negative relationship between the consumption of fruits with high anthocyanin content and oxidative stress and inflammation [54–58].

How nutrients prevent oxidative stress is not fully understood in detail. However, several molecular mechanisms have been proposed. Nutrients with antioxidant properties may prevent oxidative damage by directly interacting with free radicals [59]. Some nutrients can increase the production and activity of endogenous antioxidant enzymes. Nutrients can regulate cellular redox status by modulating key signalling pathways involved in the production and scavenging of ROS, such as the mitogen-activated protein kinase (MAPK) pathway and the NF-κB pathway [60]. In addition, many nutrients such as folic acid, B12, and zinc participate in DNA synthesis and repair [61-62].

In some studies, antioxidant nutrients were used in combination with food additives, and the potential of antioxidants to reduce oxidative stress caused by food additives was examined. These studies are summarized in Table 2.

Table 2. Effects of Antioxidant Foods on Oxidative Stress Caused by Food Preservatives.

1-2% L-Arginine and L-glutamine 6 weeks Oral [63]	0.2% Sodium nitrite 6 weeks Oral	Male albino rats	Sodium nitrite ↑ serum MDA levels, nitric oxide, arginase, GST activities, urea, and creatinine, and ↓ GSH, CAT activity, total protein, albumin, and some haematological parameters. Arginine or glutamine resulted in a significant improvement in these abnormalities, with ↓ MDA and improvement of antioxidant and hematologic parameters.
5 ml/kg garlic oil 3 months Oral [64]	Sodium nitrite 80 mg/kg 3 months Oral	Male albino rats	Sodium nitrite ↑ lipid peroxidation, ↓ CAT activity and GSH levels in the liver and kidney Garlic oil has shown improvements in oxidative parameters.
5 ml/kg garlic oil 3 months Oral [65]	Sodium nitrite 80 mg/kg 3 months Oral	Male albino rats	Sodium nitrite ↓ AChE activity as well as phospholipid, total protein, and GSH and SOD levels in serum and brain homogenates. Garlic oil significantly improved neurobiochemical impairments and ↓oxidative stress
70 mg/kg *Chlorella vulgaris* 3 months Oral [66]	Sodium nitrite 80 mg/kg 3 months Oral	Male albino rats	Sodium nitrite induced alterations in IL-1β, TNF-α, and liver enzymes. *Chlorella vulgaris* ↓ oxidative stress and inflammation in the liver.
0.5 g/kg *Thymus vulgaris* 15 days Oral [67]	Sodium nitrite 60 mg/kg on day 14 Oral	Mice	Sodium nitrite ↑ MDA, IL-1β, IL-6, and TNF-α levels. *Thymus vulgaris* has been shown to exhibit protective effects against sodium nitrite-induced hepatic oxidative stress.
0.5 g/kg *Thymus vulgaris* 15 days Oral [68]	Sodium nitrite on day 14 intraperitoneally	Male Swiss mice	Sodium nitrite ↑ Kim-1 and TNF-α mRNA expression in $NaNO_2$-induced nephritis. ↑ Bax immunoreactivity and apoptosis in renal structures. Pretreatment with thyme extract reversed its effects on tissue and serum antioxidants.
15 mg/kg glycyrrhizic acid 3 months Oral [69]	Sodium nitrite 80 mg/kg 3 months	Male albino rats	Glycyrrhizic acid facilitated a decrease in MDA, TNF-α, and IL-1β levels induced by sodium nitrite in the lung and salivary glands. It exhibited antioxidant and anti-inflammatory effects in the studied tissues.
100 mg/kg carnosine and N-acetylcysteine 7 and 5 days (Before the sodium nitrite administration) [70]	Sodium nitrite 60 mg/kg one dose Oral	Male Wistar rats	Sodium nitrite ↑ intestinal damage. Pretreated with carnosine and N-acetylcysteine, this oxidative damage was mitigated.

20 mg/kg curcumin 28 days Oral [71]	Sodium nitrite 60 mg/kg 28 days Oral	Male Wistar rats	Sodium nitrite exhibits nephrotoxic effects. Curcumin at acceptable doses can improve lipid peroxidation and alleviate kidney damage.
50-100 mg/kg Berberine 60 days Oral [72]	Sodium nitrite 80 mg/kg 60 days Oral	Male albino rats	Sodium nitrite ↑ MDA levels and ↓ GSH, SOD, GSH-PX, and CAT levels. 100 mg/kg of berberine significantly improved antioxidant biomarkers.
4% PUFA ω-3 19 days Oral [34]	Sodium nitrite (0.05%, 0.15%, and 0.25%) Oral	Pregnant albino rats	Exposure to sodium nitrite during pregnancy resulted in brain damage in fetal rats. Omega-3 fatty acids ↓ oxidative stress and brain inflammation.
25 and 50 mg/kg thymoquinone Oral [73]	Sodium nitrite 80mg/kg Oral	Male albino rats	Sodium nitrite induced renal toxicity and ↑ oxidative stress biomarkers. Thymoquinone, in a dose-dependent manner, attenuated renal toxicity by reducing oxidative damage and promoting recovery.
400 µg/mice/day Curcuma longa Oral [74]	Butylparaben 150 µg/g postnatal day 35 to 65 Oral	Prepubertal mice	Butylparaben ↑ lipid peroxidation and ↓ SOD and CAT levels. Curcuma longa has exhibited a protective effect against these adverse effects.
100 mg/kg Ascorbic acid 28 days Oral [75]	Sodium benzoate 150,300 and 600 mg/kg 28 days Oral	male Wistar rats	Sodium benzoate ↓antioxidant enzyme activities and an ↑ MDA, TNF-α, and Caspase-3 levels in the brains of rats. Ascorbic acid reversed these effects.
200 mg/kg Cymbopogon citratus ethyl acetate and Ficus carica hexane leave extract. Oral [76]	Sodium benzoate 200 mg/kg 6 weeks Oral	male albino rats	Sodium Benzoate ↓ insulin and SOD levels. Cymbopogon citratus ethyl acetate extract and Ficus carica hexane leaf extract of attenuated the oxidative damage
10 µM Catechin 10 µM Quercetin [77]	Sodium benzoate 6.25, 12.5, 25, 50, and 100 µg/mL	human erythrocytes (in vitro)	Sodium benzoate ↑ lipid peroxidation and ↓ antioxidant enzyme activities. Catechin and quercetin prevent sodium benzoate-induced toxicity in erythrocytes only at low concentrations of sodium benzoate.

Studies show that sodium nitrite can potentially increase oxidative stress and have negative effects on the antioxidant system. However, it has been shown that oxidative stress caused by sodium nitrite can be reduced by antioxidant elements such as l-arginine, l-glutamine, nigella sativa, honey, garlic oil, *thymus vulgaris*, glycyrrhizic acid, berberine, curcumin, thymoquinone [63,69,71–73,78-79] .The antioxidant properties of these compounds may contribute to the neutralization of free radicals, the regulation of cellular antioxidant systems, and the prevention of cell death. An in vitro study demonstrated that taurine exhibits protective effects against oxidative damage induced by sodium nitrite in human erythrocytes [80]. Supplementation with selenium may reduce oxidative damage caused by sodium nitrite by attenuating intracellular calcium ion imbalance, reducing antioxidant imbalance within cells, and preventing apoptosis, thereby mitigating oxidative stress [29]. Honey may exhibit protective effects against oxidative stress induced by sodium nitrite, tartrazine, or sunset yellow [78,81].In a study investigating the adverse effects of sodium nitrite and sunset yellow on the liver, the protective role of treatment with Nigella sativa (black seed) and honey against these adverse effects was examined. It was observed that sodium nitrite and sunset yellow application caused an increase in lipid levels in the liver and also caused changes in liver enzymes, but when black seed and honey were given together, these

negative effects were significantly ameliorated [78]. A study conducted on male albino rats demonstrated that administration of sodium nitrite at a dose of 80 mg/kg for 60 days induced changes in oxidative stress biomarkers in erythrocytes. However, simultaneous treatment with berberine at a dose of 100 mg/kg showed improvement in these markers. On the other hand, treatment with a lower dose of berberine (50 mg/kg) did not result in significant improvement in antioxidant markers [72]. In separate studies, the administration of sodium nitrite at a dosage of 80 mg/kg body weight to rats over a period of 3 months resulted in notable effects. These effects included a significant elevation in serum glucose, AST, ALT, ALP, bilirubin, urea, and creatinine levels. Furthermore, sodium nitrite administration led to increased levels of IL-11β and TNF-α, elevated MDA levels and lipid peroxidation, as well as a reduction in GSH content and CAT activity [66,82]. However, garlic oil and *Chlorella vulgaris* administrations ameliorated these harmful effects [66,78]. Garlic oil (5 ml/kg body weight) administration corrected these harmful effects, decreased serum glucose, bilirubin, urea and creatinine levels, and decreased the activity of AST, ALT and ALP enzymes [78]. Another study highlighted the neuroprotective potential of garlic oil, consistent with its known hepatoprotective effects [83]. In male albino rats administered 80 mg/kg sodium nitrite daily for three months, significant reductions were observed in AChE activity and phospholipid levels, alongside depleted endogenous antioxidants such as GSH and SOD [83]. However, in rats given 5 ml/kg body weight of garlic oil once a day, neurobiochemical disorders caused by sodium nitrite were significantly improved and oxidative stress was prevented. This may be related to the preservation of SOD activity and the primary mitochondrial role against nitrite-induced neurotoxicity [65]. Similarly, Elsherbini et al. demonstrated that chronic administration of nitrite at a dose equivalent to acceptable human intake (80 mg/kg) resulted in oxidative damage in the lungs and salivary glands of animals. However, simultaneous administration of glycyrrhizic acid was shown to alleviate this oxidative damage, suggesting its potential therapeutic role in mitigating nitrite-induced oxidative stress in these organs [69]. It has been demonstrated that carnosine and N-acetylcysteine exhibit protective effects against oxidative stress and DNA damage induced by acute administration of sodium nitrite in rat intestines. These compounds have shown the ability to mitigate the detrimental effects of sodium nitrite on oxidative balance and DNA integrity in the intestinal tissue [70]. The study, in which carnosine and N-acetylcysteine were administered to animals prior to sodium nitrite administration, reported the chemoprotective effects of these two compounds. Pretreatment with carnosine and N-acetylcysteine shows their potential to prevent or reduce the harmful effects of oxidative stress and DNA damage caused by sodium nitrite [70]. The animal models have demonstrated that *Thymus vulgaris*, when administered acutely, exhibits protective effects against sodium nitrite-induced oxidative damage in the liver and kidneys [67-68].

In an in vitro study, the protective effect of catechin and quercetin against sodium benzoate-induced oxidative stress in human erythrocytes was investigated. Depending on the dose of sodium benzoate, lipid peroxidation increased, and antioxidant enzyme activities decreased with increasing dose. Quercetin and catechin showed a protective effect at low concentrations of sodium benzoate. However, they did not show a protective effect at high sodium benzoate concentrations (50-100 µg/mL) [77]. In another animal study, it was demonstrated that co-administration of 600

mg/kg sodium benzoate with 100 mg/kg ascorbic acid exhibited protective effects against oxidative stress in the brains of the animals [75].

Nutrition and Antioxidant-Rich Diets: Experimental studies typically evaluate the effects of isolated antioxidants such as curcumin, berberine, or garlic oil against oxidative stress caused by protective substances, but real-life dietary habits may provide broader and more sustainable protection. Antioxidants in the diet act synergistically, and their benefits cannot be fully replicated with single-compound supplements. These concepts are among the educational targets of Functional Food Center, a long-standing not-for-profit independent scientific organization in the USA [84–86].

Epidemiological studies consistently show that adherence to diets rich in fruits, vegetables, legumes, whole grains, nuts, and olive oil, such as the Mediterranean diet, is associated with reduced oxidative stress and inflammation and a lower incidence of chronic diseases. For example, polyphenols, carotenoids, vitamins C and E, and trace elements such as selenium and zinc interact within complex nutritional matrices to modulate endogenous antioxidant defenses and maintain redox homeostasis [3-4,87]. Therefore, rather than relying on isolated compounds, promoting antioxidant-rich dietary habits should be considered a fundamental strategy for balancing the oxidative burden of food preservatives. There is increasing evidence regarding the relationship between gut microbiota and oxidative stress, both at an experimental level and clinical inferences [88–90]. Although the specific implications of this factor with preservatives metabolism remain to be ascertained, a proper protection from concomitant dysbiosis can be advisable [91-92].

This approach highlights the importance of comprehensive nutrition-based interventions and public health recommendations that promote fresh, minimally processed foods over packaged products.

DISCUSSION

The studies reviewed in this article strongly demonstrate the association between nitrites and oxidative stress. However, the doses used in animal experiments (e.g., 60–80 mg/kg) are far above the ADI established by EFSA (0.07 mg/kg) [64,66]. This indicates the need for caution when interpreting the relevance of these findings to humans. Although the individual toxicological effects of preservatives have been extensively studied, this review presents a novel synthesis that highlights a dual approach to risk reduction by comparing these risks with the protective mechanisms of specific food bioactives.

From an epidemiological perspective, the association between processed meat consumption and colorectal cancer risk has been consistently reported [93]. At the mechanistic level, N-nitroso compounds derived from nitrites and heme-mediated endogenous nitrosation processes provide a plausible explanation for this risk [27].

As also shown in the tables, nitrites can induce toxic effects in various organ systems: increased p53 expression and elevated liver enzymes, apoptosis in the kidneys, impaired reproductive functions, and mitochondrial damage in the fetal brain [16,19,33-34]. This wide spectrum of effects highlights oxidative stress as a multifaceted damage mechanism.

On the other hand, the protective effects of various antioxidant compounds have been repeatedly demonstrated. Dietary bioactive compounds have been shown to modulate oxidative stress and inflammation through redox-sensitive signaling pathways, supporting cellular defense against ROS [51]. Bioactive compounds in functional foods exert protective effects by preventing mitochondrial dysfunction, maintaining redox homeostasis, and enhancing antioxidant enzyme

activities. Natural compounds such as garlic oil, Nigella sativa and honey, curcumin, berberine, and omega-3 fatty acids have been shown to alleviate nitrite-induced oxidative stress in experimental models [34,64-65,71-72,78]. Nevertheless, most of these effects were observed at pharmacological doses, and their achievability through normal dietary intake remains questionable. In this context, standardized dietary supplements and nutraceuticals may offer a more controlled delivery method for these beneficial compounds to bridge the gap between dietary intake and therapeutic effects [94].

Importantly, these findings align with the functional foods paradigm, which posits that bioactive food components provide health benefits beyond basic nutrition. Constituents such as polyphenols, carotenoids, and omega-3 fatty acids can modulate redox signalling and inflammation at nutritionally achievable intakes [95].

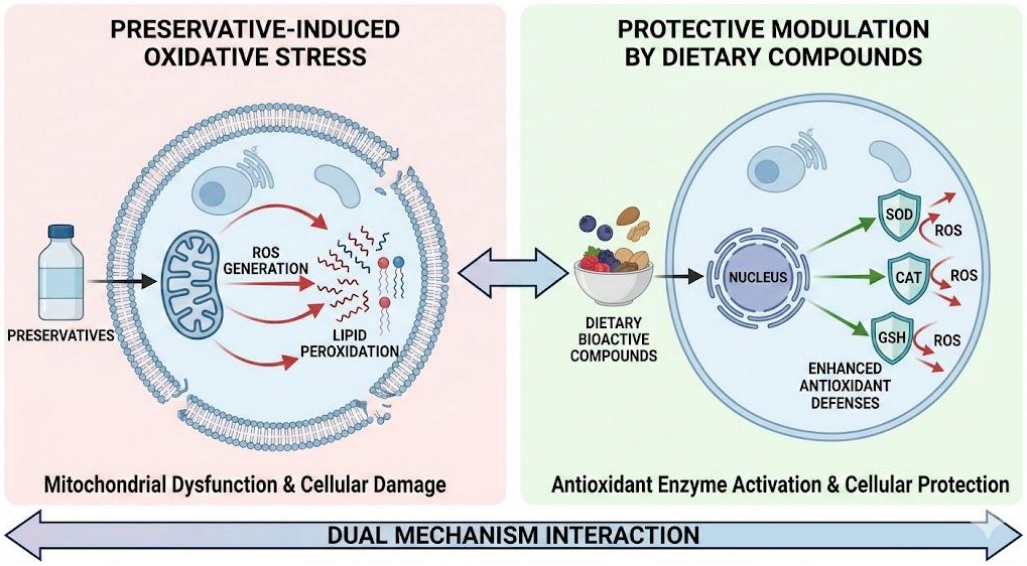


Figure 1. Schematic representation of the dual mechanism: Preservative-induced oxidative stress pathways (ROS generation, mitochondrial dysfunction, lipid peroxidation) and the protective modulation by dietary bioactive compounds through the enhancement of endogenous antioxidant defenses (SOD, CAT, GSH).

Mechanistically, a growing body of evidence shows that many dietary bioactives act through conserved redox-sensitive pathways — notably activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant response, inhibition of NF-κB pro-inflammatory signalling, and modulation of mitochondrial function — providing plausible links between habitual dietary patterns (e.g., Mediterranean-type, polyphenol-rich diets) and attenuation of preservative-induced oxidative damage [95]. Thus, while preservatives may experimentally promote ROS overproduction and mitochondrial dysfunction, functional-food-derived bioactives appear to counteract these processes by upregulating cytoprotective genes (Nrf2 targets) and downregulating pro-apoptotic/inflammatory signaling (e.g., NF-κB), offering a mechanistic rationale for dietary mitigation strategies [95]. Furthermore, recent reviews highlight the diverse potential of agricultural and food-derived bioactives in enhancing these specific protective mechanisms against oxidative stress [96-97].

Considering the heterogeneity among studies (animal species, dosage, duration, route of administration, biomarkers used), the generalizability of

the findings is limited. Future studies conducted with doses closer to human exposure levels and standardized protocols are of great importance.

From a public health perspective, the evidence supports limiting frequent consumption of processed meats as part of cancer prevention strategies. Regulatory ADIs (e.g., EFSA 0.07 mg/kg bw/day) and food-level nitrite limits are important, yet cumulative exposure from multiple sources (and endogenous nitrosation) merits further human exposure assessment and public education on processed meat consumption [98].

Future Perspectives: Future research should move beyond high-dose experimental models and focus on exposure levels closer to daily human consumption. Particular attention should be given to natural preservatives, which may offer antimicrobial efficacy without contributing to oxidative stress. Furthermore, translational research should evaluate functional-food-based interventions and natural bioactive preservatives as complementary strategies. These approaches aim to reduce exogenous nitrosating agents in foods while enhancing dietary antioxidant defenses. Indeed, recent reviews have identified scalable methods to replace or complement nitrites using plant-derived antimicrobials [99].

Additionally, accurate assessment of preservative intake requires integration of dietary records with food composition databases, allowing evaluation of both individual additive exposure and cumulative intake within dietary patterns. From a public health standpoint, studies combining preservative intake data with dietary quality and antioxidant intake are needed to better understand real-world interactions and to guide nutrition policies.

CONCLUSION

In conclusion, long-term and high doses of preservatives may lead to increases in biomarkers of oxidative stress in various tissues. Previous studies have investigated the effects of high doses of food additives and highlighted potential health effects. However, it should be noted that the doses used in these studies may not reflect realistic human exposure levels. More research is needed on human exposure levels to food additives. It should also be noted that people consume many different additives in their daily diets. Therefore, more extensive studies are needed to better understand the interactions and complex effects of additives together. Additionally, studies have shown that certain antioxidant compounds can reduce oxidative stress when used in conjunction with food additives. However, the effect of these compounds is often found to occur at high doses, and this level of intake may not be achievable through a normal diet. Therefore, it is important to adopt a comprehensive approach to nutrition, which requires a varied, adequate, and balanced diet that includes antioxidant-rich foods. In addition, the consumption of processed, packaged foods is rising steadily; thus, individuals need to improve their label-reading skills and raise awareness about healthy eating. On the other hand, reducing the consumption of packaged foods can be a difficult goal, but progress can be made by promoting informed choices and healthy lifestyles. In this context, individuals should be provided with appropriate dietary guidelines and encouraged to replace processed products with fresh and natural foods. At the same time, it is important to raise public awareness and reduce the consumption of packaged foods through campaigns and educational programs. To reduce the potential adverse effects of food additive consumption, the use of natural food additives instead of artificial food additives in the processing of packaged foods should be encouraged. Overall, while experimental studies indicate potential oxidative risks at high doses, real-world exposure is generally lower. Therefore, population-based dietary strategies emphasizing

antioxidant-rich diets may represent a practical approach to mitigating potential harms. Practically, population-level strategies that combine reduced exposure to added nitrites in processed foods with promotion of antioxidant-rich functional foods may offer a feasible approach to lower oxidative burden and long-term disease risk.

Abbreviations: The following abbreviations are utilized throughout this article to describe biochemical markers, regulatory bodies, and chemical compounds:

8-OHdG: 8-Hydroxy-2'-deoxyguanosine

AChE: Acetylcholinesterase

ADI: Acceptable Daily Intake

ALP: Alkaline Phosphatase

ALT: Alanine Aminotransferase

AST: Aspartate Aminotransferase

BHA: Butylated Hydroxyanisole

BHT: Butylated Hydroxytoluene

CAT: Catalase

DNA: Deoxyribonucleic Acid

EFSA: European Food Safety Authority

GR: Glutathione Reductase

GSH: Glutathione

GSH-Px: Glutathione Peroxidase

GST: Glutathione S-transferase

IARC: International Agency for Research on Cancer

IL-1β: Interleukin 1 beta

IL-6: Interleukin 6

Kim-1: Kidney Injury Molecule-1

MAPK: Mitogen-activated protein kinase

MDA: Malondialdehyde

NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

Nrf2: Nuclear factor erythroid 2-related factor 2

PUFA: Polyunsaturated Fatty Acids

RIPK1: Receptor-interacting serine/threonine-protein kinase 1

ROS: Reactive Oxygen Species

SOD: Superoxide Dismutase

TBHQ: Tertiary butyl hydroquinone

TNF: Tumor necrosis factor

TNF-α: Tumor necrosis factor alpha

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