Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

A rethinking of nitrate, nitrite, and nitric oxide for food preservation and human health

Xiaojing Tian[a,b], Yanan Tian[a,b], Lele Shao[c], Yu Li[d], Shaohua Meng[e], Jiansheng Zhao[e], Wenhang Wang[a,b,*]

[a] Tianjin Key Laboratory of Food Quality and Health, Tianjin University of Science & Technology, Tianjin 300457, China

[b] College of Food Science and Engineering, Tianjin University of Science & Technology, Tianjin 300457, China

[c] Key Laboratory of Jianghuai Agricultural Product Fine Processing and Resource Utilization, Ministry of Agriculture and Rural Affairs, Anhui Engineering Research Center for High Value Utilization of Characteristic Agricultural Products, College of Tea & Food Science and Technology, Anhui Agricultural University, Hefei 230036, China

[d] College of Biotechnology, Tianjin University of Science & Technology, Tianjin 300457, China

[e] Henan Shuanghui Investment & Development Co., Ltd., Luohe 462000, China

ARTICLE INFO

Article history:
Received 18 September 2024
Received in revised form 6 October 2024
Accepted 11 October 2024

Keywords:
Nitrate
Nitrite
Nitric oxide
Food preservation
Human health

ABSTRACT

Nitrate and nitrite, as long-standing additives used in food industry and particularly prevalent in meat products, are often perceived negatively by consumers due to their potential to produce carcinogenic nitrosamines. Within the past decades, the importance of nitric oxide (NO) has been established for human health, including cardiovascular health, immunizing and defending system, skeletal muscle contraction and relaxation, nervous system, and cognitive function. Gradually, nitrate and nitrite, as the main NO donors, have also been demonstrated to have numerous health benefits in clinical studies. Likewise, NO has showed positive effect on postharvest fruits and vegetables. In view of different controversies, this review comprehensively discussed the effect of nitrate, nitrite on meat products and NO on fruits and vegetables, the intake of nitrate and nitrite by diet, the physiological functions, synthesis and metabolism of nitrate, nitrite, and NO in human body. It is hoped to provide some new understanding for nitrate, nitrite, and NO in food preservation and human health.

© 2026 Beijing Academy of Food Sciences. Publishing services by Tsinghua University Press. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

In a variety of food preservatives, nitrate and nitrite still occupy a "dominant" position and are the most commonly food additives, especially in meat products. They can endow meat products stable color, inhibit microbial growth, improve flavor, and reduce lipids oxidation[1-3]. However, nitrite can interact with amino acids and secondary amines to produce *N*-nitrosamine compounds, most of which possess strong carcinogenicity[4]. As the awareness of food safety and the popularity of green food concept grow, the attitudes of consumers toward nitrate and nitrite have become increasingly negative. Consequently, the researchers and the food industry are focusing on an important issue: maintaining the flavor and functional characteristics of meat products while reducing or eliminating the use of nitrate and nitrite. Over the years, some researchers have been investigating effective or equivalent substitute for nitrate and nitrite, but so far, they have not found a complete substitute that can simultaneously play a role in color development, microbial inhibition, flavor enhancement, and oxidant resistance[2,5-7]. Likewise, as a degradation product of nitrate and nitrite, nitric oxide (NO) is increasingly applied in postharvest fruits and vegetables, including delaying softening and senescence, reducing chilling injury, and improving disease resistance[8-9].

Since the discovery of NO, its important physiological functions have been recognized increasingly. The role of NO is extremely extensive, generally, as a messenger or regulatory factor, participates in many physiological activities in human body, including the cardiovascular system, central nervous system, gastrointestinal tract, immune response and so on[10-12]. Due to its influence on physiological

* Corresponding author at: Tianjin Key Laboratory of Food Quality and Health, Tianjin University of Science & Technology, Tianjin 300457, China.
E-mail address: wangwenhang@tust.edu.cn (W.H. Wang)

Peer review under responsibility of Beijing Academy of Food Sciences.

SciOpen Publishing services by Tsinghua University Press

http://doi.org/10.26599/FSHW.2024.9250434

2213-4530/© 2026 Beijing Academy of Food Sciences. Publishing services by Tsinghua University Press. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

functions, no matter its insufficient or excessive generation will cause diseases of organs and systems, as well as immune function abnormalities, neurotoxicity, gene mutations, tumors, etc.[13-14]. Moreover, its great potential in inhibiting the formation of different bacteria and biofilms has also been reported[15]. In biomedical field, more and more researchers have begun to pay attention to NO-based biotherapy, including NO inhalation therapy, prevention of bacterial infection and promotion of wound healing[16-18].

Dietary nitrate and nitrite intake has been demonstrated to have numerous health benefits in clinical studies, especially related to improve cardiovascular function[19]. Despite the important function of NO in many physiological systems has been established, in fact, most consumers have a negative attitude towards nitrate and nitrite. The nitrogen species formed are the subject of increasing scientific controversy with respect to their effects on human health. Therefore, this review primarily concentrates on the application of nitrate, nitrite, and NO in meat products, as well as the application of NO in fruits and vegetables. It also discusses the dietary consumption of nitrate and nitrite and the physiological functions of NO in the human body. The review aims to provide a comprehensive analysis of the impacts of nitrate, nitrite, and NO on both food preservation and human health.

2. Application of nitrate, nitrite, and NO in meat products

Nitrate and nitrite are early recognized as pivotal components affecting the color and color stability of meat, later, specific effects on microbial growth, lipid oxidation, and flavor formation have also become apparent, and in recent years, NO on meat tenderization has been reported[20-21].

2.1 Effects of nitrate, nitrite, and NO on color development

2.1.1 Promote color development

Color directly determines the economic value of meat products. The color of meat is highly dependent on the state of myoglobin. Myoglobin is composed of hemoglobin and globin. The heme group has an iron atom in the center that reversibly binds oxygen molecules, and the ligand bond in the 6th position binds different ligands, thus enduing meat a different color[22]. The 5th and 6th coordination bonds of iron ions bind F8 histidine and O_2, respectively, forming oxymyoglobin. However, when the 6th coordination bond lacks a ligand, myoglobin converts into deoxymyoglobin, resulting in a change in the apparent color of meat from a bright red to a purple-red. When myoglobin is exposed to an environment containing O_2 or oxidizing agents for an extended period, water molecules become new ligands, leading to a brownish discoloration of meat. During this process, metmyoglobin becomes the predominant species[23].

It is well known that nitrate and nitrite are very important for the color development of meat. Higuero et al.[22] found no significant difference in color between loins cured with 37.5 mg/kg NO_3^-/NO_2^- and 75, 150 mg/kg NO_3^-/NO_2^-. This suggested that better color development could be achieved with low levels of NO_3^-/NO_2^-. While in recent years, the direct use of NO has also been reported. NO has shown the potential to improve the color of fresh meat[24]. In general, NO, generated from nitrate and nitrite, is the key compound responsible for the color development of cured and fermented meat products.

2.1.2 Mechanism

In the acid system, nitrite undergoes protonation to form HNO_2, which is inherently labile and successively decomposes into N_2O_3. Subsequently, N_2O_3 undergoes further dissociation, yielding NO and NO_2. As NO interacts with heme centers of myoglobin (Fe^{2+}), it binds the heme iron atom of myoglobin to form NO-myoglobin, which is the main pink pigment for cured meat products[4]. In addition, myoglobin (Fe^{2+}) can be oxidized into metmyoglobin (Fe^{3+}) by HNO_2, which then reacts with NO to form NO-metmyoglobin. NO-metmyoglobin can be further reduced to form heat-stable NO-myoglobin by some reducing substances. Ultimately, cured meat products will exhibit a bright pink color owing to the changes in the form of NO-myoglobin to stable NO-hemochrome after heating[2].

In recent years, it has been suggested that nitric oxide synthase (NOS) may be responsible for color formation in meat products (Table 1). Two types of NOS exist in meat products, including mammalian NOS (mNOS) and bacterial NOS (bNOS). Both mNOS and bNOS are capable of producing NO. Furthermore, they have been utilized to enhance the color of meat products. The former plays a major role in the formation of the color of the nitrite-free meat products[20]. As Zhang et al.[25] reported that breast meat showed lower lightness and higher redness values after NO-enhanced treatment at 7 days of refrigeration compared to the control or NOS-inhibited groups, suggesting that the lack of NO would not maintain the pink color of meat. When NOS and arginine were added into fermented sausages, some nitroso-complex formed although none of the sausages demonstrated a bright pink color[26]. Simultaneously, the addition of bNOS to meat products has been the subject of sustained attention. For instance, Luo et al.[27] clarified the formation of NO-myoglobin by *Lactobacillus fermentum* AS1.1880 in meat was due to the NO produced by NOS activity, along with a higher redness values. As a result, bNOS has received much attention because of its potential usage for nitrite substitution. In the future, NOS can be used as an alternative ingredient to achieve nitrite-free meat products[20]. However, the application of bNOS is limited because the amount of NO generated by the bacterial cells is minimal. Furthermore, NO generated by bacteria is unstable and sensitive to environment changes. For example, the relative amount of NO-myoglobin produced in meat products with the addition of coagulase-negative staphylococci strains was as little as one-tenth of the amount produced with the addition of a curing agent (nitrite)[18]. Taken together, these factors cause it difficult to control bNOS activity[20].

2.2 Effects of nitrate, nitrite, and NO on microorganisms

2.2.1 Inhibit the microbial growth

Nitrite has been used as an antibacterial agent in food preservation for centuries. An important reason for nitrite applied in meat is that it has strong inhibitory effect on *Clostridium botulinum*. *C. botulinum* is an anaerobic, spore forming gram-negative bacterium that is widely distributed in nature. It produces the strongest toxin Botulinum neurotoxin (BoNT) in food, and the intense toxicity of BoNT has made

Table 1
The advantages and disadvantages of different NO donors.

Sources	Types	Advantages	Disadvantages	References
Inorganic NO donors	$NaNO_3$, $NaNO_2$	Cheap, easy to get.	React with secondary amines to form nitrosamines	[28]
Vegetables and fruits containing endogenous nitrate	Celery, parsley, spinach, and so on	Natural, healthy, cheap, easy to get.		[6,29-30]
Alternative NO donors	NONOates	Wide range of half-lives (1.8 s–20 h), release NO in neutral media at biological level, contain the [N(O)NO]-functional group, are considered as the most attractive candidates for practical application due to their spontaneous dissociation under physiological conditions to yield 2 mol of NO per mole of [N(O)NO]-functional group and structural flexibility of synthesis.	Carcinogen	[31-32]
	RSNOs	Exist naturally in body, their toxicity to cells and tissues is relatively low.	Sensitive to light	[33-34]
Bacteria	A few lactic acid bacteria species and most Coagulase-negative Staphylococci species	High security, natural, healthy, cheap, easy to get.	Insufficient production of NO, the bNOS pathway tends to be affected by the external environment, such as the strains species, oxygen concentration, arginine concentration, and stress conditions.	[20]

this pathogen a major food safety concern. In addition, nitrites have also shown a wide range of antibacterial effects on pathogenic and spoilage bacteria such as *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus perfringens*, and so on[3,35]. However, the antibacterial behavior of nitrite is not effective against all microorganisms, and it is more effective in inhibiting Gram-positive anaerobic bacteria as opposed to Gram-negative aerobic bacteria[3]. For example, Redondo-Solano et al.[36] suggested that the addition of more than 50 mg/kg $NaNO_2$ to pork ham could significantly inhibit the growth and germination of *Clostridium perfringens* spores, especially for the treatment group that has been refrigerated for 24 h before heat treatment or abusive cooling of ham. In addition, Liu et al. confirmed that NO gas (0, 20, 40, 60, 80 μL/L) could inhibit the total bacterial count in vacuum-packaged fresh pork (within 6 h post slaughter) refrigerated for 1, 4, and 7 days[24]. Therefore, if nitrite is converted to NO in situ, different antibacterial effects may be obtained[37].

2.2.2 Mechanism

NO, as the degradation product of nitrite, showed different antibacterial effect from nitrite. For instance, Meng et al.[38] reported that *Escherichia coli* and *Shewanella oneidensis* responded differently to nitrite and NO. However, with respect to NO-induced inhibition of microbial growth, the NO also had a different effect on different bacteria, in which the NO inhibited the growth of *E. coli* but had no significant effect on *S. oneidensis*. Even more striking, in protecting *S. oneidensis* from NO, all proteins identified as being involved in NO tolerance in other bacteria appear to play a dispensable role. In other words, there is a robust but so far unknown NO-protective system in *S. oneidensis*. For nitrite, both bacteria have cytochrome haem-copper oxidase as a physiologically relevant target[38]. This phenomenon indicated that the antibacterial mechanism of nitrite and NO is different, where the antibacterial effect of nitrite may be caused by forming peroxynitrite anion ($ONOO^-$) apart from NO[1]. Nitrite releases NO, which can act on Fe-S proteins, preventing normal cellular respiration and DNA function[39]. In addition, highly reactive $ONOO^-$ are synthesized by 2 pathways. On the one hand, oxymyoglobin is oxidized to superoxide radicals (O_2^-) under acidic conditions. NO reacts with O_2^- to form $ONOO^-$. On the other hand, nitrite reacts with H_2O_2. Subsequently, $ONOO^-$ enters the bacterial cells by passive diffusion and exerts its strong oxidative function, inducing oxidation of lipids and proteins, damaging the cell membrane and targeting DNA. As mentioned above, it is the multifactorial effect that disrupts cell physiological function and ultimately leads to the death of microorganism[40].

2.3 Effects of nitrate, nitrite, and NO on meat tenderization

2.3.1 Improve the tenderness of meat

NO has been shown to appropriately disrupt the structure and change the hardness of meat by NO donors or the addition of NOS inhibitors. Liu et al.[41] prepared myofibrils (10 mg/mL) from porcine semimembranosus muscle and incubated them with *S*-nitrosoglutathione (GSNO, 0, 20, 50, 250, and 1 000 μmol/L), which is a light-sensitive NO donor. The results showed that an increase in NO concentration would lead to a decrease in the total and free thiol content of myofibrillar proteins, which was attributed to the enhanced *S*-nitrosylation of protein sulfhydryl groups by thiols through their attachment to NO. Incubation of myofibrillar proteins with purified calpain-1 revealed that 1 000 μmol/L GSNO exhibited more degradation of desmin, suggesting that GSNO can alter the degree of protein hydrolysis by releasing NO[41]. Other studies also reported that NO and its donors increased protein *S*-nitrosylation, negatively regulating μ-calpain autolysis in postmortem meat[42-43].

2.3.2 Mechanism

NO can regulate the postmortem meat tenderness by influencing the activity of calpain and the autolysis and proteolysis of proteins.

Calpain is an enzyme that can degrade proteins, especially myofibrillar proteins, and along with the tenderness of meat is improved. Calpain is a calcium (Ca^{2+})-dependent protease and can be activated by Ca^{2+} and its activity is affected by the concentration of Ca^{2+} in muscle. Calpain is classified as μ-calpain (micromolar) or m-calpain (millimolar), depending on the concentration of Ca^{2+} required to activate this protein. Liu et al.[21] demonstrated that NO induced *S*-nitrosylation of μ-calpain, blocking μ-calpain activity and cross-linking of proteins. Simultaneously, NO and calpastatin synergistically inhibited μ-calpain activity, myofibrillar protein autolysis, and protein hydrolysis, resulting in tougher meat during postmortem aging.

The activity of calpain can be regulated by NOS in meat, since the generation of NO in skeletal muscle is to a large extent determined by the NOS. Hou et al.[44] has reported that semimembranosus muscle (vacuum-package) retained NOS activity during the 14 days storage period (4 °C), although the activity of NOS and the content of neuronal NOS (nNOS) were significantly reduced after 3 and 7 days of storage compared to 1 day. This phenomenon implied that NOS may be responsible for the generation of NO in post-mortem muscle, regulating μ-calpain activity, which then has an effect on the physicochemical properties of meat, thereby regulating meat tenderness (Fig. 1).

2.4 *Effects of nitrate, nitrite, and NO on meat flavor*

2.4.1 *Improve the flavor of meat*

Flavor is an important sensory characteristic that affects the total acceptability of meat products. The addition of nitrate and nitrite significantly reduces the extent of lipid and protein oxidation, thereby preventing the formation of undesirable compounds such as aldehydes, ketones, and peroxides, with hexanal being a key product of lipid oxidation[28]. For example, Ramarathnam et al.[45] reported that the concentrations of hexanal and carbonyl compounds, such as 3-hexanone and 2-octanone, were significantly lower in the cured meat by nitrite compared to the uncured meat. In other words, the presence of nitrite favors the flavor of meat products by inhibiting the occurrence of undesired flavor compounds. Furthermore, the role of nitrate and nitrite in meat processing extends beyond this. They influence the flavor formation of meat products during heating by inhibiting lipid oxidation. Actually, early studies have indicated that 100 mg/kg of $NaNO_2$ can exhibit the favorable antioxidant effects on pork, helping to maintain the color, texture, and flavor stability of the meat[46].

2.4.2 *Mechanism*

The effect of nitrite on meat flavor are involved in the combination of different mechanisms. Firstly, the double bonds within nitrite molecules can interact with the unsaturated bonds in meat fats, forming a relatively stable structure that slows down the rate of lipid oxidation. This interaction helps to keep the lipid stable, reducing off-flavors caused by lipid oxidation. For meat products, lipid oxidation initiates a series of chemical reactions that can alter the flavor. Volatile compounds produced during lipid oxidation, such as aldehydes, ketones, alcohols, and esters, are significant contributors to the distinctive flavors. These compounds are formed during processing and storage, exerting a marked influence on the aroma and taste of meat products. For instance, excessive lipid oxidation can lead to the development of off-flavors, such as rancidity[47]. Secondly, in the meat system, nitrites can chelate with metal ions that catalyze oxidation, such as copper and iron, forming compounds that are less likely to dissociate. This reduces the pro-oxidative effects of these metal ions during the oxidation process, enhancing the antioxidant stability of the meat[48]. Thirdly, myoglobin in meat contains iron ions

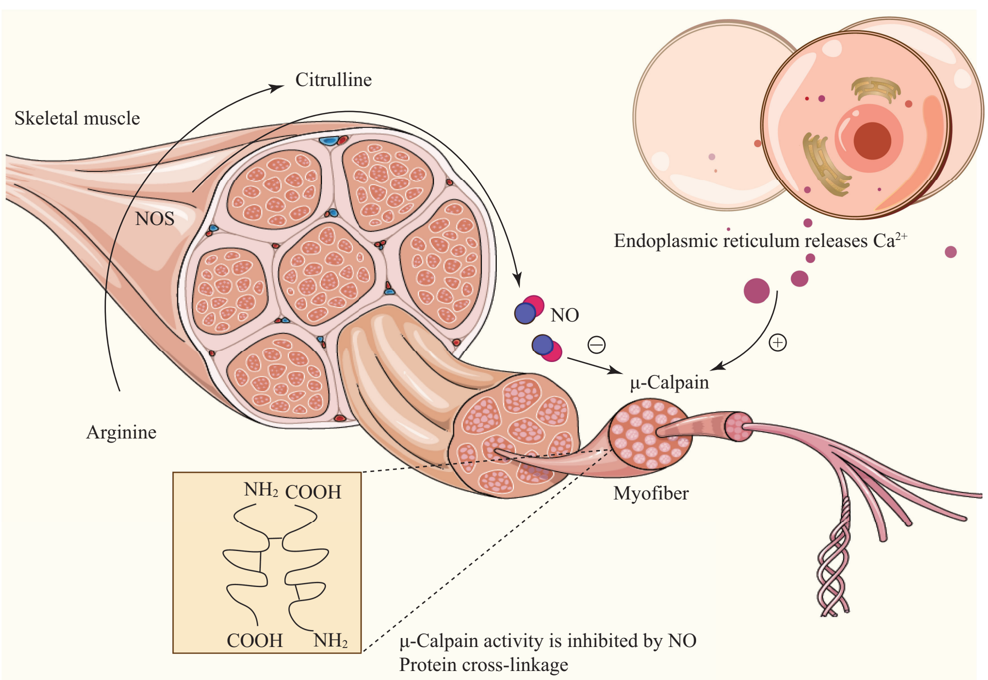

Fig. 1 NO inhibits μ-calpain (Ca^{2+}-dependent protease) activity and promotes protein cross-linkage.

that are susceptible to oxidation, and nitrites can preferentially bind these iron ions to form stable nitrosylmyoglobin complexes. These complexes not only reduce the oxidation of myoglobin itself but also prevent the chain oxidation reactions initiated by myoglobin[49]. Likewise, nitrite reacts with reactive oxygen species (ROS) or lipid peroxyl radicals to inhibit or terminate lipid oxidation[28]. Moreover, nitrite may influences the catalytic functions of endogenous enzymes in meat, such as lipases and proteases, which play crucial parts in decomposing lipids and proteins and releasing flavor precursors[48]. In addition, nitrite may indirectly influence the flavor of cured meat by affecting the structure and activity of microbial communities. These mechanisms synergistically contribute to the flavor of meat, thereby preventing the development of off-flavors.

3. Application of NO in fruits and vegetables

3.1 *Effect of NO on softening and senescence*

3.1.1 *Delay softening and senescence*

Postharvest quality deterioration interferes with the development of fruit industry. NO, as a newly emerging potential protectant, can delay fruit softening and senescence (Table 2). For example, when NO was used to fumigate 'Korla' fragrant pear during 120 days of refrigeration, the results indicated that NO treatment (20 μL/L) hindered the quality deterioration of pear, which was mainly manifested by reduction of invasion of pathogenic bacteria, decrease of accumulation of ROS, increase of epidermal waxes and enhancement of fruit hardness[8]. NO fumigation on other fruits have also yielded similar results, including strawberry, apple, mango, avocado, blueberry, grape, orange, peach, dried apricots and so on[50-53]. In addition, NO fumigation effectively reduced natural disease and moth pest incidence, decreased the total count of microorganisms, maintained higher levels of total soluble solids, ascorbic acid, reducing sugars and titratable acidity, all of which were factors that affected the quality of fruit[50,54]. Moreover, nitrate and nitrite were not significantly detected in the fruits when NO fumigation was terminated with an appropriate concentration of N_2 instead of normal air[52]. The results suggest that NO fumigation may have great potential as a safe and effective way to reduce the softness and extend the shelf life of fruits.

For vegetables, a recent study examined the effect of NO on inhibiting the softening of water bamboo shoots during storage at 4 °C for 28 days. NO-treated bamboo shoots inhibited the degradation of protopectin and the activities of pectin methylesterase and polygalacturonase, while inhibiting the activities of cinnamyl alcohol dehydrogenase, phenylalanine ammonia-lyase, laccase and peroxidase to reduce lignification. Overall, NO-treated water bamboo shoots exhibited higher cell wall integrity, delayed softening and reduced deterioration in quality[55]. Other studies also reported similar results, including lettuce, asparagus, broccoli, garlic bulb, and pepper[52,56]. Another study used different concentration of NO donor GSNO (10, 100, 1 000 μmol/L) to spray the surface of Golden papaya, and the result indicated that GSNO did not show significant effect on color, soluble solids, titratable acidity, and MDA content. However, NO controlled the ethylene biosynthesis in a dose-dependent manner, and the low dose of GSNO (10 μmol/L) treated golden papaya showed a 52% reduction in weight loss compared to the control (sprayed with distilled water) after 72 h of ripening at room temperature[57]. These results indicated that NO and its donor treatment can be effective in inhibiting the softening and senescence of fruits and vegetables during the postharvest storage period.

3.1.2 *Mechanism*

The main reason for NO to delay the senescence of fruit and vegetable is by inhibiting the biosynthesis of ethylene[57]. Ethylene is an important hormone in plants that regulates fruits and vegetables from ripening, softening to senescence. Large amounts of ethylene will cause fruits and vegetables to ripen and age rapidly, making them susceptible to pathogenic bacteria. The presence of NO inhibits the oxidation of 1-aminocyclopropane-1-carboxylate (ACC), which delays the aging of fruits and vegetables. This effect is primarily attributed to NO's ability to bind 1-aminocyclopropane-1-carboxylate oxidase (ACO), forming a stable complex (ACC-ACO-NO) that chelates with ACC and blocks the ACC oxidase enzyme, thereby inhibiting the production of ethylene[58-59].

3.2 *Effect of NO on chilling injury*

3.2.1 *Inhibit the chilling injury*

Low temperature storage is a common method to keep fruit and vegetable fresh, delay the aging and prolong the shelf life after harvest. However, fruits and vegetables are sensitive to low temperature, chilling injury often occurred during refrigeration. Relevant studies have shown that the symptoms related to chilling injury can be relieved by exogenous NO. For instance, Washington navel orange was treated with sodium nitroprusside (SNP) and then refrigerated at 3 °C. When these oranges stored for up to 5 months, the rate of cold injury was reduced by 50% and 75% in the 0.25 and 0.50 mmol/L SNP-treated groups, respectively, relative to the control group. Similar results were shown for decreasing lipid oxidation and H_2O_2 content, and improving DPPH radical scavenging and antioxidant enzyme activities. In a nutshell, NO could improve the cooling tolerance of fruits[63].

Similarly, Sun et al.[62] reported that NO inhibited the lignin accumulation and retarded the lignification process of okra pods under cold stress. In addition, Liu et al. evaluated the effects of 1.0% NO treatment (4 h and 2 °C) on 5 kinds of fresh vegetables including lettuce, broccoli, pepper, squash, and tomato, and the results demonstrated that no negative impact was observed on the quality of all kind of vegetables when the treatment was terminated by N_2 until NO was removed before exposing the product to routine storage conditions[60].

3.2.2 *Mechanism*

Scholars have extensively investigated the role of NO in mitigating chilling injury of postharvest fruits and vegetables. They have solved this issue from a molecular biology standpoint by utilizing genomic, transcriptomic, proteomic, and metabolomic technologies. The primary chilling resistance mechanisms are involved in the activation of the antioxidant system and the maintenance of energy levels of fruits and vegetables after NO treatment[59,64].

Table 2
The effects of NO on postharvest fruits and vegetables.

Application	NO or donor concentration	Treatment condition	Storage condition	Effects	References
Fruits					
'Korla' fragrant pear	NO gas, 20 μL/L	2 h	(0 ± 1) °C, 120 days	NO treatment hindered the deterioration of pear quality, exogenous NO treatment activated the activity of resistance-associated enzymes, up-regulated core genes related to the biosynthesis of pear cuticle waxes, and resulted in an increase in the total wax content.	[8]
Dried apricots	NO gas, 300, 600, 900, 1 200, 1 500 μL/L	3 h	(23 ± 2) °C, relative humidity (40 ± 5)%, 50 days	NO fumigation maintained higher levels of total soluble solids, decreased the total count of microorganisms, reducing sugars and titratable acidity.	[50]
Strawberry	NO gas, 1.0%	2 °C, 4 h	2 °C, 7 days	NO fumigation enhanced the firmness of strawberry, with brighter and richer color than the control.	[60]
Papaya fruit	Glutathione, 10, 100, 1 000 μL/L	Spraying with glutathione	(25 ± 2) °C, relative humidity 80%–90%, 72 h	NO controlled ethylene biosynthesis in a dose-dependent manner, and the low dose of GSNO (10 μmol/L) treated golden papaya showed a 52% reduction in weight loss compared to the control (sprayed with distilled water) after 72 h of ripening at room temperature.	[57]
Hami melon	NO gas, 60 μL/L	25 °C, 3 h	(1.0 ± 0.5) °C, relative humidity 75%–80%, 49 days	NO treatment could effectively reduce the degree of cold damage in Hami melon, decrease lipid peroxidation, inhibit the rate of superoxide anion (O_2^-) production, reduce the H_2O_2 content, and keep the antioxidant enzymes at a high level of activity.	[9]
Kiwifruit	NO gas, 60 μL/L	30 min	7 days	Fruits were gassed with 15 mL/L NO for 30 min, then left for 12 h and inoculated with isolated and purified *Botryosphaeria dothidea* strains. The most significant inhibition was achieved after 7 days, when the lesion area in the NO-treated group was half that of the untreated group.	[61]
'Newhall' navel orange fruit	NO gas, 15 μL/L	40 min	(5.0 ± 0.5) °C, relative humidity 85%, 180 days	NO treated orange maintained high moisture, soluble solid, titratable acid and vitamin contents, reduced the respiration rate, O_2^- and H_2O_2 generation, and showed higher antioxidant capacity and antioxidant enzyme activities than the control.	[53]
Winter jujube	NO gas, 20 μL/L	3 h	(0 ± 1) °C, relative humidity 90%–95%, 75 days	NO treatment delayed the increase in soluble pectin and inhibited the activities of pectin methyl esterase, *β*-galactosidase, polygalactur onase, and cellulase, thus prolonging fruit softening.	[54]
Apricot, blueberry, cherry, grape, pear, kiwifruit, peach, plum	NO gas, 3%	2 °C, 16 h		Nitrate and nitrite were not significantly detected in the fruit when NO fumigation was terminated with an appropriate concentration of N_2 instead of normal air.	[52]
Apple	NO gas, 5%	2 °C, 16 h			
Avocado, orange, tangerine	NO gas, 3%	5 °C, 16 h			
Mango	NO gas, 3%	13 °C, 16 h			
Squash	NO gas, 3%	8 °C, 16 h			
Strawberry	NO gas, 2.5%	2 °C, 16 h			
Vegetables					
Iceberg lettuce	NO gas, 2.0%	2, 3, 4 h	2 °C, 14 days	Complete control of Nasonovia ribisnigri on lettuce was achieved in 3, 8, and 16 h fumigation treatments with 2.0, 1.0, and 0.5% NO, respectively. Complete control of *Frankliniella occidentalis* on lettuce was also achieved in 16 h treatment with 0.5% NO.	[56]
	NO gas, 1.0%	2, 3, 4, 6, 8 h			
	NO gas, 0.5%	1, 3, 4, 5, 6, 9, 12, 16 h			
Water bamboo shoots	NO gas, 30 μL/L	Room temperature, 4 h	4 °C, in dark, 28 days	NO-treated groups inhibited the degradation of protopectin and the activities of pectin methylesterase and polygalacturonase, while inhibiting the activities of cinnamyl alcohol dehydrogenase, phenylalanine ammonia-lyase, laccase and peroxidase to reduce lignification.	[55]
Okra	Sodium nitroprusside, 0.5, 1.0, 1.5 μL/L	Soaking in sodium nitroprusside solution for 2 min each day, 4 °C	15 days	NO inhibited the synthesis of ethylene and abscisic acid and protected the ROS scavenging system and removed the MDA and H_2O_2 induced by cold stress.	[62]
Lettuce, broccoli, pepper, squash, tomato	NO gas, 2.0%	5 °C, 3 h	2 °C, 14 days	The fumigation terminated by N_2 to dilute NO before exposing the products to ambient air, had no negative impact on the quality of products; the treatment terminated by air caused injuries to the majority of the fresh products.	[60]
Peach	NO gas, 30 μL/L	20–25 °C, 4 h	20–25 °C, relative humidity 80%–90%, 5 days	NO inhibited the synthesis of ethylene, electron transport and oxygen consumption, enhanced the tricarboxylic acid cycle and the glycolysis pathway, and repressed the loss of Ca^{2+} and other structural components.	[58]

The accumulation and outbreak of ROS is the main cause of chilling injury in fruits and vegetables after harvest. Exposed to low temperature stress, fruits and vegetables will undergo peroxidation, which will eventually interfere with the structure and function of biofilm and induce chilling injury[65]. The main free radicals that can cause chilling injury of fruits and vegetables are H_2O_2 and OH[66]. Enzymes and non-enzyme free radical scavenging systems exist in fruits and vegetables, and the most important ROS scavenging enzyme system members in fruit and vegetable tissues include enzymes such as SOD, APX, CAT, POD and glutathione reductase (GR)[65]. The appropriate concentration of NO treatment can significantly improve the activities of antioxidant enzymes, so as to enhance the oxidative stress ability of fruits and vegetables and reduce chilling injury. In addition, the cold tolerance of fruits and vegetables is related to the energy level, and in which a high energy level is conducive to alleviating the chilling injury during refrigeration[67]. NO can be maintained in a running state during cold storage and have a positive effect on energy metabolism, thus improving the cold tolerance of fruits[68].

3.3 *Effect of NO on disease resistance*

3.3.1 *Improve the disease resistance*

Postharvest fruits and vegetables are susceptible to pathogens during handling and storage, and pathogenic fungi in particular are a major cause of postharvest losses, which is irreparable. NO plays an active role in reducing defense vulnerability of fruits and vegetables. A recent study reported that NO significantly inhibited the increase in lesion area in kiwifruit throughout the experimental period. Specifically, kiwifruits were gassed with 15 mL/L NO for 30 min, then left for 12 h and inoculated with isolated and purified *B. dothidea* strains. The most significant inhibition was achieved after 7 days, and the lesion area in the NO-treated group was half that of the untreated group. Transcriptome analysis showed that 46 signaling, transcriptionally regulated active genes were up-regulated by NO treatment in kiwifruit[69]. Zheng et al.[8] reported similar result. For *Alternaria* sp.-infected pears, exogenous NO treatment activated the activity of resistance-associated enzymes, up-regulated core genes related to the biosynthesis of pear cuticle waxes, and resulted in an increase in the total wax content, which improved the resistance of fruits and vegetable to pathogens.

3.3.2 *Mechanism*

The existing literature shows that the disease resistance mechanism of NO mainly includes killing pathogenic bacteria and activating enzymes activity[70-71]. The first is to directly kill pathogenic bacteria. In normal cells of fresh fruits and vegetables, ROS are maintained in a relatively balanced state. However, upon infection by pathogenic bacteria, a significant accumulation of ROS occurs, leading to the reaction of NO with ROS to form $ONOO^-$[72]. $ONOO^-$ is a cytotoxic substance that can make nitrite acylate of nucleic acid and break DNA of bacteria. It can also bind Fe-S center of enzyme to inhibit enzyme activity and have a strong destructive effect on proteins and lipids[73]. Therefore, after fruits and vegetables are infected by pathogenic bacteria, the $ONOO^-$ generated can directly kill the pathogenic bacteria, so as to improve their disease resistance[17]. On the other hand, NO can activate the activity of enzymes related to phenylpropane metabolism and induce the expression of disease-course related proteins and genes to improve the disease resistance of fruits and vegetables[74].

As mentioned above, scholars have conducted extensive research and have obtained significant findings regarding the impact of NO on the physiology and quality of fruits and vegetables. However, although the technology of using NO to treat fruits and vegetables is relatively mature in the laboratory, there are still many problems in the commercial practice of using NO gas to treat large-scale fruits and vegetables, such as the easy oxidation of NO into NO_2 and the high price, which hinder the commercial promotion of NO in fruits and vegetables. Therefore, there is a need to investigate stable NO donors or their alternatives.

4. Intake of nitrate and nitrite by diet

Table 3 shows the content of dietary nitrate and nitrite in commonly consumed foods, mainly including vegetables, fruits, grains, legumes, nuts, drinking water, and meat products. The concentration of nitrate typically exceeds that of nitrite in various foods, with the exception of meat products. It is obvious that vegetables contain higher nitrate compared to others[75]. Correspondingly, vegetables have been identified as major source of nitrate in the human diet, such as celery, lettuce, spinach, basil, and so on[75], contributing 50%–80% to the overall dietary nitrate intake[76]. Compared to vegetables, the nitrate content in fruits, grains, legumes, and nuts are relatively low[75]. However, nitrate is found in water we drink every day, although the contribution of drinking-water to nitrate intake is usually less than 14%[76-80]. As is well-known, processed meat is another source of nitrate and nitrite in our diet because the meat industry uses nitrate or nitrite as additives in the meat curing, fermenting, and preservative process[81-83,76], in which the amount of nitrite permitted for use in processed meat is currently 150 mg/kg. In addition, nitrates were also determined in fresh lamb, chicken, pork, and beef, although the content was not high[84]. As mentioned above, because nitrates and nitrites are widely available in all types of diets, humans are inevitably exposed to these substances every day. There is not much difference between the European Commission's former Scientific Committee for Food (SCF), which established an ADI of 0.06 mg/kg bw for nitrite, and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an ADI of 0.07 mg/kg bw for nitrite. For nitrate, both organizations established an ADI of 3.7 mg/kg bw[76].

Although nitrate and nitrite have been studied for a century and have always been viewed as harmful, this view is gradually being changed in recent years with the discovery of the physiological functions of NO. Research into the potential applications of dietary nitrate is still in its infancy, and there is considerable scope for future investigation in this field[85]. Moreover, rather than conducting randomized clinical trials, it is more practical to study the relationship between physiological function and nitrite intake in a larger number of subjects over the long term. This type of experimental data from real-world sources can be of great value in the design of randomized clinical trials. For example, it may be possible to get a clear picture of which groups of people are more sensitive to dietary nitrate, and might find different results for different age groups, genders, and

Table 3
Content of nitrates and nitrites in commonly consumed foods.

Foods	Number of samples	Nitrate (mg/kg)			Nitrite (mg/kg)			References
		Range	Average	SD	Range	Average	SD	
Vegetable								
Celery	21		2 610	1 600		4.3	2.9	[75]
Lettuce	41		3 650	2 320		5.4	3.1	
Basil	19		2 360	919		6.7	3.2	
Parsley	30		1 710	1 820		3.6	1.9	
Cabbage	33		1 980	1 460		5.4	2.4	
Spinach	37		1 830	1 240		4.3	2.9	
Coriander	26		2 370	1 010		4.2	1.9	
Cress	19		2 250	1 680		3.7	2.2	
Dill	20		1 830	1 400		4.8	2.6	
Fenugreek	21		6 560	418		6.0	3.2	
Leek	21		1 770	965		6.1	2.8	
Mint	21		2 790	2 480		6.7	3.7	
Tarragon	19		4 240	2 980		5.5	2.7	
Radish	22		6 260	3 180		4.9	4.0	
Carrot	33		503	297		4.8	2.8	
Tomato	35		175	116		5.5	2.6	
Cucumber	41		877	701		5.7	3.1	
Scallion	19		1 010	556		4.8	3.4	
Mushrooms	17		654	334		2.6	1.7	
Cauliflower	19		1 020	922		3.9	2.3	
Fruit								
Apple	21		103	6.38		5.1	2.7	[75]
Apricot	19		178	92.0		4.6	2.4	
Pears	17		173	103		4.3	1.8	
Peaches	25		74.9	38.0		5.4	1.8	
Cantaloupe	18		468	454		5.4	3.1	
Melon	19		223	156		4.2	3.2	
Watermelon	27		110	81.6		4.8	2.3	
Cherries	28		212	125		4.2	3.5	
Grapes	19		160	76.3		7.1	3.1	
Kiwi	19		96.5	51.4		5.5	2.2	
Lemons	30		248	93.1		5.8	2.3	
Orange	22		132	112		4.5	2.4	
Tangerine	19		326	248		5.3	2.6	
Plums	27		127	84.0		6.8	1.8	
Banana	20		444	161		5.2	2.8	
Figs	19		241	25.3		5.1	3.7	
Pomegranate	17		97.4	13.2		1.5	0.1	
Grains								
Corn	19		279	127		5.3	3.2	[75]
Barley	19		596	325		6.1	3.5	
Rice	21		243	119		6.3	3.4	
Industrial breads	31		513	215		3.9	3.3	
Traditional breads	82		512	274		3.2	2.4	
Legumes								
Soya	21		103	65.3		7.2	2.3	[75]
Cowpea	19		106	6.3		4.6	3.1	
Green pea	19		882	614		5.2	3.1	
Red bean	18		157	78.0		4.6	3.2	

Table 3 (*Continued*)

Foods	Number of samples	Nitrate (mg/kg)			Nitrite (mg/kg)			References
		Range	Average	SD	Range	Average	SD	
White bean	20		185	45.3		6.9	2.1	[75]
Chickpea	27		322	290		5.5	3.4	
Lentil	24		113	51.7		5.1	3.4	
Split pea	17		375	181		7.3	3.7	
Broad beans	23		354	241		7.7	2.5	
Nuts								
Pistachio	19		591	442		3.4	2.2	[75]
Almond	19		285	210		1.7	0.2	
Drinking water								
	1 291	2.41–8.70	5.25	1.61	0.030–0.113	0.059	0.014	[79]
	185	0.10–48.00	4.7		0.003 5–0.340 0	0.0054		[80]
	36	0.000–3.884	0.419 7		0–0.157	0.006		[77]
	48	0.001–14.086	1.348	4.020	0.001–0.005	0.002	0.001	[78]
Meat and meat products								
Fresh chicken	6	2.80–8.08	5.05	2.58	Nd	Nd	Nd	[84]
Fresh pork	6	0.87–6.24	3.99	2.24	Nd	Nd	Nd	
Fresh beef	6	0.99–7.34	3.02	2.41	Nd	Nd	Nd	
Bacon	12	17.8–223.4	64.9		18.6–21.0	8.6		[81]
Salami	28	11.6–310.6	66.0		47.3–71.4	10.5		
Ham	16	7.8–162.1	62.8		4.9	Nd		
San Daniele dry cured ham	50	< 1–11	4	3.1	< 1–2	1	0.5	[105]
Ham	15	< 8.0–52.7	12.7		< 5.0–46.4	22.8		[82]
Frankfurters	43	9.9–49.9	27.1		< 5.0–48.2	20.2		
Lamb frankfurters	6	29.8–81.4	49.1	25.7	48.0–74.6	56.7	13.4	[84]
Chicken frankfurters	6	56.9–71.2	65.5	6.12	59.5–76.2	68.5	6.53	
Dinner sausages	7	15.7–34.1	25.4		10.1–49.3	22.7		[82]
Boiled sausages called “Lastevorst”	9	14.9–23.8	18.1		14.6–61.5	29		
Other boiled sausages	18	< 8.0–36.6	26.7		< 5.0–61.4	25.8		
Semi-smoked sausages	5	23.4–38.1	28.7		10.7–23.7	18.9		
Fully smoked sausages	8	< 8.0–59.8	37.2		< 5.0–35.1	14.4		
Salami type sausages	3	19.8–76.3	45.3		6.2–54.4	30.3		
Uncooked raw sausages	10	< 8.0–41.2	21.1		< 5.0–57	17.8		
Chicken sausage	6	Nd–17.4	7.92	7.99	110–164	142	22.9	[84]
Lamb sausage	6	Nd	Nd	Nd	127–140	135	5.39	
Corned mutton	6	67.9–110.0	87.4	20.6	10.7–47.5	24.0	17.1	
Corned beef	6	71.3–124.0	105.2	24.5	16.3–47.0	30.2	13.5	
Chicken luncheon meat	6	17.9–48.8	40.7	11.8	87.8–111.0	103	8.78	
Lamb luncheon meat	6	7.36–48.8	18.0	7.80	103–140	119	18.4	

Note: Nd, Not detected.

medical conditions[85]. Such as, Kapil et al.[86] reported that the nitrate-reducing activity of oral bacteria was lower in males than in females, both at the beginning of and after supplementation with nitrate. A previous study estimated nitrate levels in the more popular healthy dietary patterns (e.g., MedDiet or DASH diets) to be approximately 1 000–1 200 mg/days, which far exceeds the ADI established by SCF and JECFA[87]. Based on different arguments, it is extremely important to understand the difference between exogenous and endogenous nitrates, nitrites, and NO in the human body, and their metabolic pathways and their potential toxic effects on the body.

5. Nitrate, nitrite, and NO and human health

5.1 *Physiological role of NO*

NO has some important functions in human body. The first known role of NO is observed in the vasculature, and decades of research have confirmed that NO reduces cardiovascular morbidity by regulating vascular endothelial cell function, dilating blood vessels, and acting as a vascular “scavenger”[88]. Moreover, NO has some physiological effects well beyond vasculature, including, in the processes as diverse as immunizing and defending system, skeletal muscle contraction and relaxation, nervous system, and cognitive function[85,89–91]. Correspondingly, NO was selected as the star molecule by *Science* in 1992 because of its roles as biological messenger molecule and cellular function regulator[92]. However, it is interesting to note that NO plays a "villain" in some cases. For septic shock, a great deal of NO is released by leucocytes to kill virus, leading to a drop in blood pressure and even coma[93].

5.2 NO generation in human body

5.2.1 L-Arginine NO synthase pathway

The classical NO synthesis pathway is *L*-arginine NOS pathway. As shown in Fig. 2, *in vivo*, NO is mainly produced through the conversion of *L*-arginine to *L*-citrulline in a reaction that requires the presence of oxygen, and this process is catalyzed by NOS[33]. In general, NOS exists in 3 forms: neuronal NOS (nNOS or NOS I), inducible NOS (iNOS or NOS II), and endothelial NOS (eNOS or NOS III)[94]. The first 2 mainly mediate and maintain the specific physiological functions of NO in tissue, including metabolism, vasodilation, anti-inflammatory, neuroprotection, apoptosis and innate immune response; while iNOS is not present in most cells under normal conditions. On the one hand, endogenous NOS inhibitors such as asymmetric-dimethyl-*L*-arginine, can inhibit NOS *in vivo* by competing with *L*-arginine at the NOS active site, thereby inhibiting NO production. This leads to *L*-arginine deficiency syndrome in humans, which is associated with vascular endothelial function, inflammation, and immune function. However, supplementation with *L*-arginine may restore NO bioavailability, suggesting that it could potentially serve as a novel therapy for metabolic syndrome, though its efficacy remains to be established[94]. On the other hand, the continuous generation of NO by tissues is essential for the maintenance of normal cellular function and the overall health of organism. Much depends on the availability of oxygen in the body. When oxygen is not available, endogenous production of NO is inhibited, leading to dysfunction of the NOS in the body and the development of some common diseases in the elderly population[95]. Consequently, this has led to the efforts to reinforce NO availability through the diet (nitrate and nitrite).

5.2.2 Nitrate-nitrite-NO pathway

Since the discovery of *L*-arginine NOS pathway, an alternate pathway nitrate-nitrite-NO for NO production, has been described[19]. As shown in Fig. 2, after ingestion of dietary nitrate, NO_3^- is converted to NO_2^- in a reaction catalyzed by bacterial NO_3^- reductase in the oral cavity. Subsequently, NO_3^- and NO_2^- are swallowed. Some of the NO_2^- is protonated in the stomach to form HNO_2, which then produces NO. Meanwhile, the remaining NO_2^- enters the systemic circulation and is distributed in the blood and body tissues, where it is reduced to NO by both enzymatic and non-enzymatic systems. The nitrate concentration in blood reached its peak at 15–30 min after eating, and the half-life was 5–8 h. Approximately 75% of nitrates in bloods is excreted by the urine and approximately 25% is absorbed by the salivary gland[96]. Salivary gland is an important organ for

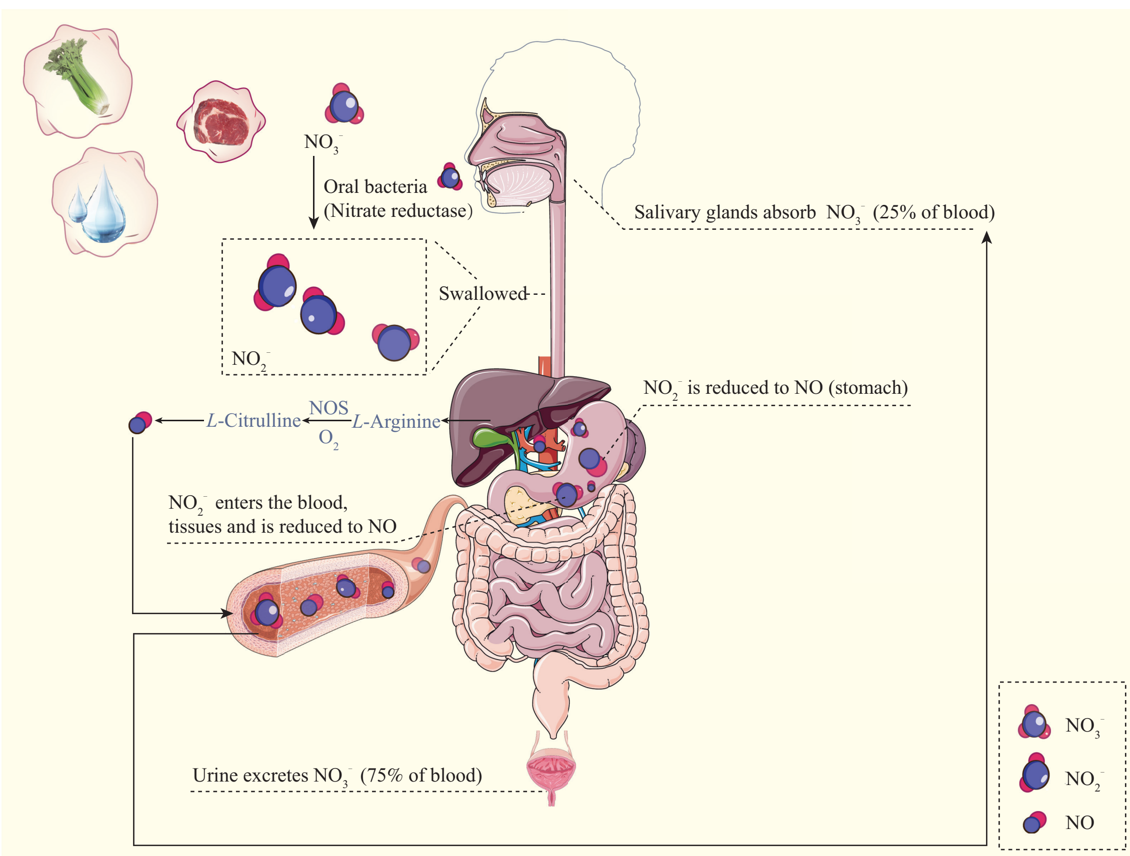

Fig. 2 *L*-Arginine NO synthase and nitrate-nitrite-NO pathway.

transporting nitrate through the nitrate transporter protein (sialin). In brief, salivary gland actively absorbs nitrate in the blood and then secretes it into the saliva. The NO_3^- in saliva is partially reduced to NO_2^- and NO under the action of oral bacteria. NO_3^- and NO_2^- enter the circulation again with swallowing and intestinal mucosal absorption. Nitrate-nitrite-NO pathway is a non-classical pathway *in vivo*, which plays an important role in physiological and pathological states, especially in hypoxia and ischemia states[97].

When NO synthesis, catalyzed by NOS pathway, is impaired in human tissues, the operation of vessels and immune system produces obstacles, and the dysfunction can easily cause angina pectoris or coronary heart disease and other cardiovascular diseases[98]. NO_2^- can be reduced to NO by several enzymatic and non-enzymatic pathways, especially under anoxic and low pH conditions[33]. Likewise, the nitrate-nitrite-NO pathway can occur under anoxic conditions. NO in this pathway is derived from endogenous oxidation of NO produced by NOS or from dietary intake[10]. Although the contribution of nitrate-nitrite-NO pathway for NO generation is < 10% in the whole human body, the lower contribution does not mean that this pathway has lower importance for NO homeostasis[99]. Notably, the normal operation of the NOS pathway is not sufficient and requires the participation of the nitrate-nitrite-NO pathway, both of which are essential for normal physiological function[10,99]. Therefore, the implication of the nitrate-nitrite-NO pathway is that dietary nitrate and nitrite are important candidates for NO production in the body[19].

Nitrate is reduced to nitrite by parthenogenetic anaerobic bacteria in the crypts of tongue, inhibiting the reproduction of pathogenic bacteria in oral cavity, and thus regulating the oral flora. Oral health has a direct impact on cardiovascular health. In a cross-sectional study of 1 182 adults, including 700 women, Mirzababaei et al.[100] found a significant negative correlation between dietary intake of nitrate and nitrite and rates of angina, suggesting that dietary adjustments, especially in older adults, may decrease angina risk. This may be due to the fact that nitrate intake increases circulating nitrite levels, and the body continues to release NO, which improves the endothelial function as well as diastolic function to deliver O_2 to the heart. This coincides with the results of a study by Cheng et al.[98], which involved 7 556 participants and showed that the benefits of dietary nitrate and nitrite far outweighed the health risks they posed, even though they exceeded the JECFA ADI by 16-fold. There are many similar findings[101-102]. Conversely, some studies have reported that the consumption of nitrate-rich fruits and vegetables does not significantly contribute to lowering blood pressure[19,103-104]. The reasons for the different results may be closely related to the duration of the studies, dietary background, populations with different disease risk.

6. Prospect and challenge

The role of the nitrate-nitrite-NO pathway in facilitating NOS within the human physiological system is of paramount importance. Postpartum breast milk contains high concentrations of nitrate and nitrite, up to more than 1 000 μmol/L, which are reduced to nitrite by the oral microbiota, and nitrite is enzymatically reduced to NO, which helps to regulate the growth and maturation of the gastrointestinal tract of newborns[106]. After being reduced to NO, nitrite plays a variety of physiological roles in the human body, not only enhancing cardiac metabolism and vascular function, lowering blood pressure[19], but also playing a role in the treatment of stroke and gastric ulcer disease[107].

Nitrate and nitrite in food have gained much attention, especially for meat products. Proteins are degraded by endogenous proteases and microbial enzymes and amines are produced (mainly biogenic amines and natural polyamines) in meat products, which are either de-ammoniated cyclization or proteins are over-oxidized to secondary amines. When nitrate and nitrite are added into meat products, they can decompose into HNO_2 to react with secondary amines to form nitrosamine compounds. Volatile *N*-nitrosamines have been linked to the development of a variety of cancers, and non-volatile *N*-nitrosamines are considered weakly carcinogenic or non-carcinogenic[108]. Correspondingly, even though nitrites are currently widely used in food, however, as early as in the 1970s, nitrate and nitrite were controversial and even banned in food due to the production of carcinogens nitrosamines. Heating method, temperature and time, fat content, moisture content, and nitrite concentration all affect the amount of nitrosamine produced[109]. Therefore, the composition of raw materials and the processing of meat products should be paid more attention to reduce the production of nitrosamines. Likewise, the consumption of red meat, even when unprocessed, carries an increased risk of cardiovascular disease. In the meantime, it should also be considered for its impact of heme iron's on nitroso compound formation, oxidative stress, and disease induction[110-111]. In addition, for meat products, appropriate addition of antioxidants can reduce the potential risk of nitrate and nitrite in processed meats to human health[112].

For nitrate-rich fruits and vegetables, although they contain higher levels of nitrates (Table 3), they have never been classified as carcinogens, possibly because they contain high levels of dietary fiber and vitamin C[113]. In fact, whether nitrate and nitrite in fruits, vegetables and meat have the same biological function after being ingested by the human body should be studied in the future. Additionally, it is important to note that lifestyle and healthiness of individual will affect the amounts of nitrosamines produced in the body. For example, people with *Helicobacter pylori* infection (reduced utilization of vitamin C) and insufficient stomach acid will accumulate higher levels of N-nitrosamines[114-115]. Also, 3-month-old infants are susceptible to methemoglobinemia induced by nitrate metabolites. So special attention should be paid to the diet of different individuals[113].

7. Conclusion

In summary, nitrate and nitrite show commendable color development, antimicrobial and tenderizing effects on meat products. NO, as the decomposition product of nitrite, inhibits the reproduction of microorganisms, increases the redness values and the tenderness of meat, and also avoid the threat of *N*-nitrosamines to a large extent by avoiding the reaction between nitrosyl compounds and amines. In addition, NO and its donors have also been used in a variety of post-harvest preservation of fruits and vegetables, by delaying senescence, improving cold resistance and antimicrobial activity. In view of the amount of nitrate in meat products is much less than vegetables, and NO plays an important role in the body, dietary nitrate and nitrite by meat products may obtain a new understanding.

Declaration of interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (32102052), Key Technology Integration and Industrialization Demonstration of Digitization Unmanned Factory for Cooked Meat Products (2023YFD2100105-4), and by the Project Program of Tianjin Key Laboratory of Food Quality and Health, China (TJS202303).

References

[1] D. Majou, S. Christieans, Mechanisms of the bactericidal effects of nitrate and nitrite in cured meats, Meat Sci. 145 (2018) 273-284. https://doi.org/10.1016/j.meatsci.2018.06.013.

[2] H.I. Yong, T. Kim, H.D. Choi, et al., Clean label meat yechnology: pre-converted nitrite as a natural curing, Food Sci. Anim. Resour. 41 (2021) 173-184. https://doi.org/10.5851/kosfa.2020.e96.

[3] P. Bernardo, M.J. Fernandes, M.H. Fernandes, et al., Effects of *Thymus citriodorus* and *Salvia elegans* extracts combined with *S. equorum* on a clean label fermented cured meat sausage, Meat Sci. 232(c) (2026) 109994. https://doi.org/10.1016/j.meatsci.2025.109994.

[4] A.U. Alahakoon, D.D. Jayasena, S. Ramachandra, et al., Alternatives to nitrite in processed meat: up to date, Trends Food Sci. Technol. 45 (2015) 37-49. https://doi.org/10.1016/j.tifs.2015.05.008.

[5] J. de D. Hernández, A. Castell, N. Arroyo-Manzanares, et al., Toward nitrite-free curing: evaluation of a new approach to distinguish real uncured meat from cured meat made with nitrite, Foods 10 (2021) 313. https://doi.org/10.3390/foods10020313.

[6] G. Riel, A. Boulaaba, J. Popp, et al., Effects of parsley extract powder as an alternative for the direct addition of sodium nitrite in the production of mortadella-type sausages-impact on microbiological, physicochemical and sensory aspects, Meat Sci. 131 (2017) 166-175. https://doi.org/10.1016/j.meatsci.2017.05.007.

[7] Y. Zhu, L. Guo, Q. Yang, Partial replacement of nitrite with a novel probiotic *Lactobacillus plantarum* on nitrate, color, biogenic amines and gel properties of Chinese fermented sausages, Food Res. Int. 137 (2020) 109351. https://doi.org/10.1016/j.foodres.2020.109351.

[8] S. Zheng, R. Xu, J. Wei, et al., Nitric oxide effects on postharvest and Alternaria-infected pear fruit, Postharvest Biol. Technol. 195 (2023) 112118. https://doi.org/10.1016/j.postharvbio.2022.112118.

[9] T. Zhang, F. Che, H. Zhang, et al., Effect of nitric oxide treatment on chilling injury, antioxidant enzymes and expression of the CmCBF1 and CmCBF3 genes in cold-stored Hami melon (*Cucumis melo* L.) fruit, Postharvest Biol. Technol. 127 (2017) 88-98. https://doi.org/10.1016/j.postharvbio.2017.01.005.

[10] A.M. Jones, C. Thompson, L.J. Wylie, et al., Dietary nitrate and physical performance, Annu. Rev. Nutr. 38 (2018) 303-328. https://doi.org/10.1146/annurev-nutr-082117-051622.

[11] T. Clifford, A. Babateen, O.M. Shannon, et al., Effects of inorganic nitrate and nitrite consumption on cognitive function and cerebral blood flow: a systematic review and meta-analysis of randomized clinical trials, Crit. Rev. Food Sci. Nutr. 59 (2019) 2400-2410. https://doi.org/10.1080/10408398.2018.1453779.

[12] L. Tan, L. Stagg, E. Hanlon, et al., Associations between vegetable nitrate intake and cardiovascular disease risk and mortality: a systematic review, Nutrients 16 (2024) 1511. https://doi.org/10.3390/nu16101511.

[13] C.P. Bondonno, A.H. Liu, K.D. Croft, et al., Absence of an effect of high nitrate intake from beetroot juice on blood pressure in treated hypertensive individuals: a randomized controlled trial1, Am. J. Clin. Nutr. 102 (2015) 368-375. https://doi.org/10.3945/ajcn.114.101188.

[14] A.T. Williams, C.R. Muller, K. Govender, et al., Control of systemic inflammation through early nitric oxide supplementation with nitric oxide releasing nanoparticles, Free Radical. Bio. Med. 161 (2020) 15-22. https://doi.org/10.1016/j.freeradbiomed.2020.09.025.

[15] S. Hasan, N. Thomas, B. Thierry, et al., biodegradable nitric oxide precursor-loaded micro- and nanoparticles for the treatment of *Staphylococcus aureus* biofilms, J. Mater. Chem. B 5 (2017) 1005-1014. https://doi.org/10.1039/C6TB03290G.

[16] F. Sodano, E. Gazzano, R. Fruttero, et al., NO in viral infections: role and development of antiviral therapies, Molecules 27 (2022) 2337. https://doi.org/10.3390/molecules27072337.

[17] Y. Sun, R.L. Wen, D. Yu, et al., Flexible electrostatic hydrogels from marine organism for nitric oxide-enhanced photodynamic therapy against multidrug-resistant bacterial infection, Sci. China Mater. 65 (2022) 2850-2860. https://doi.org/10.1007/s40843-022-2024-6.

[18] S. Huang, H. Liu, K. Liao, et al., Functionalized GO nanovehicles with nitric oxide release and photothermal activity-based hydrogels for bacteria-infected wound healing, ACS Appl. Mater. Interfaces 12 (2020) 28952-28964. https://doi.org/10.1021/acsami.0c04080.

[19] C.P. Bondonno, K.D. Croft, J.M. Hodgson, Dietary nitrate, nitric oxide, and cardiovascular health, Crit. Rev. Food Sci. (2016). https://doi.org/10.1080/10408398.2013.811212.

[20] P. Huang, H. Luo, C. Chen, et al., Bacterial nitric oxide synthase in colorizing meat products: current development and future directions, Crit. Rev. Food Sci. Nutr. 64 (2024) 4362-4372. https://doi.org/10.1080/10408398.2022.2141679.

[21] R. Liu, S. Lonergan, E. Steadham, et al., Effect of nitric oxide and calpastatin on the inhibition of μ-calpain activity, autolysis and proteolysis of myofibrillar proteins, Food Chem. 275 (2019) 77-84. https://doi.org/10.1016/j.foodchem.2018.09.104.

[22] N. Higuero, I. Moreno, G. Lavado, et al., Reduction of nitrate and nitrite in Iberian dry cured loins and its effects during drying process, Meat Sci. 163 (2020) 108062. https://doi.org/10.1016/j.meatsci.2020.108062.

[23] S. Ragucci, N. Landi, A. Di Maro, Myoglobin as a molecular biomarker for meat authentication and traceability, Food Chem. 458 (2024) 140326. https://doi.org/10.1016/j.foodchem.2024.140326.

[24] R. Liu, L. Yang, T. Yang, et al., Effect of nitric oxide treatment on pork meat quality, microstructure, and total bacterial count during postmortem aging, Meat Sci. 190 (2022) 108806. https://doi.org/10.1016/j.meatsci.2022.108806.

[25] W. Zhang, A.H. Marwan, H. Samaraweera, et al., Breast meat quality of broiler chickens can be affected by managing the level of nitric oxide, Poult Sci. 92 (2013) 3044-3049. https://doi.org/10.3382/ps.2013-03313.

[26] M. Zając, K. Zając, J. Dybaś, The effect of nitric oxide synthase and arginine on the color of cooked meat, Food Chem. 373 (2022) 131503. https://doi.org/10.1016/j.foodchem.2021.131503.

[27] H. Luo, P. Li, H. Zhang, et al., Nitrosylmyoglobin formation in meat by *Lactobacillus fermentum* AS1.1880 is due to its nitric oxide synthase activity, Meat Sci. 166 (2020) 108122. https://doi.org/10.1016/j.meatsci.2020.108122.

[28] K. Jo, S. Lee, H.I. Yong, et al., Nitrite sources for cured meat products, LWT- Food Sci. Technol. 129 (2020) 109583. https://doi.org/10.1016/j.lwt.2020.109583.

[29] M.C. Golden, L.M. McDonnell, V. Sheehan, et al., Inhibition of *Listeria monocytogenes* in deli-style turkey breast formulated with cultured celery powder and/or cultured sugar-vinegar blend during storage at 4 ℃, J. Food Prot. 77 (2014) 1787-1793. https://doi.org/10.4315/0362-028X.JFP-14-059.

[30] T.K. Kim, M.A. Lee, J.M. Sung, et al., Combination effects of nitrite from fermented spinach and sodium nitrite on quality characteristics of cured pork loin, Asian-Australas J. Anim. Sci. 32 (2019) 1603-1610. https://doi.org/10.5713/ajas.18.0903.

[31] J. Kim, Y. Lee, K. Singha, et al., NONOates-polyethylenimine hydrogel for controlled nitric oxide release and cell proliferation modulation, Bioconjugate Chem. 22 (2011). https://doi.org/10.1021/bc100405c.

[32] H.S. Oh, F. Constancias, C. Ramasamy, et al., Biofouling control in reverse osmosis by nitric oxide treatment and its impact on the bacterial community, Membr. Sci. 550 (2018) 313-321. https://doi.org/10.1016/j.memsci.2018.01.012.

[33] M. Abu-Alghayth, A. Vanhatalo, L.J. Wylie, et al., *S*-Nitrosothiols, and other products of nitrate metabolism, are increased in multiple human blood compartments following ingestion of beetroot juice, Redox Biol. 43 (2021) 101974. https://doi.org/10.1016/j.redox.2021.101974.

[34] W. Li, D. Wang, K.U. Lao, et al., Buffer concentration dramatically affects the stability of *S*-nitrosothiols in aqueous solutions, Nitric Oxide 118 (2022) 59-65. https://doi.org/10.1016/j.niox.2021.11.002.
[35] A. Lamas, J.M. Miranda, B. Vázquez, et al., An evaluation of alternatives to nitrites and sulfites to inhibit the growth of *Salmonella enterica* and *Listeria monocytogenes* in meat products, Foods 5 (2016) 74. https://doi.org/10.3390/foods5040074.
[36] M. Redondo-Solano, C. Valenzuela-Martinez, D.A. Cassada, et al., Effect of meat ingredients (sodium nitrite and erythorbate) and processing (vacuum storage and packaging atmosphere) on germination and outgrowth of *Clostridium perfringens* spores in ham during abusive cooling, Food Microbiol. 35 (2013) 108-115. https://doi.org/10.1016/j.fm.2013.02.008.
[37] T. Chatkitanan, N. Harnkarnsujarit, Effects of nitrite incorporated active films on quality of pork, Meat Sci. 172 (2021) 108367. https://doi.org/10.1016/j.meatsci.2020.108367.
[38] Q. Meng, J. Yin, M. Jin, H. Gao, Distinct nitrite and nitric oxide physiologies in *Escherichia coli* and *Shewanella oneidensis*, Appl. Environ. Microbiol. 84 (2018) e00559-18. https://doi.org/10.1128/AEM.00559-18.
[39] A.P. Landry, X. Duan, H. Huang, et al., Iron-sulfur proteins are the major source of protein-bound dinitrosyl iron complexes formed in *Escherichia coli* cells under nitric oxide stress, Free Radic. Biol. Med. 50 (2011) 1582-1590. https://doi.org/10.1016/j.freeradbiomed.2011.03.005.
[40] C. Prolo, M.N. Alvarez, R. Radi, Peroxynitrite, a potent macrophage-derived oxidizing cytotoxin to combat invading pathogens, Biofactors 40 (2014) 215-225. https://doi.org/10.1002/biof.1150.
[41] R. Liu, S. Lonergan, E. Steadham, et al., Effect of nitric oxide on myofibrillar proteins and the susceptibility to calpain-1 proteolysis, Food Chem. 276 (2019) 63-70. https://doi.org/10.1016/j.foodchem.2018.10.005.
[42] C. Zhang, R. Liu, A. Wang, et al., Regulation of calpain-1 activity and protein proteolysis by protein nitrosylation in postmortem beef, Meat Sci. 141 (2018) 44-49. https://doi.org/10.1016/j.meatsci.2018.03.017.
[43] Y. Li, R. Liu, W. Zhang, et al., Effect of nitric oxide on μ-calpain activation, protein proteolysis, and protein pxidation of pork during post-mortem aging, J. Agric. Food Chem. 62 (2014) 5972-5977. https://doi.org/10.1021/jf501332d.
[44] Q. Hou, R. Liu, W. Zhang, et al., Nitric oxide synthase in beef semimembranosus muscle during postmortem aging, Food Chem. 288 (2019) 187-192. https://doi.org/10.1016/j.foodchem.2019.02.128.
[45] N. Ramarathnam, L.J. Rubin, L.L. Diosady, Studies on meat flavor. 1. Qualitative and quantitative differences in uncured and cured pork, J. Agric. Food Chem. 39 (1991) 344-350. https://doi.org/10.1021/jf00002a024.
[46] S.K. Han, K. Yamauchi, The effects of nitrite treatment on the lipid composition, fatty acid composition, and susceptibility to oxidation of pork biceps femoris muscle, Asian Australas. J. Anim. Sci. 13 (2000) 1764-1769. https://doi.org/10.5713/ajas.2000.1764.
[47] Y. Ren, Y. Wang, Y. Zhang, et al., Formation and regulation strategies for volatile off-flavor compounds in livestock meat, poultry meat, and their products: a comprehensive review, Trends Food Sci. Technol. 152 (2024) 104689. https://doi.org/10.1016/j.tifs.2024.104689.
[48] Y. Zhang, Y. Zhang, J. Jia, et al., Nitrite and nitrate in meat processing: functions and alternatives, Curr. Res. Food Sci. 6 (2023) 100470. https://doi.org/10.1016/j.crfs.2023.100470.
[49] A. Bonifacie, A. Promeyrat, G. Nassy, et al., Chemical reactivity of nitrite and ascorbate in a cured and cooked meat model implication in nitrosation, nitrosylation and oxidation, Food Chem. 348 (2021) 129073. https://doi.org/10.1016/j.foodchem.2021.129073.
[50] Y. Chen, H. Deng, J. Zhang, et al., Effect of nitric oxide fumigation on microorganisms and quality of dried apricots during storage, Food Process Preserv. 45(12) (2021) e15725. 10.1111/jfpp.15725.
[51] Y. Zhang, J.R. Liang, Y.G, Xing, et al., Hypobaric with nitric oxide fumigation treatment alleviates chilling injury in prune by regulating antioxidant defense and phenolic accumulation. Postharvest Biol. Technol. 239 (2026) 114370. https://doi.org/10.1016/j.postharvbio.2026.114370.
[52] X. Yang, Y.B. Liu, Residual analysis of nitric oxide fumigation on fresh fruit and vegetables, Postharvest Biol. Technol. 132 (2017) 105-108. https://doi.org/10.1016/j.postharvbio.2017.06.006.
[53] L. Zhu, R. Yang, Y. Sun, et al., Nitric oxide maintains postharvest quality of navel orange fruit by reducing postharvest rotting during cold storage and enhancing antioxidant activity, Physiol. Mol. Plant P 113 (2021) 101589. https://doi.org/10.1016/j.pmpp.2020.101589.
[54] Y. Zhao, X. Zhu, Y. Hou, et al., Effects of nitric oxide fumigation treatment on retarding cell wall degradation and delaying softening of winter jujube (*Ziziphus jujuba* Mill. cv. Dongzao) fruit during storage, Postharvest. Biol. Tec. 156 (2019) 110954. https://doi.org/10.1016/j.postharvbio.2019.110954.
[55] X. Qi, Z. Ji, C. Lin, et al., Nitric oxide alleviates lignification and softening of water bamboo (*Zizania latifolia*) shoots during postharvest storage, Food Chem. 332 (2020) 127416. https://doi.org/10.1016/j.foodchem.2020.127416.
[56] X. Yang, Y.B. Liu, Nitric oxide fumigation for postharvest pest control on lettuce, Pest Manag. Sci 75(2) (2019) 390-395. https://doi.org/10.1002/ps.5123.
[57] M.R. Machado, J.C. da Veiga, N.M. Silveira, et al., Nitric oxide supply reduces ethylene production, softening and weight loss in papaya fruit, Bragantia 81 (2022) e1222. https://doi.org/10.1590/1678-4499.20210109.
[58] R. Kang, L. Zhang, L. Jiang, et al., Effect of postharvest nitric oxide treatment on the proteome of peach fruit during ripening, Postharvest Biol. Tec. 112 (2016) 277-289. https://doi.org/10.1016/j.postharvbio.2015.08.017.
[59] S. Pols, B. Van de Poel, M.L.A.T.M. Hertog, et al., The regulatory role of nitric oxide and its significance for future postharvest applications, Postharvest Biol. Tec. 188 (2022) 111869. https://doi.org/10.1016/j.postharvbio.2022.111869.
[60] Y.B. Liu, Nitric oxide fumigation for control of western flower thrips and its safety to postharvest quality of fresh fruit and vegetables, Asia-Pac. Entomol. 19(4) (2016) 1191-1195. https://doi.org/10.1016/j.aspen.2016.10.013.
[61] R. Yang, J. Wang, Z. Cai, et al., Transcriptome profiling to elucidate mechanisms of the enhancement of the resistance to *Botryosphaeria dothidea* by nitric oxide in postharvest kiwifruit during storage, LWT-Food Sci. Technol. 159 (2022) 113187. https://doi.org/10.1016/j.lwt.2022.113187.
[62] M. Sun, X.L. Yang, Z.P. Zhu, et al., Comparative transcriptome analysis provides insight into nitric oxide suppressing lignin accumulation of postharvest okra (*Abelmoschus esculentus* L.) during cold storage, Plant Physiol. Biochem. 167 (2021) 49-67. https://doi.org/10.1016/j.plaphy.2021.07.029.
[63] B. Ghorbani, Z. Pakkish, M. Khezri, Nitric oxide increases antioxidant enzyme activity and reduces chilling injury in orange fruit during storage, Crop Hortic. Sci. 46 (2017) 1-16. https://doi.org/10.1080/01140671.2017.1345764.
[64] C. Li, W. Yu, W. Liao, Role of nitric oxide in postharvest senescence of fruits, Int. J. Mol. Sci 23 (2022) 10046. https://doi.org/10.3390/ijms231710046.
[65] H. Zhao, B. Liu, W. Zhang, et al., Enhancement of quality and antioxidant metabolism of sweet cherry fruit by near-freezing temperature storage, Postharvest Biol. Technol. 147 (2019) 113-122. https://doi.org/10.1016/j.postharvbio.2018.09.013.
[66] M. Koushesh Saba, S. Moradi, Sodium nitroprusside (SNP) spray to maintain fruit quality and alleviate postharvest chilling injury of peach fruit, Sci. Hortic. 216 (2017) 193-199. https://doi.org/10.1016/j.scienta.2017.01.009.
[67] M.S. Aghdam, A. Jannatizadeh, Z. Luo, et al., Ensuring sufficient intracellular ATP supplying and friendly extracellular ATP signaling attenuates stresses, delays senescence and maintains quality in horticultural crops during postharvest life, Trends Food Sci. Technol. 76 (2018) 67-81. https://doi.org/10.1016/j.tifs.2018.04.003.
[68] Y. Wang, Z. Luo, Z.U. Khan, et al., Effect of nitric oxide on energy metabolism in postharvest banana fruit in response to chilling stress, Postharvest Biol. Technol. 108 (2015) 21-27. https://doi.org/10.1016/j.postharvbio.2015.05.007.
[69] X.X. Zuo, Y.C. Li, J. Yang, Involvement of AcWRKY22 in nitric oxide-induced kiwifruit resistance against *Botryosphaeria dothidea* by regulating NO synthesis and phenylpropanoid pathway. Postharvest Biol. Technol. 233 (2025) 114047. https://doi.org/10.1016/j.postharvbio.2025.114047.
[70] R. Bodanapu, S.K. Gupta, P.O. Basha, et al., Nitric oxide overproduction in tomato shr mutant shifts metabolic profiles and suppresses fruit growth and ripening, Front Plant Sci. 7 (2016) 1714. https://doi.org/10.3389/fpls.2016.01714.
[71] M. Liu, F. Zhang, B. Liu, et al., Mechanisms and technology of marine oligosaccharides to control postharvest disease of fruits, Food Chem. 404 (2022) 134664. https://doi.org/10.1016/j.foodchem.2022.134664.

[72] M.A. Muñoz-Vargas, S. González-Gordo, A. Cañas, et al., Endogenous hydrogen sulfide (H_2S) is up-regulated during sweet pepper (*Capsicum annuum* L.) fruit ripening. *In vitro* analysis shows that NADP-dependent isocitrate dehydrogenase (ICDH) activity is inhibited by H_2S and NO, Nitric Oxide 81 (2018) 36-45. https://doi.org/10.1016/j.niox.2018.10.002.

[73] A.P. Pereira Barbosa-Carvalho, D. do S. Texeira Costa Leitão, F. Campos de Siqueira, et al., Antrocaryon amazonicum: an unexploited Amazonian fruit with high potential of scavenging reactive oxygen and nitrogen species, J. Food Sci. 86 (2021) 4045-4059. https://doi.org/10.1111/1750-3841.15868.

[74] Y. Zheng, J. Xiao, K. Zheng, et al., Transcriptome profiling reveals the effects of nitric oxide on the growth and physiological characteristics of watermelon under aluminum stress, Genes 12 (2021) 1735. https://doi.org/10.3390/genes12111735.

[75] Z. Bahadoran, P. Mirmiran, S. Jeddi, et al., Nitrate and nitrite content of vegetables, fruits, grains, legumes, dairy products, meats and processed meats, Food Compos. Anal. 51 (2016) 93-105. https://doi.org/10.1016/j.jfca.2016.06.006.

[76] M. Karwowska, A. Kononiuk, Nitrates/nitrites in food—risk for nitrosative stress and benefits, Antioxidants 9 (2020) 241. https://doi.org/10.3390/antiox9030241.

[77] I. Alam, J.U. Rehman, S. Nazir, et al., Health risk assessment in different age-group due to nitrate, fluoride, nitrite and geo-chemical parameters in drinking water in Ahmadpur East, Punjab, Pakistan, HumEcol Risk Assess 27 (2021) 1747-1763. https://doi.org/10.1080/10807039.2021.1902264.

[78] A. Hameed, S. Nazir, J.U. Rehman, et al., Assessment of health hazards related to contaminations of fluorides, nitrates, and nitrites in drinking water of Vehari, Punjab, Pakistan, HumEcol Risk Assess 27(6) (2021) 1509-1522. https://doi.org/10.1080/10807039.2020.1858021.

[79] W.I. Mortada, A.A. Shokeir, Does nitrite and nitrate levels in drinking water impact the health of people in Dakahlia governorate, Egypt? Environ. Sci. Pollut. Res. 25 (2018) 19728-19738. https://doi.org/10.1007/s11356-018-2156-2.

[80] A.D. van den Brand, M. Beukers, M. Niekerk, et al., Assessment of the combined nitrate and nitrite exposure from food and drinking water: application of uncertainty around the nitrate to nitrite conversion factor, Food Addit. Contam. Part A 37 (2020) 568-582. https://doi.org/10.1080/19440049.2019.1707294.

[81] G. Berardi, M. Albenzio, R. Marino, et al., Different use of nitrite and nitrate in meats: a survey on typical and commercial Italian products as a contribution to risk assessment, LWT-Food Sci. Technol. 150 (2021) 112004. https://doi.org/10.1016/j.lwt.2021.112004.

[82] A. Elias, S. Jalakas, M. Roasto, et al., Nitrite and nitrate content in meat products and estimated nitrite intake by the Estonian children, Food Addit. Contam. Part A 37 (2020) 1229-1237. https://doi.org/10.1080/19440049.2020.1757164.

[83] G. Isci, Health risk assessment of nitrite and nitrate residues in processed meat products from the Turkish market. Food Res. Int. 227 (2025) 118110, https://doi.org/10.1016/j.foodres.2025.118110.

[84] A.A. Chetty, S. Prasad, O.C. Pinho, et al., Estimated dietary intake of nitrate and nitrite from meat consumed in Fiji, Food Chem. 278 (2019) 630-635. https://doi.org/10.1016/j.foodchem.2018.11.081.

[85] M. Siervo, A.M. Hussin, P. Calella, et al., Associations between aging and vitamin D status with whole-body nitric oxide production and markers of endothelial function, J. Nutr. 154 (2024) 469-478. https://doi.org/10.1016/j.tjnut.2023.12.002.

[86] V. Kapil, K.S. Rathod, R.S. Khambata, et al., Sex differences in the nitrate-nitrite-NO· pathway: role of oral nitrate-reducing bacteria, Free Radical Biol. Med. 126 (2018) 113-121. https://doi.org/10.1016/j.freeradbiomed.2018.07.010.

[87] A.M. Babateen, G. Fornelli, L.M. Donini, et al., Assessment of dietary nitrate intake in humans: a systematic review, Am. J. Clin. Nutr. 108 (2018) 878-888. https://doi.org/10.1093/ajcn/nqy108.

[88] C.C. Helms, M.T. Gladwin, D.B. Kim-Shapiro, Erythrocytes and vascular function: oxygen and nitric oxide, Front. Physiol. 9 (2018). https://doi.org/10.3389/fphys.2018.00125.

[89] E.G. Heiland, F. Lindh, C. Regan, et al., A randomised crossover trial of nitrate and breakfast on prefrontal cognitive and haemodynamic response functions, Npj Sci. Food 8 (2024) 64. https://doi.org/10.1038/s41538-024-00308-4.

[90] W. Liu, Y. Wang, Z. Leng, et al., Nitric oxide plays a crucial role in midgut immunity under microsporidian infection in *Antheraea pernyi*, Mol. Immunol. 126 (2020) 65-72. https://doi.org/10.1016/j.molimm.2020.07.018.

[91] D.C. Poole, S.K. Ferguson, T.I. Musch, et al., Role of nitric oxide in convective and diffusive skeletal muscle microvascular oxygen kinetics, Nitric Oxide 121 (2022) 34-44. https://doi.org/10.1016/j.niox.2022.01.005.

[92] Y. Luo, Y. Zhu, W. Basang, et al., Roles of nitric oxide in the regulation of reproduction: a review, Front. Endocrinol 12 (2021)752410. https:// doi.org/10.3389/fendo.2021.752410.

[93] B. Liu, H. Su, Luteolin improves vasoconstriction function and survival of septic mice *via* AMPK/NF-κB pathway, Heliyon 9 (2023) e13330. https://doi.org/10.1016/j.heliyon.2023.e13330.

[94] J. Lorin, M. Zeller, J.C. Guilland, et al., Arginine and nitric oxide synthase: regulatory mechanisms and cardiovascular aspects, Mol. Nutr. Food Res. 58 (2014) 101-116. https://doi.org/10.1002/mnfr.201300033.

[95] M. Kina-Tanada, M. Sakanashi, A. Tanimoto, et al., Long-term dietary nitrite and nitrate deficiency causes the metabolic syndrome, endothelial dysfunction and cardiovascular death in mice, Diabetologia 60 (2017) 1138-1151. https://doi.org/10.1007/s00125-017-4259-6.

[96] N.S. Bryan, S. Ahmed, D.J. Lefer, et al., Dietary nitrate biochemistry and physiology. An update on clinical benefits and mechanisms of action, Nitric Oxide 132 (2023) 1-7. https://doi.org/10.1016/j.niox.2023.01.003.

[97] X.M. Qu, Z.F. Wu, B.X. Pang, et al., From nitrate to nitric oxide: the role of salivary glands and oral bacteria, J. Dent. Res. 95 (2016) 1452-1456. https://doi.org/10.1177/0022034516673019.

[98] C.J. Cheng, Y.T. Kuo, J.W. Chen, et al., Probabilistic risk and benefit assessment of nitrates and nitrites by integrating total diet study-based exogenous dietary exposure with endogenous nitrite formation using toxicokinetic modeling, Environ. Int. 157 (2021) 106807. https://doi.org/10.1016/j.envint.2021.106807.

[99] A. Ghasemi, Quantitative aspects of nitric oxide production from nitrate and nitrite, Excel J. 21 (2022) 470-486. https://doi.org/10.17179/excli2022-4727.

[100] A. Mirzababaei, M. Mahmoodi, A. Keshtkar, et al., Association between dietary intakes of nitrate and nitrite with angina and atherogenic index in adults: a cross-sectional study from Tehran University of Medical Sciences employees` cohort (TEC) study, Curr. Prob. Cardiol. 49 (2024) 102206. https://doi.org/10.1016/j.cpcardiol.2023.102206.

[101] C.M.T. van der Avoort, D.S.M. ten Haaf, C.C.W.G. Bongers, et al., Increasing nitrate-rich vegetable intake lowers ambulatory blood pressure in (pre) hypertensive middle-aged and older adults: a 12-wk randomized controlled trial, J. Nutr. 151 (2021) 2667-2679. https://doi.org/10.1093/jn/nxab157.

[102] C.M.T. van der Avoort, K.L. Jonvik, J. Nyakayiru, et al., A nitrate-rich vegetable intervention elevates plasma nitrate and nitrite concentrations and reduces blood pressure in healthy young adults, J. Acad. Nutr. Diet. 120 (2020) 1305-1317. https://doi.org/10.1016/j.jand.2020.02.014.

[103] A.W. Ashor, J. Lara, M. Siervo, Medium-term effects of dietary nitrate supplementation on systolic and diastolic blood pressure in adults: a systematic review and meta-analysis, J. Hypertens 35 (2017) 1353-1359. https://doi.org/10.1097/HJH.0000000000001305.

[104] L.C. Blekkenhorst, J.R. Lewis, R.L. Prince, et al., Nitrate-rich vegetables do not lower blood pressure in individuals with mildly elevated blood pressure: a 4-week randomized controlled crossover trial, Am. J. Clin. Nutr 107 (2018) 894-908. https://doi.org/10.1093/ajcn/nqy061.

[105] L. Iacumin, P. Cattaneo, C. Zuccolo, et al., Natural levels of nitrites and nitrates in San Daniele dry cured ham PDO, and in meat, salt and sugna used for its production, Food Control 100 (2019) 257-261. https://doi.org/10.1016/j.foodcont.2019.01.016.

[106] N. Ohta, H. Tsukahara, Y. Ohshima, et al., Nitric oxide metabolites and adrenomedullin in human breast milk, Early Hum. Dev. 78 (2004) 61-65. https://doi.org/10.1016/j.earlhumdev.2004.04.002.

[107] J.O. Lundberg, E. Weitzberg, M.T. Gladwin, The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics, Nat. Rev. Drug Discov. 7 (2008) 156-167. https://doi.org/10.1038/nrd2466.

[108] M. Nader, B. Hosseininezhad, E. Berizi, et al., The residual nitrate and nitrite levels in meat products in Iran: a systematic review, meta-analysis and health risk assessment, Environ. Res. 207 (2022) 112180. https://doi.org/10.1016/j.envres.2021.112180.

[109] W. Bedale, J.J. Sindelar, A.L. Milkowski, Dietary nitrate and nitrite: benefits, risks, and evolving perceptions, Meat Sci. 120 (2016) 85-92. https://doi.org/10.1016/j.meatsci.2016.03.009.

[110] D.D. Wang, Y. Li, X.M. Nguyen, et al., Red meat intake and the risk of cardiovascular diseases: a prospective cohort study in the million veteran program, J. Nutr. 154(3) (2023) 886-895. https://doi.org/10.1016/j.tjnut.2023.12.051.

[111] F. Guéraud, C. Héliès-Toussaint, J. Dupuy, et al., Meat and digestive cancers, in Encyclopedia of Meat Sciences (third edition), Elsevier Oxford (2024) 684-694. https://doi.org/10.1016/B978-0-323-85125-1.00126-5.

[112] Y. Xie, Y. Geng, J. Yao, et al., *N*-Nitrosamines in processed meats: exposure, formation and mitigation strategies, J. Agr. Food Res. 13 (2023) 100645. https://doi.org/10.1016/j.jafr.2023.100645.

[113] T.Y.K. Chan, Vegetable-borne nitrate and nitrite and the risk of methaemoglobinaemia, Toxicol. Lett 200 (2011) 107-108. https://doi.org/10.1016/j.toxlet.2010.11.002.

[114] J.W. Dallinga, D.M.F.A. Pachen, A.H.P. Lousberg, et al., Volatile N-nitrosamines in gastric juice of patients with various conditions of the gastrointestinal tract determined by gas chromatography–mass spectrometry and related to intragastric pH and nitrate and nitrite levels, Cancer Lett. 124 (1998) 119-125. https://doi.org/10.1016/S0304-3835(97)00467-9.

[115] L. López-Carrillo, J. Torres-López, M. Galván-Portillo, et al., *Helicobacter pylori*-CagA seropositivity and nitrite and ascorbic acid food intake as predictors for Gastric Cancer, Eur J. Cancer 40 (2004) 1752-1759. https://doi.org/10.1016/j.ejca.2004.04.025.