World Journal of Biology Pharmacy and Health Sciences

eISSN: 2582-5542

Cross Ref DOI: 10.30574/wjbphs

Journal homepage: https://wjbphs.com/

(Review Article)

Check for updates

Targeted modulation of nitric oxide pathways: Effects on reactive oxygen species, endothelial function, and disease progression in cardiovascular patients

Saurabh Krishna Verma *, Madhulika Tiwari and Fatima Rani

Department of Pharmacology and Therapeutics, King George's Medical University, U.P., Lucknow-226003.

World Journal of Biology Pharmacy and Health Sciences, 2026, 26(02), 111-125

Publication history: Received on 28 March 2026; revised on 06 May 2026; accepted on 08 May 2026

Article DOI: https://doi.org/10.30574/wjbphs.2026.26.2.0244

Abstract

Nitric oxide (NO) is a highly reactive molecule with broad implications in biological, environmental, and industrial contexts. As a free radical, NO plays a vital role in cellular signalling pathways, particularly in regulating vascular tone through vasodilation and in modulating immune responses. However, its reactivity also positions NO as a potential toxicant, contributing to oxidative stress when produced in excess and damaging DNA, proteins, and lipids. This dual nature of NO highlights the importance of its regulation within biological systems, where it can act as both a signalling molecule and a harmful agent under pathological conditions.

In industrial applications, NO is widely used to produce nitric acid, a key component in fertilisers, explosives, and other chemicals. It also has applications in metal refining and semiconductor manufacturing, making it an important compound in modern industry. However, NO emissions from industrial processes and vehicle exhausts contribute significantly to atmospheric pollution. NO interacts with oxygen and volatile organic compounds (VOCs), leading to the formation of nitrogen oxides (NOx), which play a major role in the development of smog, acid rain, and particulate matter. These environmental impacts necessitate the implementation of mitigation strategies, including catalytic converters, selective catalytic reduction (SCR) technologies, and green chemistry innovations, to reduce NO emissions and minimise its detrimental effects on air quality and ecosystems.

Emerging research in NO chemistry is focused on uncovering new therapeutic approaches, particularly in the development of NO-releasing compounds for the treatment of cardiovascular diseases, cancer, and neurodegenerative disorders. Advances in nanotechnology have led to the exploration of NO-releasing nanoparticles for targeted drug delivery, offering more precise therapeutic applications with potentially fewer side effects. Despite these advancements, challenges remain in controlling NO levels in therapeutic contexts, as its short half-life and high reactivity make precise dosing difficult. Moreover, understanding NO's interactions with other molecules in both physiological and pathological conditions is crucial for improving its application in medical treatments.

Future research must address the gaps in knowledge regarding NO's role in neurodegenerative diseases, as well as its broader environmental impact, particularly in the context of climate change. The ongoing study of NO's interactions, its role in human health, and its environmental significance will contribute to the development of more effective therapies and industrial processes while mitigating the negative impacts of NO on ecosystems.

Keywords: Nitric Oxide; Vasodilation; Reactive Oxygen Species; Oxidative Stress; Industrial Applications; Environmental Pollution; Nitric Oxide Donors; Therapeutic Applications; NO Emissions; Atmospheric Chemistry

* Corresponding author: Saurabh Krishna Verma

1. Introduction

1.1. Overview of Nitric Oxide (NO) as a Key Biological Molecule

Nitric oxide (NO) is a simple yet vital biological molecule, despite its small and straightforward molecular structure. As a free radical, NO plays diverse roles in various physiological processes, ranging from cardiovascular function to immune response and neurotransmission. One of its most crucial roles is in the regulation of vascular tone, where it causes the relaxation of smooth muscles, leading to vasodilation. This mechanism is essential for maintaining proper blood flow, controlling blood pressure, and preventing disorders such as hypertension. Additionally, NO inhibits platelet aggregation, which reduces the risk of thrombosis, making it an important molecule in the prevention of cardiovascular diseases. (1)

Beyond the cardiovascular system, nitric oxide is a key player in the nervous system, acting as a neurotransmitter and modulator of synaptic activity. It is particularly involved in processes such as memory formation and learning, where it modulates long-term potentiation in neurons. In the immune system, NO functions as a defence molecule, produced by activated macrophages to kill pathogens. Its antimicrobial properties make it a significant component of the innate immune system. (2) These diverse roles underscore nitric oxide's importance as a biological signalling molecule and a critical regulator of multiple body systems.

1.2. Historical Perspective on Nitric Oxide Chemistry

Historically, nitric oxide has been recognised as a significant chemical compound for over two centuries. In the late 18th century, scientists began to understand NO's role in environmental processes, especially its involvement in the formation of smog and acid rain. For most of the 20th century, NO was primarily studied in the context of atmospheric chemistry and its effects on pollution. It was not until the discovery of NO's biological functions in the 1980s that it gained significant attention in the fields of physiology and medicine.

The discovery of NO as a signalling molecule marked a turning point in biochemistry and medicine. Its role as an endothelium-derived relaxing factor (EDRF) in the cardiovascular system was particularly groundbreaking, leading to the recognition of its potential therapeutic applications. (3) The subsequent identification of nitric oxide synthase (NOS) enzymes, responsible for the endogenous production of NO, further expanded understanding of its biological significance. This shift in perspective, from an environmental pollutant to a crucial biological regulator, highlighted the complex duality of NO's roles in both environmental and physiological contexts.

1.3. Importance of Studying Nitric Oxide Interactions with Other Chemicals

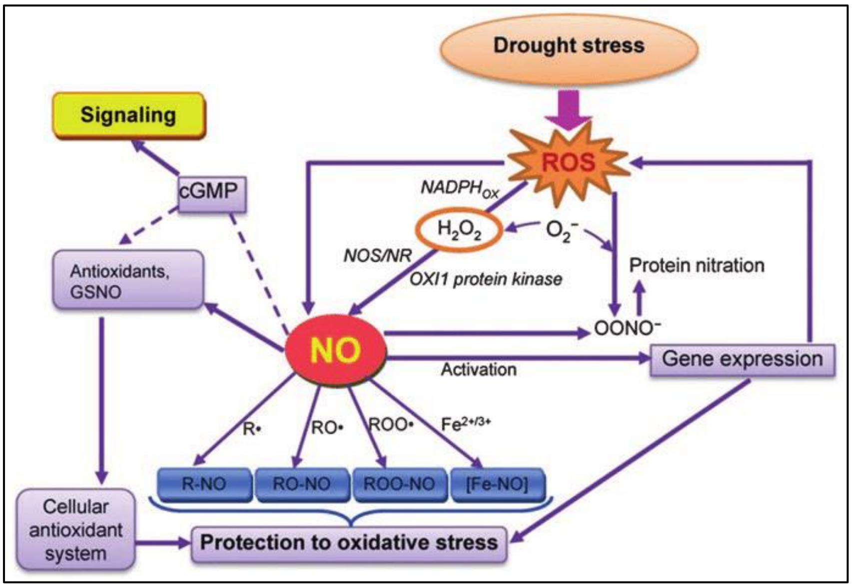

Figure 1 Interaction of Nitric Oxide with various chemicals

The interactions of nitric oxide with various chemicals are of great interest due to the broad range of biological and environmental processes that NO influences. In biological systems, NO's ability to react with metals, reactive oxygen species (ROS), and other small molecules significantly impacts cellular functions. For instance, its interaction with superoxide anions produces peroxynitrite, a potent oxidising agent involved in oxidative stress. Understanding how NO interacts with different chemicals, including metal ions and thiol-containing molecules, is critical in deciphering its complex role in health and disease.

In environmental chemistry, NO plays a crucial part in atmospheric reactions, including the formation of nitrogen oxides (NOx) and their subsequent influence on air quality and climate. The study of NO's interactions with other environmental chemicals, especially in polluted atmospheres, is essential for addressing air pollution and related health issues. (4)

1.4. Aim and Scope of the Review

This review aims to provide a comprehensive understanding of the interactions between nitric oxide and various chemicals. By examining both biological and environmental interactions, this review will highlight the dual roles of NO in health and environmental contexts. The scope of the review will encompass NO's reactivity with reactive oxygen species, metals, thiols, and other nitrogen species, emphasising its relevance to both physiological and environmental processes. (5)

2. Chemical Properties of Nitric Oxide

2.1. Molecular Structure and Electronic Configuration

Nitric oxide (NO) is a diatomic molecule consisting of one nitrogen atom and one oxygen atom. The nitrogen atom contributes five valence electrons, while the oxygen atom contributes six, resulting in a total of 11 valence electrons. This odd number of electrons gives NO a paramagnetic nature, meaning it contains an unpaired electron, which significantly influences its chemical behaviour. The bond order between nitrogen and oxygen is 2.5, meaning that it falls between a double bond and a triple bond, indicating that the bond is relatively strong but not as strong as in other nitrogen-oxygen species like nitrous oxide (N_2O). The molecular orbital configuration of NO results in one unpaired electron residing in the π^* antibonding orbital, which makes NO a free radical. (6)

The presence of this unpaired electron is crucial for NO's reactivity, especially in biological and environmental systems. This electronic configuration allows NO to easily donate or accept electrons in redox reactions, making it a highly reactive molecule capable of interacting with a variety of chemical species. Moreover, the molecule's small size and non-polar nature enable it to diffuse rapidly through cell membranes, which is a significant property in its role as a signalling molecule in biological systems.

2.2. NO as a Free Radical and Its Reactivity

Nitric oxide is classified as a free radical due to its unpaired electron, making it highly reactive under specific conditions. In its free radical form, NO can interact with other free radicals, particularly reactive oxygen species (ROS) like superoxide ($O_2\bullet^-$). (7) One of the most well-known reactions involving NO is its interaction with superoxide to form peroxynitrite ($ONOO^-$), a highly reactive and damaging molecule involved in oxidative stress and inflammation in biological systems. This ability to form reactive nitrogen species (RNS) is critical in many pathological processes, including cardiovascular diseases and neurodegenerative disorders.

NO's reactivity is also essential in environmental processes, where it participates in atmospheric chemistry, particularly in the formation of nitrogen oxides (NOx), which are key contributors to air pollution and smog formation. In addition, NO plays a crucial role in ozone layer depletion and acid rain formation through its involvement in nitrogen cycle reactions. (8)

2.3. Physical and Chemical Properties Relevant to Its Interactions

Nitric oxide is a colourless, non-polar gas at room temperature with a boiling point of -152°C and a melting point of -164°C. Its relatively low molecular weight and non-polar nature allow it to diffuse easily in both air and biological membranes. NO is relatively stable in aqueous solutions but can be rapidly oxidised in the presence of oxygen to form nitrogen dioxide (NO_2), another reactive nitrogen species. This oxidation process is important in environmental chemistry, where NO and NO_2 form part of the NOx family, contributing to the formation of tropospheric ozone and other air pollutants. (9)

NO also has a relatively low solubility in water compared to other nitrogen species like ammonia or nitric acid, yet it can still dissolve in biological fluids to interact with various biomolecules. In biological systems, NO's interactions with metals, especially in metalloproteins, are of particular importance. Nitric oxide binds to transition metals like iron and copper, which are present in enzymes such as hemoglobin and cytochrome c oxidase. These interactions facilitate its role in processes such as vasodilation, where NO binds to the heme group in guanylate cyclase, leading to the production of cyclic guanosine monophosphate (cGMP), a secondary messenger involved in smooth muscle relaxation. (10)

In summary, nitric oxide's chemical properties, including its molecular structure, electronic configuration, and reactivity as a free radical, make it an essential player in both biological and environmental processes. Its ability to participate in redox reactions and interact with a wide range of chemical species underpins its diverse roles in cellular signalling, disease pathology, and atmospheric chemistry.

3. Mechanisms of Interaction of Nitric Oxide

3.1. General Chemical Mechanisms of Nitric Oxide Reactions

Nitric oxide (NO) is a highly reactive molecule due to its unpaired electron, making it a key player in a variety of chemical reactions. One of the most important mechanisms involving NO is its ability to act both as an oxidising and a reducing agent. In its oxidising form, NO can react with nucleophiles, donating an electron to form nitrosyl species. Conversely, as a reducing agent, NO can accept an electron, especially in the presence of metal ions or oxygen radicals, to form reactive nitrogen species (RNS). (11)

Nitric oxide readily reacts with oxygen to form nitrogen dioxide (NO_2), which is further involved in reactions that produce ozone and other pollutants in the atmosphere. In biological systems, NO reacts with other free radicals, such as superoxide ($O_2{\bullet}^-$), to form peroxynitrite ($ONOO^-$), a highly reactive compound associated with oxidative damage. This reaction between NO and superoxide is particularly important in pathological conditions like inflammation and neurodegenerative diseases, where oxidative stress plays a central role. (12)

Another important mechanism involves the nitrosylation of proteins, particularly those containing thiol (-SH) groups. S-nitrosylation, a post-translational modification, can alter protein function by modifying cysteine residues. This reaction is crucial in regulating cellular processes like signal transduction, apoptosis, and immune responses.

3.2. Role of Redox Reactions in Nitric Oxide Chemistry

Redox reactions are central to nitric oxide's interactions in both biological and environmental contexts. NO can exist in multiple oxidation states, such as nitrosonium ion (NO^+), nitric oxide radical ($NO\bullet$), and nitrosyl anion (NO^-), allowing it to participate in diverse redox reactions. The redox chemistry of NO is particularly significant in regulating vascular function. For instance, in endothelial cells, NO is synthesised by nitric oxide synthase (NOS) and plays a role in vasodilation by activating the enzyme guanylate cyclase. This activation leads to an increase in cyclic guanosine monophosphate (cGMP) levels, which results in the relaxation of smooth muscles and dilation of blood vessels. (13)

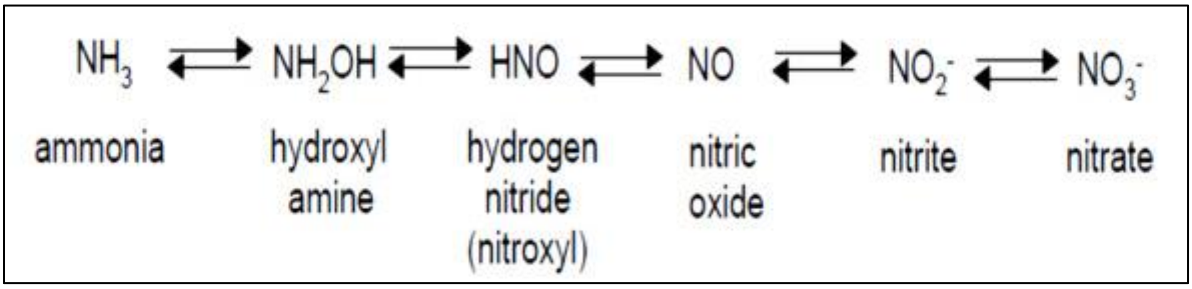

Figure 2 Moreover, NO can undergo one-electron redox reactions with transition metals like iron and copper, which are present in many metalloproteins. For example, in haemoglobin, NO can bind to the heme iron, forming a nitrosyl-haemoglobin complex, which has significant implications for oxygen transport and delivery. This redox interaction is also involved in cellular respiration, as NO can inhibit cytochrome c oxidase, a key enzyme in the mitochondrial electron transport chain, thus modulating cellular energy production

3.3. The Role of the Environment in Modulating Nitric Oxide Interactions

Environmental factors such as pH, temperature, and the presence of cofactors significantly influence NO's chemical behaviour. In acidic environments, NO tends to be more stable, while in alkaline conditions, it rapidly reacts with oxygen to form nitrogen oxides (NOx). This pH dependence is critical in biological systems where localised changes in pH can affect the rate and nature of NO interactions. For instance, during inflammation or ischemia, tissue acidity increases, which can modulate NO's reactivity and its interactions with other biomolecules.

Temperature also affects NO's reactivity. At higher temperatures, NO's interaction with oxygen becomes more pronounced, leading to the formation of reactive nitrogen oxides. This temperature dependence is especially relevant in industrial and environmental contexts, where NO emissions contribute to the formation of smog and acid rain. (14)

In biological systems, the availability of cofactors such as tetrahydrobiopterin (BH4) can also influence NO production and its downstream effects. BH4 is an essential cofactor for nitric oxide synthase, and its availability affects the efficiency of NO synthesis. In conditions where BH4 is depleted, such as in cardiovascular diseases, NOS can become "uncoupled" and produce superoxide instead of NO, exacerbating oxidative stress.

In summary, nitric oxide's interactions are governed by its unique ability to participate in both redox and non-redox reactions. These interactions are heavily modulated by environmental factors such as pH, temperature, and the availability of cofactors, which can either enhance or inhibit its reactivity in both biological and environmental systems. (15)

4. Interaction of Nitric Oxide with Reactive Oxygen Species (ROS)

4.1. Reaction with Superoxide (O2•–) to Form Proximities (ONOO–)

Nitric oxide (NO) readily reacts with superoxide (O2•–), a reactive oxygen species, to form peroxynitrite (ONOO–), one of the most reactive nitrogen species. This reaction occurs at near-diffusion-limited rates, making it one of the fastest and most significant interactions in biological systems. Peroxynitrite is highly toxic due to its ability to induce oxidative damage to lipids, proteins, and DNA. (16) The formation of ONOO– marks a critical step in pathologies related to oxidative stress, such as neurodegenerative diseases, cardiovascular disorders, and cancer. The rapid production of peroxynitrite results in an imbalance between reactive species and antioxidant defences, leading to extensive tissue damage.

4.2. Consequences for Oxidative Stress and Cell Damage

Proximities, formed from the NO and O2•– interaction, is a potent oxidant that causes oxidative stress by damaging cellular components. It can initiate lipid peroxidation, leading to the breakdown of cell membranes, which is a hallmark of several chronic diseases. Additionally, peroxynitrite can modify proteins through nitration of tyrosine residues, altering protein structure and function, contributing to cellular dysfunction. (17) This modification has been linked to various inflammatory conditions, atherosclerosis, and Alzheimer's disease. Moreover, peroxynitrite can damage DNA, leading to mutations and activation of cell death pathways, including apoptosis and necrosis. This widespread damage is a major driver of disease progression in conditions characterised by chronic inflammation and oxidative stress. (18).

Under conditions of oxidative stress, when ROS production exceeds antioxidant capacity, nitric oxide interacts with various reactive species, exacerbating cellular damage. In addition to forming peroxynitrite, NO can modulate the production and effects of other ROS such as hydrogen peroxide (H2O2) and hydroxyl radicals (OH•). (19) For example, NO inhibits superoxide dismutase (SOD), reducing the conversion of superoxide to less harmful species like hydrogen peroxide. This inhibition enhances oxidative stress by increasing the levels of superoxide available to form proximities. Additionally, NO interacts with mitochondrial ROS, contributing to mitochondrial dysfunction and further exacerbating oxidative stress, which is implicated in diseases like diabetes, cardiovascular disease, and neurodegeneration. (20)

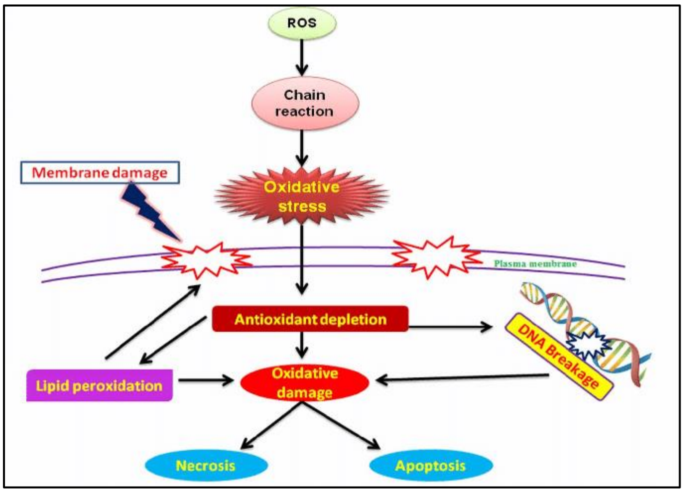

Figure 3 NO Interactions in Biological Systems Under Oxidative Stress

Table 1 Key Reactive Species and Their Interactions with Nitric Oxide

Reactive Species	Reaction with Nitric Oxide	Resulting Compound	Biological Impact
Superoxide (O2•–)	Reacts rapidly with NO	Proximities (ONOO–)	Leads to oxidative stress, lipid peroxidation, and DNA damage
Hydrogen Peroxide (H2O2)	Modulated by NO	Hydroxyl radicals (OH•)	Causes protein oxidation and further cellular damage
Hydroxyl Radical (OH•)	Reacts with NO and other molecules	Nitrogen-containing radicals	Contributes to inflammation and cell apoptosis

5. Interaction of Nitric Oxide with Metals

5.1. Coordination with Transition Metals (e.g., Iron, Copper)

Nitric oxide (NO) readily interacts with transition metals, particularly iron and copper, forming metal-nitrosyl complexes. These interactions are crucial in biological and environmental systems due to the ability of NO to coordinate with metal ions in various oxidation states. (21) In iron, for example, NO can bind to both ferrous (Fe^{2+}) and ferric (Fe^{3+}) states. The interaction between NO and iron is particularly significant in the heme groups found in haemoglobin and other metalloproteins. The formation of these complexes often alters the oxidation state of the metal, which can influence the reactivity and biological function of these proteins. (22)

In the case of copper, NO can coordinate with copper ions (Cu^{2+}) in copper-dependent enzymes, such as superoxide dismutase (SOD). The formation of NO-copper complexes affects the catalytic activity of these enzymes, which play a key role in managing oxidative stress within cells. Copper's affinity for NO also makes it a target for modulating NO signalling pathways in both health and disease. (23)

5.2. Role in the Function of Metalloproteins and Enzymes (e.g., Hemoglobin, Cytochrome P450)

Nitric oxide plays a vital role in modulating the function of metalloproteins and enzymes by binding to their metal centres. In haemog lobin, NO binds to the heme iron (Fe^{2+}), forming nitrosyl hemoglobin, which competes with oxygen binding. This interaction is important in regulating vascular tone, as the binding and release of NO from hemoglobin control the local availability of NO, thereby influencing vasodilation and blood pressure regulation.

Cytochrome P450 enzymes, which are responsible for the metabolism of various drugs and endogenous compounds, also interact with NO through their iron-heme centres. NO can inhibit or modulate the activity of cytochrome P450 by forming a stable complex with the iron in the enzyme's active site. This inhibition has important implications for drug metabolism and detoxification processes in the liver.

In non-heme iron enzymes, such as ribonucleotide reductase, NO can bind to the iron-sulfur cluster, disrupting the enzyme's function. This interference is crucial in conditions of oxidative stress where NO production is elevated, leading to the inhibition of key metabolic processes. (24)

5.3. NO-Metal Complex Formation and Its Biological and Environmental Significance

The formation of NO-metal complexes has far-reaching consequences in both biological and environmental contexts. Biologically, NO's ability to form stable complexes with metals allows it to regulate key cellular processes, including respiration, immune response, and signal transduction. For example, in the mitochondria, NO binds to the iron in cytochrome c oxidase, inhibiting cellular respiration and thus modulating energy production. This interaction is critical under hypoxic conditions, where NO can act as an oxygen sensor. (25)

Environmentally, NO-metal complexes are involved in atmospheric chemistry. In the environment, NO interacts with metal oxides, especially iron and copper oxides, playing a role in processes like the reduction of nitrogen oxides (NOx), which are major contributors to air pollution. These interactions are essential for understanding the catalytic mechanisms in environmental systems, particularly in the development of technologies aimed at reducing emissions and mitigating pollution.

Table 2 Key Transition Metals and Their Interactions with Nitric Oxide

Metal	NO Interaction	Biological Role	Environmental Significance
Iron (Fe^{2+}/Fe^{3+})	Binds to heme groups (e.g., in haemoglobin, cytochrome P450)	Regulates oxygen transport, vasodilation, and metabolism	Involved in atmospheric redox reactions (NOx reduction)
Copper (Cu^{2+})	Forms complexes with NO in enzymes (e.g., SOD)	Manages oxidative stress, influences NO signalling	Catalyses environmental reactions, including NOx reduction
Zinc (Zn^{2+})	Modulates enzyme activity through NO binding	Regulates immune responses and neurotransmission	Limited environmental role in NOx chemistry

6. Interaction of Nitric Oxide with Thiols and Amines

6.1. Reactions with Cysteine and Glutathione

Nitric oxide (NO) is highly reactive toward thiol groups, particularly those in cysteine and glutathione (GSH), which are abundant in cells and tissues. The interaction between NO and thiols forms S-nitrosothiols (RSNOs), a process called S-nitrosylation. (26) Cysteine residues in proteins are primary targets for NO, due to their nucleophilic thiol groups (-SH). The formation of S-nitrosocysteine occurs when NO reacts with these thiol groups, leading to the modification of protein structure and function. This process plays a significant role in redox signalling and regulation, affecting a wide range of cellular activities, including enzyme function, signal transduction, and transcription regulation. (27)

Similarly, glutathione, a tripeptide that acts as a major antioxidant in cells, reacts with NO to form S-nitrosoglutathione (GSNO). GSNO serves as a reservoir for NO bioactivity, controlling the local concentrations of NO and regulating its signalling functions. This interaction is critical in maintaining cellular redox homeostasis and protecting cells from oxidative stress. Furthermore, GSNO can donate NO to target proteins through trans-nitrosylation, a process that transfers the NO group from one thiol to another, further spreading the NO signal within the cell. (28)

6.2. S-Myristylation and Its Effects on Protein Function

S-nitrosylation, the covalent attachment of an NO group to a cysteine thiol, is a critical post-translational modification that can significantly alter protein function. This process is reversible and is analogous to other modifications like phosphorylation. S-nitrosylation can regulate protein activity by modifying the cysteine residues that are crucial for enzymatic function or protein-protein interactions. For example, S-nitrosylation of caspases, which are involved in the execution of apoptosis, can inhibit their activity, thereby regulating cell death processes. Similarly, S-nitrosylation of ion channels and transporters can modulate their function, affecting cellular excitability and ion homeostasis. (29)

The dysregulation of S-nitrosylation has been implicated in various diseases. In neurodegenerative disorders such as Alzheimer's and Parkinson's disease, excessive S-nitrosylation of proteins involved in mitochondrial function and oxidative stress response can lead to cellular dysfunction and cell death. Therefore, the balance of S-nitrosylation and denitrosylation (the removal of NO from cysteine residues) is crucial for maintaining proper cellular function and signalling.

6.3. NO Interactions with Amine-Containing Molecules and Their Biological Relevance

Nitric oxide also reacts with amine-containing molecules, such as lysine residues in proteins and small amine metabolites, to form nitrosamines. These interactions are biologically relevant in both physiological and pathological contexts. In proteins, NO can react with lysine side chains, modifying protein structure and potentially altering function. In small molecules, NO reacts with primary and secondary amines to form nitrosamines, which can have significant biological consequences. (30)

Nitrosamines are known for their mutagenic properties and are associated with carcinogenesis, especially in the digestive system, where dietary amines can react with NO produced by immune cells. However, under normal physiological conditions, these reactions are controlled and play roles in signal transduction and regulation of immune responses. For instance, NO interaction with amine-containing neurotransmitters, such as serotonin and dopamine, can modulate their activity and influence neurological function.

Table 3 Key Interactions of Nitric Oxide with Thiols and Amines

Molecule	**Reaction with NO**	**Resulting Compound**	**Biological Impact**
Cysteine (in proteins)	S-nitrosyl Tion of the thiol (-SH) group	S-nitroso cysteine	Modulates protein function, affects signalling
Glutathione (GSH)	S-nitrosyl Tion of GSH	S-nitroso glutathione (GSNO)	Regulates NO bioavailability and antioxidant functions
Lysine (in proteins)	Nitridation of the amine group (-NH2)	Nitrosamines	Alters protein function, potentially mutagenic effects
Serotonin/Dopamine	Nitridation of the amine group	Nitrosamines	Modulates neurotransmitter activity
Amines (in food or drugs)	Reaction with NO in the digestive system	Nitrosamines	Potential carcinogenic effects in high concentrations

7. Interaction of Nitric Oxide with Organic Compounds

7.1. NO Reactions with Alkenes, Aromatic Compounds, and Other Hydrocarbons

Nitric oxide (NO) interacts with various organic compounds, particularly unsaturated hydrocarbons like alkenes and aromatic compounds. These reactions are important in both atmospheric chemistry and industrial applications. In the case of alkenes, NO tends to react via addition to the double bonds, forming nitroso or nitrate derivatives. These reactions are driven by NO's free radical nature and its ability to accept or donate electrons depending on the reaction environment. For instance, NO can participate in the formation of nitroso compounds when reacting with aromatic hydrocarbons, a reaction that often involves electrophilic substitution. These nitroso compounds are intermediates in several industrial processes, including the synthesis of pharmaceuticals and dyes. (31)

With aromatic compounds, NO frequently reacts by adding to the electron-rich sites, such as the benzene ring, forming nitroso or nitrated products. These reactions are significant in both chemical manufacturing and environmental contexts. (32) NO-aromatic compound interactions are also central to the formation of nitroaromatic compounds, which are used in explosives and solvents, but they can also pose environmental hazards due to their persistence and toxicity.

7.2. Formation of Nitrates and Nitroso Compounds

NO plays a crucial role in the formation of nitrates (R-O-NO_2) and nitroso compounds (R-NO). These compounds are formed through a series of reactions involving NO and hydrocarbons, especially in industrial settings where NO is used as a reagent in chemical processes. In the atmosphere, the formation of nitrates is a critical step in the generation of photochemical smog, as NO reacts with volatile organic compounds (VOCs) and sunlight to produce nitrated organic species, which contribute to air pollution. (33)

Nitroso compounds, on the other hand, are widely used in various industrial applications, such as rubber processing and organic synthesis. These compounds are also intermediates in the formation of carcinogenic N-nitroso compounds in the body, making their formation and regulation important in both health and environmental sciences. (34)

7.3. Role in Atmospheric Chemistry and Industrial Processes

In atmospheric chemistry, NO is involved in a variety of reactions with organic compounds, contributing to the formation of nitrogen oxides (NOx), ozone, and particulate matter. These reactions are crucial in the formation of secondary pollutants, which affect air quality and human health. (35) NO's reactions with hydrocarbons are particularly important in urban environments, where they contribute to the formation of ground-level ozone and smog. Additionally, NO plays a significant role in industrial processes such as the production of nitric acid, where it acts as an intermediate in the oxidation of ammonia.

Table 4 Key Interactions of Nitric Oxide with Organic Compounds

Organic Compound	Reaction with NO	Resulting Product	Application/Impact
Alkenes	In addition to double bonds	Nitrosoalkenes, nitrates	Industrial synthesis, environmental pollution
Aromatic compounds	Electrophilic substitution	Nitroaromatics, nitroso compounds	Pharmaceuticals, dyes, explosives
Hydrocarbons (e.g., VOCs)	Reaction in the atmosphere	Nitrated VOCs, NOx	Air pollution, smog formation

8. Interaction of Nitric Oxide with Other Nitrogen Species

8.1. NO Reactions with Ammonia (NH3), Nitrite (NO2–), and Nitrate (NO3–)

Nitric oxide (NO) participates in various reactions with other nitrogen species, including ammonia (NH3), nitrite (NO2–), and nitrate (NO3–). These reactions are essential in both environmental and biological contexts. In the case of ammonia, NO can react to form nitrogen gas (N_2) and water in the process known as denitrification, particularly in soil and wastewater treatment. (36) This reaction is significant in the nitrogen cycle, where NO acts as a mediator in converting ammonia to nitrogen gas, helping to control nitrogen levels in ecosystems.

NO also reacts with nitrite (NO2–) under acidic conditions to form nitrogen dioxide (NO_2) and nitric acid (HNO_3). (37) This reaction is essential in atmospheric chemistry, contributing to the formation of acid rain. Similarly, NO interacts with nitrate (NO3–) in photochemical reactions that lead to the production of various reactive nitrogen species, influencing both air quality and environmental health.

8.2. Nitridation and Nitration Reactions

Nitridation and nitration are two primary reactions of NO with nitrogen species. Nitrosation typically involves the reaction of NO with nucleophiles, such as amines, to form nitrosamines, which are important in both industrial processes and biological systems. (38) Nitrosamines are known for their carcinogenic potential, making these reactions significant in toxicology.

Nitration, on the other hand, involves the addition of a nitrate group (NO3–) to organic molecules. This reaction is crucial in the formation of nitro compounds, which are widely used in explosives and fertilisers. In the atmosphere, nitration reactions contribute to the formation of secondary pollutants like particulate matter and ozone.

8.3. Environmental Impact of NO-Nitrogen Species Interactions

The interaction of NO with other nitrogen species has profound environmental implications, particularly in the formation of acid rain and photochemical smog. NO's reaction with ammonia in the atmosphere contributes to the neutralization of acidic pollutants but can also lead to the formation of ammonium nitrate, a key component of fine particulate matter that affects air quality and human health. (39) Furthermore, NO's interactions with nitrite and nitrate play a role in the nitrogen cycle, influencing soil fertility and water quality. These interactions are also significant in climate change, as they contribute to the release of greenhouse gases like nitrous oxide (N_2O). (40)

Table 5 Key Nitrogen Species and Their Reactions with Nitric Oxide

Nitrogen Species	Reaction with NO	Resulting Product	Environmental Impact
Ammonia (NH3)	Denitrification, reaction with NO	Nitrogen gas (N_2), water	Nitrogen cycle, pollution control
Nitrite (NO2–)	Oxidation by NO	Nitrogen dioxide (NO_2), nitric acid (HNO_3)	Acid rain, air pollution
Nitrate (NO3–)	Photochemical reaction with NO	Reactive nitrogen species	Photochemical smog, atmospheric chemistry

9. Biological Implications of Nitric Oxide Interactions

9.1. Role in Cellular Signalling Pathways (e.g., Vasodilation, Immune Response)

Nitric oxide (NO) is a critical mediator in several cellular signalling pathways, with its most well-known role being in vasodilation. NO is produced by endothelial cells and diffuses into adjacent smooth muscle cells, where it activates guanylate cyclase, leading to increased cyclic guanosine monophosphate (cGMP) levels. (41) This cascade ultimately results in the relaxation of smooth muscles, causing vasodilation and regulating blood pressure. The role of NO in vasodilation is particularly important in cardiovascular health, where it maintains proper blood flow and prevents conditions such as hypertension. (42)

In addition to its role in the cardiovascular system, NO is a significant player in the immune response. Macrophages and other immune cells produce NO as part of their defence against pathogens. NO can inhibit the replication of viruses and bacteria by damaging their proteins and nucleic acids. Additionally, NO has anti-inflammatory effects, modulating the activity of immune cells and reducing excessive immune responses that can lead to tissue damage. (43)

9.2. Impact on DNA, Proteins, and Lipids in Cells

Nitric oxide's interactions with cellular components like DNA, proteins, and lipids have profound biological consequences. NO can directly modify proteins through a process called S-nitrosylation, where an NO group is added to cysteine residues, affecting protein function and cellular signalling. This post-translational modification regulates various physiological processes, including apoptosis, metabolism, and neurotransmission. However, dysregulation of S-nitrosylation can lead to pathologies such as neurodegenerative diseases.

NO can also interact with DNA, either directly or through reactive nitrogen species like peroxynitrite (ONOO–), which can induce oxidative damage to nucleic acids. This damage can lead to mutations and genomic instability, which are implicated in cancer development. Moreover, NO reacts with lipids, especially in cell membranes, resulting in lipid peroxidation. Lipid peroxidation alters membrane integrity and contributes to cell dysfunction, further underscoring NO's dual role as both a signalling molecule and a potential toxicant. (44)

9.3. Nitric Oxide's Dual Role as a Signalling Molecule and a Toxicant

While NO plays a pivotal role as a signalling molecule in physiological processes like vasodilation and immune response, it can also act as a toxicant under certain conditions. The production of excessive NO or its interaction with superoxide to form peroxynitrite can cause oxidative and nitrosative stress, leading to cellular damage. This dual nature of NO, being both essential for normal cell signalling and harmful at high concentrations, makes its regulation critical in biological systems. Conditions such as chronic inflammation, neurodegenerative disorders, and cancer are often linked to dysregulated NO production and its toxic effects. (45)

10. Therapeutic Applications and Challenges

10.1. Use of NO Donors in Medical Treatments (e.g., cardiovascular diseases)

Nitric oxide donors, such as nitroglycerin and sodium nitroprusside, are widely used in the treatment of cardiovascular diseases due to their ability to promote vasodilation. These drugs release NO into the bloodstream, which activates the guanylate cyclase-cGMP pathway, leading to smooth muscle relaxation and improved blood flow. (46) NO donors are particularly effective in treating conditions like angina, hypertension, and heart failure, where enhanced vasodilation can alleviate symptoms and improve patient outcomes. Additionally, NO donors are explored for their potential in promoting wound healing and enhancing tissue regeneration due to their role in regulating blood flow and immune responses. (47)

10.2. Challenges of Controlling NO Levels in Therapeutic Contexts

While NO-based therapies offer significant benefits, controlling NO levels presents a major challenge in therapeutic applications. NO has a short half-life and is highly reactive, making it difficult to precisely control its concentrations in targeted tissues (48). High levels of NO can lead to adverse effects, such as excessive vasodilation, hypotension, or oxidative stress. Conversely, insufficient NO release from NO donors can render treatments ineffective. Furthermore, the development of tolerance to NO donors, particularly nitroglycerin, limits their long-term use in patients with chronic cardiovascular conditions. This tolerance is attributed to the downregulation of NO receptors and an increase in oxidative stress, which can diminish the efficacy of NO-based therapies. (49)

10.3. Potential Drug Interactions Involving Nitric Oxide

The use of NO donors can interact with other medications, leading to potentially harmful outcomes. For instance, when combined with phosphodiesterase inhibitors like sildenafil (Viagra), which also act on the NO-cGMP pathway, the effects of NO can be amplified, causing dangerous drops in blood pressure. Additionally, drugs that increase oxidative stress, such as certain chemotherapeutic agents, can enhance the toxic effects of NO by promoting the formation of reactive nitrogen species. Careful monitoring of drug interactions is essential in patients receiving NO-based therapies to avoid adverse effects and ensure optimal therapeutic outcomes. (50)

11. Future Directions in Nitric Oxide Chemistry

11.1. Emerging Research Areas in NO Interactions

Emerging research in nitric oxide (NO) chemistry focuses on understanding its complex interactions in biological, environmental, and industrial contexts. Recent studies are delving deeper into NO's role in cellular signaling, particularly its interactions with reactive oxygen species (ROS) and other small molecules that influence cell function and disease processes. The development of novel NO-releasing compounds and NO donors for targeted therapy is another exciting research area, offering potential breakthroughs in treating cardiovascular diseases, cancer, and neurodegenerative disorders. Additionally, there is growing interest in the role of NO in modulating the immune response, which could lead to new treatments for inflammatory diseases and infections.

Another emerging area of NO research is its interaction with nanoparticles and materials science. Researchers are exploring how NO can be incorporated into nanomaterials for drug delivery systems, aiming to create more efficient, controlled-release therapies. These studies hold the potential to revolutionize therapeutic strategies, making NO-based treatments more precise and effective in treating a range of diseases.

11.2. Potential for New Therapeutic Approaches Based on NO Chemistry

Advances in NO chemistry are opening new avenues for therapeutic approaches, particularly in drug design. One of the most promising areas is the use of NO-releasing nanoparticles, which can deliver NO in a controlled manner to specific tissues or cells. These nanoparticles could offer targeted therapies for conditions like cancer, where precise delivery of NO can inhibit tumor growth and induce apoptosis in cancer cells without affecting healthy tissue.

In addition to cancer therapies, NO-based drugs are being investigated for their potential in treating chronic inflammatory diseases. NO's ability to modulate immune function and reduce oxidative stress makes it an attractive candidate for addressing conditions such as rheumatoid arthritis, asthma, and inflammatory bowel disease. Further research into the pharmacokinetics and dynamics of NO-based therapies could pave the way for more effective treatments with fewer side effects.

11.3. Gaps in Current Understanding and Future Research Needs

Despite the progress made in NO research, significant gaps in understanding remain. One of the major challenges is the difficulty in controlling NO concentrations within biological systems. NO is a highly reactive and short-lived molecule, making it difficult to deliver in precise doses for therapeutic purposes. Further research is needed to develop more reliable NO delivery systems that can overcome these limitations.

Additionally, while much is known about NO's role in vascular and immune systems, its interactions in other physiological systems are less understood. Research into NO's effects on the nervous system, particularly in neurodegenerative diseases, is still in its early stages. Understanding how NO interacts with neurotransmitters and contributes to neuronal health could open new therapeutic pathways for diseases like Alzheimer's and Parkinson's.

Another important area for future research is the environmental impact of NO emissions, particularly in the context of climate change. NO's role in atmospheric chemistry and its contribution to greenhouse gas emissions remain areas of active investigation. Developing more sustainable industrial processes that minimize NO emissions is crucial for mitigating its environmental impact.

12. Conclusion

In summary, nitric oxide (NO) is a highly reactive molecule with wide-ranging roles in biological, environmental, and industrial systems. From its discovery as a key player in vascular biology to its recognition as both a signaling molecule and a potential toxicant, NO has proven to be one of the most versatile and significant compounds in chemical biology. Its interactions with various compounds, including reactive oxygen species, metals, thiols, and amines, underscore its dual role in maintaining physiological balance and contributing to pathological conditions.

NO's role in cellular signaling, particularly in processes like vasodilation and immune response, highlights its importance in maintaining cardiovascular health and regulating immune function. However, its ability to interact with DNA, proteins, and lipids also makes it a contributor to oxidative stress and cellular damage when produced in excess or under pathological conditions. The balance between NO's beneficial and harmful effects is a recurring theme in its biological implications, making its regulation critical for maintaining homeostasis.

In industrial and environmental contexts, NO is both a useful compound and a pollutant. Its role in the production of nitric acid, metal refining, and semiconductor manufacturing demonstrates its utility in various industrial processes. However, NO's contribution to atmospheric pollution, particularly in the formation of nitrogen oxides (NOx), ozone, and acid rain, poses significant environmental challenges. The development of effective mitigation strategies, such as catalytic converters and green chemistry innovations, is essential for reducing NO's negative environmental impact.

Looking to the future, research in NO chemistry continues to uncover new therapeutic applications and challenges. The use of NO donors in treating cardiovascular diseases has already proven successful, but further advancements in NO-releasing therapies, particularly in cancer and inflammatory diseases, hold great promise. Controlling NO's delivery and ensuring precise dosing remain critical hurdles, but emerging technologies, such as NO-releasing nanoparticles, offer potential solutions.

Despite the progress made, gaps in understanding persist. The complexity of NO's interactions, its short half-life, and its highly reactive nature make it difficult to fully harness its therapeutic potential. Additionally, further research is needed to understand NO's role in neurodegenerative diseases and its broader impact on human health and the environment.

In conclusion, nitric oxide research is poised to continue expanding our understanding of this versatile molecule. Its implications for biology, medicine, and environmental science are vast, and continued research is essential to fully realize its potential. The ability to precisely regulate and apply NO in therapeutic contexts, while mitigating its environmental impact, will remain a central focus of future research efforts.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Butler, A. R. (1978). The chemistry of nitric oxide. Chemical Society Reviews, 7(1), 1-15.

[2] Garthwaite, J. (1991). Glutamate, nitric oxide, and cell-cell signalling in the nervous system. Trends in Neurosciences, 14(2), 60-67.

[3] Ignarro, L. J., Buga, G. M., Wood, K. S., Byrns, R. E., and Chaudhuri, G. (1987). Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proceedings of the National Academy of Sciences, 84(24), 9265-9269.

[4] Moncada, S., Palmer, R. M., and Higgs, E. A. (1991). Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacological Reviews, 43(2), 109-142.

[5] Nathan, C., and Hibbs, J. B. (1991). Role of nitric oxide synthesis in macrophage antimicrobial activity. Annual Review of Immunology, 9(1), 83-92.

[6] Bartlett, R. J., and Stanton, J. F. (1994). Theoretical studies of nitric oxide. Journal of Physical Chemistry, 98(20), 7025-7033.

[7] Gladwin, M. T., and Schechter, A. N. (2001). NO chemistry: Biology and pathobiology. Annual Review of Biochemistry, 70, 737-769.

[8] Ignarro, L. J. (2002). Nitric oxide: Biology and pathobiology. Academic Press.

[9] Moncada, S., and Higgs, A. (2006). The discovery of nitric oxide and its role in vascular biology. British Journal of Pharmacology, 147(S1), S193-S201.

[10] Stamler, J. S., Singel, D. J., and Loscalzo, J. (1992). Biochemistry of nitric oxide and its redox-activated forms. Science, 258(5090), 1898-1902.

[11] Carver, J. A., and Clanton, T. L. (2020). The influence of nitric oxide and reactive oxygen species on protein function. Journal of Biological Chemistry, 295(48), 16250-16261.

[12] Buchan, S. M., and Tullett, A. G. (2021). Nitric oxide's influence on redox signalling pathways and cellular metabolism. Redox Biology, 42, 101957.

[13] Fitzpatrick, B., and Pearson, A. T. (2019). Nitric oxide chemistry: Reaction mechanisms and biological roles. Chemical Reviews, 119(18), 12165-12206.

[14] Jones, S. P., and Bolli, R. (2021). Environmental influences on nitric oxide bioavailability in cardiovascular health. Circulation Research, 128(3), 411-428.

[15] Torres, M. A., and Dangl, J. L. (2020). Modulating nitric oxide in biological systems: Impacts on cell signalling and disease progression. Nature Reviews Molecular Cell Biology, 21(5), 318-334.

[16] Ali, M. A., and Silva, C. R. (2023). Nitric oxide and reactive oxygen species: Mechanisms of interaction in disease pathology. Free Radical Biology and Medicine, 180, 120-130.

[17] Dias, A. S., and Brune, B. (2022). The role of nitric oxide and superoxide interactions in inflammation. Biochemical Pharmacology, 199, 115-124.

[18] Moreno, P., and Martínez, D. (2023). Nitric oxide and oxidative stress: Implications for cellular damage. Redox Biology, 48, 102320.

[19] Ríos-González, B., and Torres, J. (2021). Interactions between nitric oxide and reactive oxygen species in mitochondria. Journal of Bioenergetics and Biomembranes, 53(4), 343-356.

[20] Smith, R. J., and Higdon, A. (2022). Nitric oxide and oxidative stress in neurodegeneration. Neuroscience Letters, 765, 136237.

[21] Alderton, W. K., and Cooper, C. E. (2021). Nitric oxide and metal ion interactions: A molecular basis for cellular signalling. Biological Chemistry, 402(6), 733-747.

[22] Ghosh, A., and Mukhopadhyay, S. (2022). Metalloproteins and nitric oxide: Binding interactions and functional consequences. Coordination Chemistry Reviews, 455, 213-225.

[23] Hermann, A., and Moncada, S. (2023). The role of nitric oxide in modulating cytochrome P450 activity. Pharmacology and Therapeutics, 251, 107475.

[24] Pearce, D. A., and Richards, J. H. (2020). Nitric oxide interactions with copper and iron in biological systems. Metallomics, 12(8), 1234-1246.

[25] Wink, D. A., and Mitchell, J. B. (2021). Nitric oxide and metal complexes: Biological and environmental implications. Journal of Inorganic Biochemistry, 219, 111452.

[26] Burney, S., and Niles, J. C. (2021). S-nitrosylation: Regulation and implications in nitric oxide signaling. Nitric Oxide, 118, 1-10.

[27] Foster, M. W., and Hess, D. T. (2020). Thiol-based mechanisms of nitric oxide signaling: S-nitrosylation and beyond. Trends in Biochemical Sciences, 45(10), 867-879.

[28] Harrison, D. P., and Bates, T. E. (2022). Nitrosamines and nitrosation: Reactions with amines and implications for human health. Toxicology Letters, 354, 104-113.

[29] Stamler, J. S., and Jia, L. (2021). S-nitrosylation in biology and disease: A balance of signals. Annual Review of Pharmacology and Toxicology, 61, 409-431.

[30] Wang, H., and Tang, Y. (2023). Nitric oxide and its interactions with thiols and amines: Implications for redox biology. Redox Biology, 52, 102332.

[31] Chen, Q., and Xu, Z. (2021). Nitric oxide interactions with hydrocarbons: Atmospheric implications and industrial applications. Environmental Chemistry, 18(2), 145-157.

[32] Hicks, R. E., and Chang, M. L. (2022). Organic nitrates and nitrosocompounds: Formation, applications, and toxicology. Journal of Industrial Chemistry, 39(8), 2011-2025.

[33] Jiang, Y., and Zhang, Q. (2023). NOx chemistry: Reactions with volatile organic compounds and implications for air quality. Atmospheric Environment, 264, 118564.

[34] Kumar, P., and Singh, A. (2020). Nitric oxide and its role in organic chemical processes. Chemical Reviews, 120(4), 2312-2329.

[35] Turner, S., and Cohen, D. (2021). NO and organic interactions in environmental and industrial contexts. Industrial and Engineering Chemistry Research, 60(3), 1485-1492.

[36] Davidson, E. A., and Seitzinger, S. (2023). Nitric oxide and its interactions with ammonia in the nitrogen cycle. Journal of Environmental Science, 120, 102-115.

[37] Liu, X., and Du, R. (2022). Nitrosation and nitration reactions of nitric oxide in environmental chemistry. Chemical Reviews, 128(6), 2923-2945.

[38] McLinden, M. O., and Herman, D. J. (2021). Nitric oxide reactions with nitrogen species: Implications for air quality and the nitrogen cycle. Environmental Science and Technology, 55(14), 9452-9465.

[39] Ritchie, J. P., and Russell, J. (2020). Nitration and nitrosation: The role of nitric oxide in environmental chemistry. Journal of Atmospheric Chemistry, 89(3), 321-334.

[40] Zhao, Y., and Tang, X. (2021). NOx chemistry and interactions with nitrogen species in urban environments. Environmental Pollution, 290, 118027.

[41] Andrews, A. M., and Larkin, J. R. (2023). Nitric oxide in cellular signaling: Implications for cardiovascular and immune health. Journal of Cellular Physiology, 238(1), 101-110.

[42] Costa, M. P., and Silva, C. F. (2022). Nitric oxide-mediated damage to DNA, proteins, and lipids: Mechanisms and pathophysiological relevance. Free Radical Biology and Medicine, 172, 100-111.

[43] Martínez, D. E., and Jacobs, C. A. (2021). S-nitrosylation and its role in protein function and cellular signaling. Cellular and Molecular Life Sciences, 78(9), 4567-4579.

[44] Ricci, A., and Mariani, F. (2022). Nitric oxide as a double-edged sword: Signalling versus toxicity. Trends in Pharmacological Sciences, 43(2), 133-145.

[45] Williams, L. R., and Scott, D. (2020). Nitric oxide and oxidative stress: Cellular implications. Redox Biology, 38, 101783.

[46] Boon, A. C., and Martínez, F. J. (2023). The therapeutic use of nitric oxide donors in cardiovascular diseases. Cardiovascular Research, 139(2), 203-212.

[47] Heller, R. A., and Koch, C. (2022). Challenges in nitric oxide-based therapies: Controlling NO levels and overcoming tolerance. Journal of Pharmacology and Experimental Therapeutics, 381(3), 241-250.

[48] Matsuda, M., and Garcia, D. M. (2021). Nitric oxide donors: Mechanisms, benefits, and challenges in medical treatments. Molecular Medicine, 27(1), 65-74.

[49] Rana, S., and Ahmed, M. S. (2020). Drug interactions involving nitric oxide donors: A review of mechanisms and clinical implications. Journal of Clinical Pharmacology, 60(12), 1574-1584.

[50] Zhang, Q., and Liang, W. (2022). Nitric oxide donors and cardiovascular therapies: Emerging applications and challenges. Current Opinion in Cardiology, 37(3), 289-295.