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PHARMACOLOGICAL MODULATION OF NITRIC OXIDE: A REVIEW

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Nitric Oxide

Nitric oxide (NO) is the smallest endogenous signaling molecule produced in the human body. It was identified in the 1980s as an important biological mediator involved in several physiological processes.

The concept of a relaxing factor released from the endothelium was first proposed by Robert Furchgott and John Zawadzki, who suggested that endothelial cells produce a soluble substance responsible for vascular relaxation, which they termed endothelium-derived relaxing factor (EDRF). [1] Later, in 1987, Louis Ignarro confirmed that EDRF is chemically identical to nitric oxide. This discovery significantly advanced the understanding of vascular physiology and cell signaling.[2] In recognition of their contributions, Robert Furchgott, Ferid Murad, and Louis Ignarro were awarded the Nobel Prize in Physiology or Medicine 1998.[3]

Major Actions of Nitric Oxide

Nitric oxide plays multiple important roles in the body:

- It causes relaxation of vascular and visceral smooth muscle, leading to vasodilation
- It inhibits platelet aggregation
- It acts as a neurotransmitter in both the central and peripheral nervous systems
- It contributes to the microbicidal activity of macrophages
- It is involved in various pathological conditions such as inflammatory diseases, septic shock, and pulmonary hypertension

Generation and Fate of Nitric Oxide

Nitric oxide (NO) is synthesized endogenously from the amino acid L-arginine by the enzyme nitric oxide synthase (NOS). This enzymatic reaction requires molecular oxygen and reducing equivalents from NADPH. Several cofactors are essential for this process, including flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), tetrahydrobiopterin (BH_4), and heme. During the reaction, L-arginine is converted into L-citrulline, with the simultaneous release of nitric oxide.

Once formed, NO is a highly diffusible and short-lived free radical. It rapidly diffuses from endothelial cells to adjacent smooth muscle cells, where it exerts its biological effects. However, due to its reactive nature, NO undergoes several metabolic fates in the body.

In the presence of oxygen, nitric oxide is oxidized to form nitrite (NO_2^-) and subsequently nitrate (NO_3^-), which represent its stable end products in biological systems. Additionally, NO can interact with hemoglobin to form nitrosylated compounds, contributing to its rapid inactivation in circulation.

Another important pathway involves the reaction of NO with superoxide anion (O_2^-), leading to the formation of peroxynitrite ($ONOO^-$), a highly reactive and cytotoxic species. Peroxynitrite is capable of inducing lipid peroxidation, protein modification, and cellular injury, thereby contributing to pathological processes.

Thus, while nitric oxide plays a crucial physiological role, its reactive intermediates and metabolites are also implicated in tissue damage under conditions of oxidative stress.[4,5]

Nitric Oxide Synthase (NOS): Isoforms, Localization, and Functions

Nitric oxide is synthesized by a family of enzymes known as nitric oxide synthases (NOS). There are three main isoforms, neuronal (nNOS), inducible (iNOS), and endothelial (eNOS) each differing in their location, regulation, and function.

Neuronal Nitric Oxide Synthase (nNOS / NOS-1)

Neuronal NOS is mainly found in neurons of the brain, spinal cord, and peripheral nerves. It is also present in skeletal muscle. This isoform is constitutively expressed, meaning it is continuously produced at a relatively low level.

Its activity depends on intracellular calcium and calmodulin. When calcium levels rise, nNOS is activated and produces nitric oxide. Functionally, nNOS plays an important role in neurotransmission, neuronal signaling, and synaptic plasticity.[6]

Inducible Nitric Oxide Synthase (iNOS / NOS-2)

Inducible NOS is primarily expressed in macrophages, monocytes, neutrophils, hepatocytes, and smooth muscle cells. Unlike the other isoforms, iNOS is not normally present under resting conditions. Its expression is induced during inflammatory states, particularly by bacterial endotoxins and cytokines such as interferon-γ, interleukin-1β, and tumor necrosis factor-α.

Once induced, iNOS produces large amounts of nitric oxide over a prolonged period. Its activity is largely independent of calcium. The nitric oxide generated by iNOS contributes to host defense by promoting microbial killing, but excessive production can lead to tissue damage and inflammation.[7]

Endothelial Nitric Oxide Synthase (eNOS / NOS-3)

Endothelial NOS is located mainly in vascular endothelial cells and platelets, and to some extent in cardiac myocytes. Like nNOS, it is constitutively expressed and produces nitric oxide at a steady rate.

Its activation is calcium-calmodulin dependent. eNOS-derived nitric oxide plays a crucial role in maintaining vascular homeostasis. It causes vasodilation, helps regulate blood pressure, and inhibits platelet aggregation, thereby preventing thrombosis. [7,8]

Actions and Role of Nitric Oxide in the Vascular System

Nitric oxide (NO) is a major endogenous regulator of vascular tone and plays a central role in maintaining vascular homeostasis. It is synthesized in endothelial cells by endothelial nitric oxide synthase (eNOS) in response to physiological stimuli such as shear stress and receptor-mediated agonists including acetylcholine.

Following its synthesis, NO diffuses into adjacent vascular smooth muscle cells, where it activates soluble guanylyl cyclase, resulting in increased intracellular cyclic guanosine monophosphate (cGMP) levels. This leads to activation of protein kinase G, which reduces intracellular calcium concentration through multiple mechanisms, including inhibition of calcium influx and enhancement of calcium sequestration. [7] The decrease in intracellular calcium suppresses myosin light chain kinase activity and promotes myosin light chain dephosphorylation, thereby inhibiting actin–myosin interaction and causing smooth muscle relaxation. Additionally, NO modulates ion channel activity, further contributing to vasodilation.

Overall, NO-mediated vasodilation is essential for the regulation of blood pressure, tissue perfusion, and prevention of platelet aggregation. Impairment of this pathway is implicated in the pathogenesis of cardiovascular diseases such as hypertension and atherosclerosis.[9]

Role of Nitric Oxide in Platelet Function

Nitric oxide (NO) plays a crucial role in the regulation of platelet activity and thrombus formation. It is synthesized by endothelial cells and diffuses readily into circulating platelets, where it exerts potent antiplatelet effects.

Within platelets, NO activates soluble guanylyl cyclase, leading to an increase in intracellular cyclic guanosine monophosphate (cGMP) levels. Elevated cGMP inhibits platelet activation by reducing intracellular calcium concentration and interfering with signaling pathways required for platelet aggregation.[10]

As a result, NO suppresses platelet adhesion, activation, and aggregation, thereby preventing thrombus formation. This mechanism is essential for maintaining blood fluidity and protecting against pathological thrombosis.[11]

In conditions where endothelial function is impaired, such as atherosclerosis, reduced production or bioavailability of NO leads to enhanced platelet aggregation and an increased risk of thrombus formation. Thus, the antiplatelet action of nitric oxide represents a key protective mechanism in cardiovascular physiology.

Role of Nitric Oxide in Infection, Inflammation, and Immune Function

Nitric oxide (NO) plays a significant role in host defense, inflammation, and immune regulation. It is primarily produced by inducible nitric oxide synthase (iNOS) in activated macrophages and other immune cells in response to inflammatory stimuli such as bacterial endotoxins and pro-inflammatory cytokines.

During infection, activation of macrophages leads to the production of large amounts of NO over a sustained period. This high-output NO reacts with reactive oxygen species, particularly superoxide anion, to form peroxynitrite, a highly reactive molecule with potent cytotoxic properties. These reactive nitrogen species contribute to the destruction of a wide range of pathogens, including bacteria, viruses, fungi, and protozoa. [12]

In addition to its antimicrobial activity, NO plays a complex role in inflammation. It promotes vasodilation and increases vascular permeability, facilitating the migration of immune cells to sites of infection or injury. Nitric oxide also modulates the production of

inflammatory mediators, including prostaglandins, thereby influencing the inflammatory response.[7]

However, excessive or prolonged production of NO can contribute to tissue injury and pathological inflammation. High levels of reactive nitrogen species may lead to oxidative damage, lipid peroxidation, and cellular dysfunction, which are implicated in conditions such as septic shock and chronic inflammatory diseases.[13] Thus, nitric oxide has a dual role in immune function—providing essential antimicrobial defense while also contributing to inflammatory tissue damage when produced in excess.

Detrimental Effects of Excess and Prolonged Nitric Oxide Production

Although nitric oxide (NO) plays an essential role in physiological processes, excessive and sustained production can lead to significant tissue injury and contribute to various pathological conditions. This is particularly evident in inflammatory states where inducible nitric oxide synthase (iNOS) generates large amounts of NO over prolonged periods.

High concentrations of NO readily react with reactive oxygen species, especially superoxide anion, forming peroxynitrite and other reactive nitrogen species. These highly reactive molecules can induce oxidative stress, leading to lipid peroxidation, protein modification, DNA damage, and ultimately cellular dysfunction and death. [14]

In respiratory conditions such as asthma, increased expression of iNOS in the bronchial epithelium results in elevated NO levels, which contribute to airway inflammation and hyperresponsiveness. Similarly, in chronic inflammatory disorders, excessive NO production within inflamed tissues exacerbates local tissue damage.[7] In the gastrointestinal tract, particularly in inflammatory bowel disease, elevated NO levels are associated with mucosal injury and disease progression. The persistent presence of reactive nitrogen species in such conditions further amplifies inflammatory cascades and cellular injury.[15] Thus, while nitric oxide is essential for host defense and physiological regulation, its overproduction represents a double-edged sword, contributing to the pathogenesis of several inflammatory and degenerative diseases.

Role of Nitric Oxide in the Nervous System

Nitric oxide (NO) functions as an important neurotransmitter and neuromodulator in both the central and peripheral nervous systems. Unlike classical neurotransmitters, NO is not stored in synaptic vesicles; instead, it is synthesized on demand and diffuses freely across cell membranes.

In the nervous system, NO is primarily produced in neurons by neuronal nitric oxide synthase (nNOS). Excitatory glutamatergic neurons represent a major source of NO production, particularly following activation of N-methyl-D-aspartate (NMDA) receptors, which leads to calcium influx and subsequent activation of nNOS.[16]

Nitric oxide plays a diverse role in neural function. It is involved in the modulation of nociception and contributes to both central and peripheral pain pathways. In the brain, NO regulates cerebral blood flow by inducing vasodilation, thereby ensuring adequate oxygen and nutrient delivery to neural tissue. [17]

Additionally, NO is critically involved in higher brain functions, including learning and memory. It facilitates synaptic plasticity, particularly in processes such as long-term potentiation, which underlies memory formation. Through these mechanisms, NO acts as a key signaling molecule in neuronal communication and functional adaptation. [17]

However, excessive production of NO in the nervous system may contribute to neurotoxicity through the formation of reactive nitrogen species, highlighting its dual role in both physiological and pathological processes.

Nitric Oxide and Excitotoxicity in the Nervous System

Excess production of nitric oxide (NO) in the nervous system can be harmful and is involved in a process called excitotoxicity. This mainly occurs when glutamate activity is increased, especially through overactivation of NMDA receptors.[18]

When NMDA receptors are excessively stimulated, there is a continuous influx of calcium ions into the neuron. This rise in intracellular calcium activates neuronal nitric oxide synthase (nNOS), leading to increased formation of nitric oxide. In such conditions, NO reacts with superoxide radicals to form highly reactive compounds like peroxynitrite. [19]

These reactive molecules can damage cell structures by causing lipid peroxidation, protein damage, mitochondrial dysfunction, and DNA injury. Over time, this leads to neuronal cell death.

This mechanism is believed to play an important role in neurodegenerative diseases such as Parkinson's disease, Huntington's disease, and Amyotrophic lateral sclerosis.[7] Thus, nitric oxide has a dual role in the nervous system. While it is necessary for normal neuronal signaling, its excessive production can contribute to neuronal injury and disease.

Role of Nitric Oxide in the Genitourinary and Gastrointestinal Systems

Nitric oxide (NO) also functions as an important neurotransmitter in the genitourinary and gastrointestinal systems. It is released from non-adrenergic, non-cholinergic (NANC) neurons, which play a key role in regulating smooth muscle activity in these organs.

In the gastrointestinal tract, NO contributes to smooth muscle relaxation and helps coordinate processes such as peristalsis and sphincter control.

In the genitourinary system, nitric oxide is essential for penile erection. During sexual stimulation, activation of pelvic nerves leads to the release of NO from NANC neurons in the corpora cavernosa. Nitric oxide then causes relaxation of smooth muscle in the penile vasculature, resulting in increased blood flow and engorgement of erectile tissue. [20] This mechanism forms the physiological basis for erection, and impairment of NO signaling can lead to erectile dysfunction.

Role of Nitric Oxide in the Lungs

Nitric oxide (NO) plays an important role in controlling blood flow in the lungs by reducing pulmonary vascular resistance. Decreased NO activity is seen in Pulmonary arterial hypertension, where pulmonary artery pressure increases.

Inhaled NO is used in clinical practice to dilate pulmonary vessels and reduce pulmonary pressure, especially in newborns with severe respiratory distress and pulmonary hypertension. It helps improve oxygenation without affecting systemic blood pressure significantly.

NO also has a mild bronchodilator effect. Drugs like Sildenafil enhance the action of NO and are commonly used in the treatment of pulmonary arterial hypertension. [7,21]

Drugs Modulating Nitric Oxide

Several drugs act by increasing or decreasing nitric oxide (NO) activity through different mechanisms.

NO donors such as Nitroglycerin increase intracellular cGMP levels by directly releasing nitric oxide, leading to vasodilation.

Phosphodiesterase-5 inhibitors like Sildenafil prevent the breakdown of cGMP, thereby enhancing the effects of NO.

Soluble guanylyl cyclase stimulators such as Riociguat directly activate guanylyl cyclase and increase cGMP production.

Drugs like L-arginine act as substrates for nitric oxide synthase (NOS) and increase NO production, while ACE inhibitors and statins improve endothelial function and enhance NO availability.

On the other hand, NOS inhibitors reduce NO formation, and agents like Methylene blue block NO-mediated signaling.

Some beta-blockers, such as Nebivolol and Celiprolol, have additional NO-releasing properties. Drugs like Nicorandil act partly through nitrate-like mechanisms. [22,23]

NO Donors: Nitrates

NO donors are drugs that release nitric oxide (NO) or a similar substance in the body. This release usually occurs through enzymatic processes and leads to relaxation of smooth muscle, especially in blood vessels.

Commonly used NO donors include organic nitrates, nitrites, and Sodium nitroprusside. Different NO donors produce different patterns of vasodilation. This depends on how quickly and how much nitric oxide is released from each drug. [7]

Common NO Donors and Their Actions

Glyceryl trinitrate mainly acts on veins and coronary arteries, so it is considered a preferential venodilator. It releases nitric oxide through mitochondrial aldehyde dehydrogenase. Tolerance can develop with its repeated use.

Isosorbide dinitrate and Isosorbide mononitrate mainly cause venodilation at low doses, while at higher doses they can also dilate arterioles. Their exact mechanism of nitric oxide release is not clearly understood. These drugs are known to develop tolerance relatively quickly.

Sodium nitroprusside dilates both veins and arterioles equally. It acts by directly activating guanylyl cyclase and does not usually show tolerance.

Amyl nitrite dilates both arteries and veins, including coronary vessels. Its mechanism of nitric oxide release is not well defined, and tolerance is generally not seen. [24,25]

Pharmacokinetics of Nitrates

Nitrates are lipid-soluble drugs, which allows them to cross biological membranes easily. They are well absorbed from the buccal mucosa, gastrointestinal tract, and even through the skin.

These drugs can be given orally, but they are also commonly administered by sublingual, transdermal, or intravenous routes depending on the clinical need.

After absorption, nitrates are rapidly metabolized in the body, mainly by enzymes such as glutathione reductase and aldehyde dehydrogenase. This metabolism leads to the release of nitric oxide.

The duration of action of nitrates depends on how quickly they are metabolized and the route by which they are administered.[7,26]

Therapeutic Uses of Nitrates

Nitrates are mainly used in the management of cardiovascular conditions. They are widely used in Angina pectoris, including both classical and variant types, where they relieve chest pain by reducing myocardial oxygen demand.

They are also useful in acute coronary syndromes such as unstable angina and NSTEMI, and in Myocardial infarction to improve coronary blood flow.

In patients with Congestive heart failure, nitrates help by reducing preload and afterload, thereby decreasing pulmonary congestion and improving cardiac function.

Apart from cardiac uses, nitrates can relieve smooth muscle spasm. They are helpful in conditions like biliary colic and esophageal spasm, where they reduce pain by causing muscle relaxation.

In cases of Cyanide poisoning, agents like Amyl nitrite are used as part of the treatment protocol. [27, 28]

Adverse Effects of Nitrates

- The most common adverse effect of nitrates is a throbbing headache, which occurs due to vasodilation of cerebral vessels.
- Patients may also experience symptoms such as sweating, weakness, flushing, palpitations, dizziness, and fainting. These effects are mainly related to postural hypotension caused by vasodilation.
- Methemoglobinemia is a rare but important adverse effect, especially with high doses.
- Skin rashes may occur occasionally and are more commonly seen with drugs like Pentaerythritol tetranitrate. [7, 27]

Tolerance to Nitrates

Tolerance is a well-known problem with prolonged use of nitrates, where the response to the drug gradually decreases over time.

One important mechanism is reduced production of nitric oxide due to decreased activity of mitochondrial aldehyde dehydrogenase. Increased formation of reactive oxygen species also reduces the availability of nitric oxide.

In addition, the body activates compensatory mechanisms such as fluid retention, increased sympathetic activity, and activation of the renin–angiotensin system. These changes oppose the vasodilatory effect of nitrates.

Because of these factors, higher doses may be required with continued use, which can further worsen tolerance. [27]

Drug Interactions of Nitrates

Nitrates show important drug interactions, mainly due to their strong vasodilatory effect.

Co-administration of nitrates with phosphodiesterase-5 inhibitors such as Sildenafil can lead to a marked increase in cGMP levels, resulting in severe hypotension. This combination is contraindicated, as it may lead to serious complications including myocardial infarction and even death.

Nitrates may also interact with other vasodilators, leading to additive hypotensive effects. Therefore, caution is required when they are used together. [27]

Phosphodiesterase-5 (PDE-5) Inhibitors

Nitric oxide (NO) causes smooth muscle relaxation by increasing the levels of cyclic guanosine monophosphate (cGMP).

cGMP is normally broken down by the enzyme phosphodiesterase-5 (PDE-5). Inhibition of this enzyme prevents the breakdown of cGMP, leading to its accumulation.

As a result, the effect of nitric oxide is enhanced and prolonged, causing sustained smooth muscle relaxation and vasodilation. Drugs such as Sildenafil act through this mechanism. [7,27]

Common PDE-5 Inhibitors

Sildenafil has a half-life of about 4 hours and reaches peak plasma levels within 1–2 hours. Its oral bioavailability is around 40%. It mainly inhibits PDE-5 but can also affect PDE-6, which explains the side effect of blue vision.

Tadalafil has a longer half-life of about 18 hours, with peak levels reached in 30 minutes to 2 hours. Its oral bioavailability is around 25–30%. It also has some activity on PDE-6 and PDE-2, and may cause back pain and muscle pain.

Vardenafil has a half-life of about 4–5 hours and reaches peak plasma levels in 30 minutes to 2 hours. Its oral bioavailability is about 15%. It is more selective for PDE-5 but may cause QT interval prolongation.[7]

Adverse Effects of PDE-5 Inhibitors

- Most adverse effects of PDE-5 inhibitors are due to vasodilation.
- Common effects include headache, nasal congestion, dizziness, and facial flushing. A fall in blood pressure may also occur, especially when combined with other vasodilators.
- Some patients may experience gastrointestinal symptoms such as loose motions, gastric reflux, and dyspepsia.
- Visual disturbances, particularly impairment of colour vision, are mainly associated with Sildenafil due to its action on PDE-6 in the retina. [27,28]

Contraindications and Precautions of PDE-5 Inhibitors

PDE-5 inhibitors should be used with caution in patients with Coronary heart disease, especially where there is a risk of hypotension.

They should not be used along with nitrates, and nitrates must be avoided for at least 24 hours after taking drugs like Sildenafil due to the risk of severe hypotension.

Patients with conditions such as Leukemia, Sickle cell anemia, and Multiple myeloma are at increased risk of priapism and should be treated carefully.

These drugs should also be used cautiously in patients with liver disease, kidney disease, peptic ulcer, and bleeding disorders.[7]

Drug Interactions of PDE-5 Inhibitors

PDE-5 inhibitors are mainly metabolized by the CYP3A4 enzyme system. Drugs that inhibit this enzyme can increase the levels and effects of PDE-5 inhibitors. Common CYP3A4 inhibitors include Erythromycin, Ketoconazole, Verapamil, and Cimetidine.

When used together, these drugs can enhance the effects of PDE-5 inhibitors and increase the risk of adverse effects, so caution is required. [7,27]

sGC Stimulator: Riociguat

Riociguat is a drug that directly acts on soluble guanylyl cyclase (sGC), an important enzyme in the nitric oxide pathway.

It works by directly stimulating sGC and also by increasing its sensitivity to endogenous nitric oxide. This leads to increased production of cGMP, resulting in vasodilation.

Riociguat is mainly used in the treatment of Chronic thromboembolic pulmonary hypertension and Pulmonary arterial hypertension.[29]

Pharmacokinetics of Riociguat

Riociguat has high oral bioavailability of about 94%. It reaches peak plasma concentration within approximately 1.5 hours after administration.

Food does not significantly affect its absorption. The drug has a volume of distribution of around 30 L and is transported by P-glycoprotein.

Riociguat is metabolized in the liver mainly by cytochrome P450 enzymes, including CYP1A1, CYP3A, CYP2C8, and CYP2J2. It is also known to cross the placenta.[7]

Adverse Effects of Riociguat

Riociguat is associated with some important adverse effects.

It can cause serious fetal harm and is contraindicated in pregnancy due to the risk of birth defects. Hypotension is another significant adverse effect, resulting from its vasodilatory action.

There is also an increased risk of bleeding, including bleeding from the respiratory tract. In some patients, symptoms may worsen in conditions associated with veno-occlusive disease.

Common adverse effects include headache, dizziness, indigestion, and peripheral edema such as swelling of the hands, legs, feet, and ankles. Gastrointestinal symptoms like nausea, diarrhea, and vomiting may also occur. [7,30]

Contraindications of Riociguat

Riociguat is contraindicated in pregnancy due to its teratogenic potential and risk of serious fetal harm.

It should also be avoided in patients with pulmonary hypertension associated with Idiopathic interstitial pneumonia, as it may worsen clinical outcomes in these patients.

Drug Interactions of Riociguat

Riociguat shows several important drug interactions due to its vasodilatory effects and hepatic metabolism.

Concomitant use with nitrates or nitric oxide donors can lead to severe hypotension and is contraindicated. Similarly, its use with phosphodiesterase-5 inhibitors (such as Sildenafil) is also contraindicated due to additive hypotensive effects.

- Antacids can reduce the absorption of riociguat and should be administered with a time gap.
- Smoking significantly reduces the bioavailability of riociguat, leading to decreased therapeutic response. [31,32]
- Drugs that inhibit CYP enzymes, such as Cimetidine, Ketoconazole, and Ritonavir, can increase riociguat levels and enhance hypotensive effects.
- On the other hand, enzyme inducers like Rifampicin, Phenytoin, Carbamazepine, and Phenobarbital can reduce its plasma levels and effectiveness.

Recent Advances in Nitric Oxide Modulating Drugs

Recent developments in nitric oxide–based therapy have focused on newer drugs and targeted delivery systems.

Berdazimer sodium is a recently approved topical nitric oxide–releasing drug. It received approval in January 2024 for the treatment of Molluscum contagiosum.

Latanoprostene bunod is another important advancement. It is used in the management of Glaucoma and ocular hypertension. It combines prostaglandin activity with nitric oxide release to improve aqueous humor outflow.

Newer strategies include nitric oxide–releasing drugs and advanced drug delivery systems that allow controlled and sustained release of nitric oxide.

“Smart” nitric oxide donors are also being developed. These are designed to release nitric oxide in response to specific stimuli such as changes in pH, enzymatic activity, or near-infrared light, allowing site-specific and controlled drug action. [33,34]

Emerging Drug Delivery Systems in Nitric Oxide Therapy

Recent research has focused on developing more stable and targeted nitric oxide delivery systems.

Stable nitric oxide donors such as S-nitrosothiols (e.g., S-nitrosoglutathione) allow sustained and localized release of nitric oxide, improving therapeutic efficacy while reducing systemic side effects.

Advanced drug delivery systems are being widely explored. Nanoparticles are used for targeted delivery, especially in tumor therapy. Hydrogels are useful in wound healing by providing controlled nitric oxide release at the site of injury. Graphene-based systems have a high capacity for nitric oxide loading, while cyclodextrins are being studied for dual delivery of drugs along with nitric oxide.

These approaches have important clinical implications. Nitric oxide–based systems show strong antimicrobial and anti-biofilm activity, promote tissue regeneration, and are being explored in precision cardiovascular therapy, including nitric oxide–eluting systems.[35,36]

CONCLUSION

Nitric oxide is an important signaling molecule involved in many physiological functions such as control of vascular tone, platelet activity, nerve signaling, and immune responses. Drugs acting on the nitric oxide pathway, including nitrates, phosphodiesterase-5 inhibitors, and soluble guanylyl cyclase stimulators like Riociguat, have an established role in the treatment of cardiovascular and pulmonary diseases.

At the same time, their clinical use is limited by problems such as development of tolerance with nitrates, significant drug interactions, and adverse effects. Careful understanding of these limitations is necessary for their rational and safe use in patients.

In recent years, newer approaches such as novel nitric oxide donors, advanced drug delivery systems, and stimulus-responsive ("smart") release mechanisms have shown encouraging results. These strategies aim to provide more targeted and controlled delivery of nitric oxide.

In conclusion, nitric oxide–modulating drugs remain a dynamic and evolving area in pharmacology, with scope for wider clinical applications in the future.

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