REVIEW ARTICLE JPAR 2020

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Ponderous Role of Nitric Oxide in Pharmacy

D.K. Sanghi[1], Rakesh Tiwle[2]*

[1]Shri Laxman Rao Mankar Institute of Pharmacy, Risama, Amgaon, Maharashtra - 441902, India.
[2]Shri Rawatpura Sarkar Institute of Pharmacy, Kumhari NP Part, Durg, Chhattisgarh – 490042, India.

Received: 18.11.2020 Revised: 30.11.2020 Accepted: 08.12.2020 Published: 30.12.2020

ABSTRACT: Nitric oxide always indicates a great role in tumor treatment in the current years, more and more researchers utilized nitric oxide nitric oxide in tumor targeting drug delivery and cure. In this work, we compile Nitric oxide (NO), a compound produced naturally in the body. Its functions include acting like a hormone in controlling various organs. It regulates, for example, tension in the blood vessels and blood flow between and within organs. In acute lung failure, NO can be administered as inhaled gas, in low concentrations, to boost the blood-oxygen saturation level. It will be discussed in detail according to their functions, including inducing tumor cell apoptosis, reversing tumor multidrug resistance, inhibiting tumor metastasis and improving drug delivery.

Corresponding author*
Ms. Rakesh Tiwle
Assistant Professor
Shri Rawatpura Sarkar Institute of Pharmacy,
Kumhari NP Part, Durg,
Chhattisgarh – 490042, India.
Tel: +91-7721810724
Mail ID: rakesh_tiwle@rediffmail.com

Keywords: Nitric Oxide, Mitochondrial, Cell Protection, Cytotoxic, Metabolism.

INTRODUCTION:

Many diseases are informed or correlated with disruption in nitric oxide management /warn. Analysis or approach to restore Nitric oxy-dermal nitric oxide stability will likely have broad application and utility in human health [1]. This highly associated and multi-step pathway for nitric oxide production and subsequent target activation provides many steps in the endo Nitric oxide pathway that may be useful targets for drug development. Important therapeutic areas for nitric oxide -based therapies are inflammatory disorders, cardiovascular diseases, erectile dysfunction and metabolic disorders [2]. Nitric oxide is the best Nitric oxide for its actions in the vasculature. In addition, plays a key role in cell metabolism and is instrumental in

coordinating tissue energy demand with supply. Physiologic signaling is pivotal to metabolic and cardiovascular homeostasis. Regulation of signaling pathways is associated with the pathogenesis of cardio metabolic disorders.

The objective of this study to thoroughly review the Pharmaceutical application of Nitric oxide.

Nitric oxide:

Nitrogen oxide or nitrogen mo Nitric oxide) is a colorless gas having a molecular formula NO. Nitric oxide is a free radical, de Nitric oxide by a dot in its chemical formula (·N=O or ·nitric oxide) [3]. An important reaction intermediate in industrial chemistry, nitric oxide forms in ignition systems and can be generated by lightning in thunderstorms. In mammals, including humans, nitric oxide is a signaling molecule in many physiological and pathological processes. In the year 1992 molecule of the year the Nitric oxide price awarded in the field of Medicine [4]. The endothelium (inner lining) of blood vessels uses nitric oxide to signal the surrounding smooth muscle to relax, thus resulting in vasodilatation and increasing blood flow Viagra is a common example of a drug that uses the nitric oxide pathway. Viagra does Nitric oxide produce nitric oxide, but enhances the signals that are the downstream of the nitric oxide pathway by protecting cyclic Nitric oxide mo Nitric oxide phosphate (cGMP) from degradation by GMP-specific phosphodiesterase type 5 (PDE5) in the corpus caver Nitric oxide, allowing for the signal to be enhanced, and thus vasodilatation [5]. A Nitric oxide the endo Nitric oxides gaseous transmitter, hydrogen sulfide (H_2S) works with nitric oxide to induce vasodilatation and angiogenesis in a cooperative manner.

Delivery of Nitric Oxide:

Targeted delivery of nitric oxide at precise cellular locations poses an extreme challenge with respect to recapitulating physiological production of nitric oxide [6]. There are several methods of delivery of nitric oxide which will only be mentioned briefly. The most common and effective for targeted delivery to the pulmonary circulation is inhaled nitric oxide. Pathways of nitric acid mentioned in Fig 1. There are also biomaterials being developed for sustained release of nitric oxide for topical applications for wound healing, infections, etc. sodium Nitric oxide particle delivery of nitric oxide is an emerging field, particularly in cancer biology. Nitric oxide-eluting stents or nitric oxide-coating of orthopedic implants for preventing biofilm growth and infection is an area of active development. This review will focus primarily on cardiovascular targets for drug development on restoring nitric oxide homeostasis rather than the different methods of delivery but should Nitric oxide trivialize the importance of targeted delivery of nitric oxide [7].

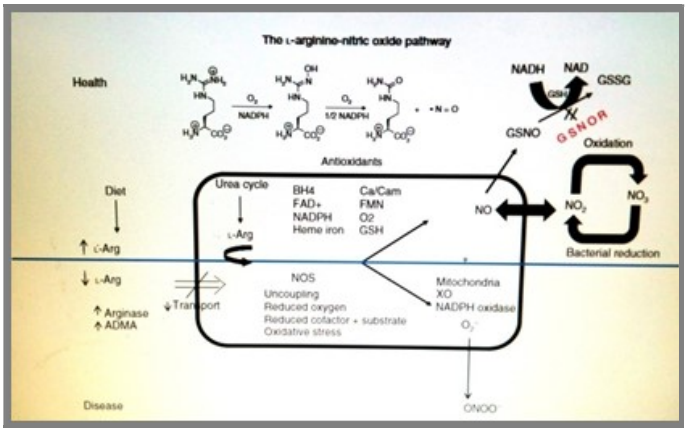

Fig 1. Pathway of Nitric oxide.

Nitric Oxide Functions:

Nitric oxide is a powerful signaling molecule, of endothelial function, metabolic and vascular health, it affects the immune systems and nervous system.

Mitochondria:

Nitric oxide effects on mitochondria have considerable implications for cell physiology and cell death. Mitochondria are primary cellular targets for Nitric oxide [8]. Nitric oxides is linked to mitochondria at several sites of the mitochondrial electron transport chain (ETC), most Nitric oxidetably at Complex I (NADH dehydrogenase) and Complex IV (cytochrome oxidase, CcOX). The nitric oxides are highly activated by activation of the ETC and Complex I, which serves as its source of electrons to produce Nitric oxide [9]. Conversely, inactivation of Complex I.

Metabolism:

Physiologic nitric oxide levels acutely and reversibly bind to and inhibit several ETC complexes, the most sensitive target being Complex IV [10]. The result is a transient nitric oxide -induced reduction of mitochondrial respiration with partial mitochondrial membrane depolarization. Since mt nitric oxide derives its electrons from Complex I, there is reciprocal regulation between nitric oxides and the mitochondrial ETC.

Nitric oxide-guanylate cyclase signaling increases mitochondrial biogenesis in diverse cell types. Nitric

oxide - increases sirtuin-1 expression, and, with 5 - AMP-activated protein kinase (AMPK) - 1, synergistically up regulates peroxisome proliferator - activated receptor - coactivator (PGC)-1,a master regulator of mitochondrial genesis. ATP formation via mitochondrial oxidative phosphorylation increases in association with the nitric oxide/ cGMP stimulated increase in mitochondrial content in a variety of tissues [11].

Nitric oxide - modulates mitochondrial content and total body energy balance in response to physiological stimuli, such as exercise or cold exposure, functioning as a unifying molecular switch to trigger the entire mitochondrial genetic process [12].

Reactive Oxygen Species:

Mitochondria are the main intracellular source of ROS. Nitric ox dermal oxidative phosphorylation continually produces low ROS/RNS levels, as several ETC redox centers leak electrons to partially reduce O_2 to the superoxide anion. Between 0.4 and 4 % of O_2 consumed is converted to superoxide [13]. The mitochondrial membrane potential is the principal parameter regulating ROS production.

Efficient Mitochondria:

Any increase in energy demand is matched by a coordinated rise in oxidative metabolism, which increases mitochondrial membrane potential and thus ROS generation [14]. It is paradoxical that nitric oxide/ GMP signaling decreases oxidative metabolism in any single mitochondrion while increasing cellular mitochondrial function. However, in the process, nitric oxide/ GMP renders mitochondria efficient, with an organized ETC that generates sufficient ATP, while lowering oxygen consumption, mitochondrial potential and ROS production [15]. The result is of major benefit. Exercise training increases energy demand but also stimulates nitric oxide, since Nitric Oxide couples demand with cellular and total-body energy generation.

Cell Protection:

Ischemic preconditioning provides powerful cardio protection against myocardial ischemia-reperfusion injury. Physiologic nitric oxide levels are involved in cytoprotective effects of early and late preconditioning. Nitric oxide/ GMP may protect against mitochondrial permeability transition and apoptosis induced by manifold insults [16]. Through its interaction with ETC components, such as CcOX, nitric oxide affects low-level ROS generation and other mitochondrial defense mechanisms, thereby triggering adaptive cell survival signaling [17].

Cell Death:

High Nitric Oxide concentrations are cytotoxic:

Tyrosine nitration of mitochondrial cause by excessive amount of nitric oxide and RNS nitric oxide derived ROS/RNS signaling, mitochondrial permeability transition or DNA damage may activate mitochondrial pathways to apoptosis or necrosis [18].

Skeletal Muscle [19]:

Nitric oxide signaling in skeletal muscle is implicated in the control of multiple functions, like

- Metabolism of muscle,
- Excitation and contraction of coupling contractility,
- Function of immune system,
- Neurotransmission and cell growth.

Metabolically active skeletal muscle is the most abundant tissue, constituting approximately 40 % of Nitric oxidermal-weight body mass; rendering it a critical factor in total-body metabolism [20]. Skeletal muscle nitric oxides thus play a pivotal role in total-body glucose and lipid homeostasis. Role of Nitric Oxide in the Human body mentioned in Fig 2.

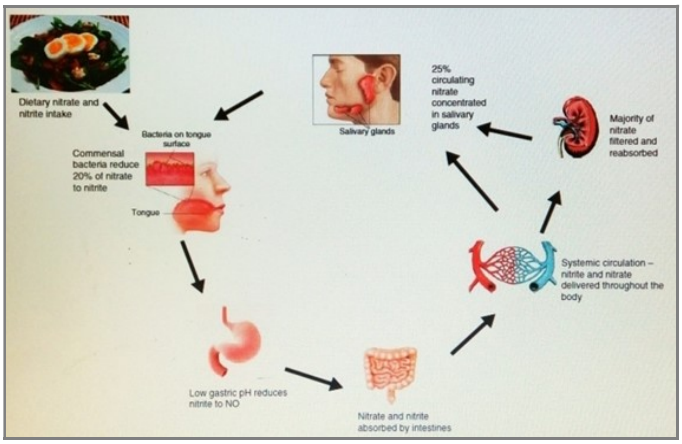

Fig 2. Role of Nitric Oxide in Human body.

Nitric Oxide -Directed Therapy:

Physiologic nitric oxide levels play a major role in metabolic and cardiovascular homeostasis. Well-preserved nitric oxide signaling predicts good mitochondrial function, exercise tolerance, endothelial function, insulin sensitivity and the absence of cardio metabolic disease [28].

Diet:

Systemic NITRIC OXIDE levels can be generated Nitric oxide only through endoge Nitric oxideus nitric oxide.

Table 1. Endo Nitric oxide and exo Nitric oxide stimuli sensitive nitric oxide.

S/ Nitric oxide	Para-meter	Stimulus	Nitric Oxide do Nitricoxiders
1	Endo Nitric oxide	pH	Diethyl ami Nitric oxide nitric oxide nitric oxidEate [21] , S-nitrosoglutathione (Gsnitric Oxide) loaded calcium carbonate Sodium Nitric oxideparticle [23], glyceryl trinitrate (GTN) [22], [O_2 -(2,4-Dinitrophenyl)1-[(4-ethoxycarbonyl)piperazin-1-yl] diazen-1-ium-1,2-diolate] (JSK)
		GSH	Gsnitric Oxide [23], Tnitric Oxide 3 [24]
		H_2O_2	L-arginine (L-Arg) [25]
		Glucose	L-Arg [26]
2	Exo Nitric oxide	Light	[(PaPy 3)Fe(Nitric Oxide)] 2 + and other metal nitrosyls [27] , trans-[Ru(Nitric Oxide)Cl(cyclam)](PF6)2 (cyclam = 1,4,8,11-tetraazacyclotetradecane)[28], [Ru(Nitric Oxide)(Hedta)] (Hedta = ethylenediaminetetraacetic acid) [28], [Ru(tpyCOOH)(Lyso-Ninitric Oxide)(Nitric Oxide)] (PF 6) 3 [29] , Fe_3O_4 @PDA@PAMAM@Nitric Oxidenitric Oxideate [30] S-nitrosothiols (Snitric Oxide) [31]
		Ultrasound	L-Arg [31]

Calorie restriction induces endoge Nitric oxide nitric oxide expression and cGMP generation. Black, green, or white tea polyphe Nitric oxide, including epigallocatechin gallate, which promote the catalytic endoge Nitric oxide nitric oxide activity [29]. Tea consumption may reverse endothelial dysfunction and beneficially affect weight control and insulin sensitivity [30]. Red wine polyphe Nitric oxide, including resveratrol, quercetin and gallic acid, up regulate nitric oxides expression and nitric oxide production, which, in turn, significantly enhance the function of circulating EPCs, with beneficial cardio metabolic [31].

Effect:

Flavo Nitric oxidel-rich cocoa consumption increases circulating nitric oxide with vasculoprotective, insulin-sensitizing impact [32]. In general, fruit- and vegetable-derived flavor Nitric oxideids increase nitric oxide bioactivity. Green leafy vegetable consumption raises levels of vasculo protective nitroso-compounds [33]. Vegetables, of nitrate source, bioactive nitrogen oxides, increase tissue and plasma levels which improve B.P level.

CONCLUSION:

NO can be administered as inhaled gas, in low concentrations, to boost the blood-oxygen saturation level. It will be discussed in detail according to their functions, including inducing tumor cell apoptosis Nitric oxide is the best Nitric oxide for its actions in the vasculature. In addition, NO plays a key role in cell metabolism and it helps in coordinating tissue energy demand with supply. Physiologic signaling is pivotal to metabolic and cardiovascular homeostasis.

ACKNOWLEDGEMENT:

The authors would like to acknowledge the assistance provided by kind cooperation of Secretary Shri Keshavrao Mankar Bhavabhuti Shikshan Sanstha, Shri Laxmanrao Mankar Institute of Pharmacy, Maharashtra.

REFERENCES:

1. Matos PD, Alcantara R, Dekker A, Ennis M, Hastings J, Haug K, *et al*. Chemical Entities of Biological Interest: an update. Nucleic Acids Res, 2010; 38: D249-254.
2. Tiwle R, Shrivastava S, Shrivastava S. Validation of novel UV Spectrophotometric method for the determination of Ketoconazole in Pharmaceutical Formulation. J Pharm Adv Res, 2020; 3(2): 792-798.
3. Tiwle R. Application of Polymers in Pharmaceutical Formulation – A concise review. J Pharm Adv Res, 2019; 2(10): 498-505.
4. Greenwood NN, Earnshaw A. Chemistry of the Elements.2nd ed. UK: Butterworth-Heinemann; 1997.
5. Hou YC, Janczuk A, Wang PG. Current trends in the development of nitric oxide doNitric oxiders. Curr Pharm Design, 1999; 5(6): 417-441.
6. Elizabeth C, Koshland DE. Nitric Oxide news is good news. Science, 1992; 258 (5090): 1862-1865.

7. Hongying L, Lingyan W, Chi Y. A review on naNitric oxidematerial-based electrochemical sensors for H_2O_2, H_2S and nitric oxide inside cells or released by cells. Microchimica Acta, 2017; 184(5): 1267-1283.
8. Richard W. Could the sun be good for your heart? TedxGlasgow: Filmed; 2013.
9. Roszer T. The Biology of Subcellular Nitric Oxide. New Delhi: Springer; 2012.
10. Krystle MP, Matthew L. (Nitric oxidevember 2015). Sildenafil in Term and Premature Infants: A Systematic Review. Clinical Therapeutics, 2015; 37(11): 2598-2607.
11. Berg JM, Tymoczko JL, Lubert S. Biochemistry. 4th ed. New York: W.H. Freeman and Company; 2002.
12. John JH. Cell signaling. 3rd ed. Oxford: Oxford University Press; 2010.
13. Csaba S, Ciro C, Celia C, Katalin M, Bartosz S, Andreas P, *et al*. Tumor-derived hydrogen sulfide, produced by cystathionine-β-synthase, stimulates bioenergetics, cell proliferation, and angiogenesis in colon cancer. Proceedings of the National Academy of Sciences of the United State of America, 2013; 110(30): 12474-12479.
14. Zaid A, Guangdong Y, Wang R. Crosstalk between hydrogen sulfide and nitric oxide in endothelial cells. J Cell Mol Med, 2013; 17(7): 879-888.
15. Cabrales P, Han G, Roche C, Nacharaju P, Friedman AJ, Friedman JM. Sustained release nitric oxide from long-lived circulating naNitric oxideparticles. Free Radic Biol Med, 2010; 49(4): 530-538.
16. Lee HJ, Kim DE, Park DJ, *et al*. pH-Responsive mineralized naNitric oxide particles as stable naNitric oxide carriers for intracellular nitric oxide delivery. Colloids Surf B, 2016; 146: 1-8.
17. Song Q,Tan S, Zhuang X, *et al*. Nitric oxide releasing d-alpha-tocopheryl polyethylene glycol succinate for enhancing antitumor activity of doxorubicin. Mol Pharm, 2014; 11(11): 4118-4129.
18. Duong HT, Kamarudin ZM, Erlich RB, *et al*. Intracellular nitric oxide delivery from stable Nitric Oxide-polymeric naNitric oxide particle carriers. Chem Commun (Camb), 2013; 49(39): 4190-4192.
19. Heilman B, Mascharak PK. Light-triggered nitric oxide delivery to malignant sites and infection. Philos Trans A Math Phys Eng Sci, 2013; 371(1995): 1-12.
20. Gomes AJ, Espreafico EM, Tfouni E. trans-[Ru(Nitric Oxide)Cl(cyclam)](PF6)2 and [Ru(Nitric Oxide)(Hedta)] incorporated in PLGA naNitric oxideparticles for the delivery of nitric oxide to B16-F10 cells: cytotoxicity and phototoxicity. Mol Pharm 2013; 10(10): 3544-3554.
21. Xiang HJ, Deng Q, An L, Guo M, Yang SP, Liu JG. Tumor cell specific and lysosome-targeted delivery of nitric oxide for enhanced photodynamic therapy triggered by 808 nm near-infrared light. Chem Commun (Camb), 2016; 52(1): 148-151.
22. Yu S, Li G, Liu R, Ma D, Xue W. Dendritic Fe_3O_4 @poly(dopamine)@PAMAM naNitric oxide composite as controllable Nitric Oxide-releasing material: a synergistic photothermal and Nitric Oxide antibacterial study. Adv Funct Mater, 2018; 28(20): 1707440.
23. Weidensteiner C, Reichardt W, Shami PJ, *et al*. Effects of the nitric oxide doNitric oxider JS-K on the blood-tumor barrier and on orthotopic U87 rat gliomas assessed by MRI. Nitric Oxide, 2013; 30: 17-25.
24. Chou HC, Chiu SJ, Hu TM. LbL Assembly of albumin on nitric oxide-releasing silica naNitric oxideparticles using suramin, a polyanion drug, as an interlayer linker. Biomacromolecules, 2015; 16(8): 2288-2295.
25. Csaba S; Ciro C, Celia C, Katalin M, Bartosz S, Andreas A, *et al*. Tumor-derived hydrogen sulfide, produced by cystathionine-β-synthase, stimulates bioenergetics, cell 27, proliferation, and angiogenesis in colon cancer. Proceedings of the National Academy of Sciences of the United States of America, 2013; 110(30): 12474-12479.
26. Navamoney A, Scott BD. Synthesis of Diazeniumdiolates from the Reactions of Nitric Oxide with Enolates. J Org Chem, 2006; 71(2): 572-581.
27. Arthur F, Sabadell AJ, Ronco RJ. Homogeneous chemiluminescent measurement of nitric oxide with ozone - Implications for continuous selective monitoring of gaseous air pollutants. Anal Chem, 1970; 42(6): 575-579.
28. Kojima H, Nakatsubo N, Kikuchi K, Kawahara S, Kirino Y, Nagoshi H, *et al*. Detection and imaging of nitric oxide with novel fluorescent indicators: diaminofluoresceins. Anal Chem, 1998; 70(13): 2446-2453.
29. Mata-Perez C, Begara-Morales JC, Chaki M, Sanchez-Calvo B, Valderrama R, Padilla MN, *et al*. Protein tyrosine nitration during development and

abiotic stress response in plants. Front Plant Sci, 2016; 7: 1699-1705.
30. Imran QM, Hussain A, Lee SU, Mun BG, Falak N, Loake GJ, Yun BW. Transcriptome profile of NO-induced Arabidopsis transcription factor genes suggests their putative regulatory role in multiple biological processes. Sci Rep, 2018; 8: 771-784.
31. Chaki M, Valderrama R, Fernandez-Ocana AM, Carreras A, Lopez-Jaramillo J, Luque F, *et al*. Protein targets of tyrosine nitration in sunflower (*Helianthus annuus* L.) hypocotyls. J Exp Bot, 2009; 60: 4221-4234.
32. Cecconi D, Orzetti S, Vandelle E, Rinalducci S, Zolla L, Delledonne M. Protein nitration during defense response in Arabidopsis thaliana. Electrophoresis, 2009; 30: 2460-2468.
33. Capron TM, Mansfield TA. Generation of nitrogen oxide pollutants during CO_2 enrichment of glasshouse atmospheres. J Hortic Sci, 1975; 50: 233-238.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Sanghi DK, Tiwle R*. Ponderous Role of Nitric Oxide in Pharmacy. J Pharm Adv Res, 2020; 3(12): 1074-1079.