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Advanced Nitric Oxide Generating Nanomedicine for Therapeutic Applications

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Abstract

Nitric oxide (NO), a gaseous transmitter extensively present in the human body, regulates vascular relaxation, immune response, inflammation, neurotransmission, and other crucial functions. Nitrite donors have been used clinically to treat angina, heart failure, pulmonary hypertension, and erectile dysfunction. Based on NO's vast biological functions, it further can treat tumors, bacteria/biofilms and other infections, wound healing, eye diseases, and osteoporosis. However, delivering NO is challenging due to uncontrolled blood circulation release and a half-life of under five seconds. With advanced biotechnology and the development of nanomedicine, NO donors packaged with multifunctional nanocarriers by physically embedding or chemically conjugating have been reported to show improved therapeutic efficacy and reduced side effects. Herein, we review and discuss recent applications of NO nanomedicines, their therapeutic mechanisms, and the challenges of NO nanomedicines for future scientific studies and clinical applications. As NO enables the inhibition of the replication of DNA and RNA in infectious microbes, including COVID-19 coronaviruses and malaria parasites, we highlight the potential of NO nanomedicines for anti-pandemic efforts. This review aims to provide deep insights and practical hints into design strategies and applications of NO nanomedicines.

Graphical Abstract

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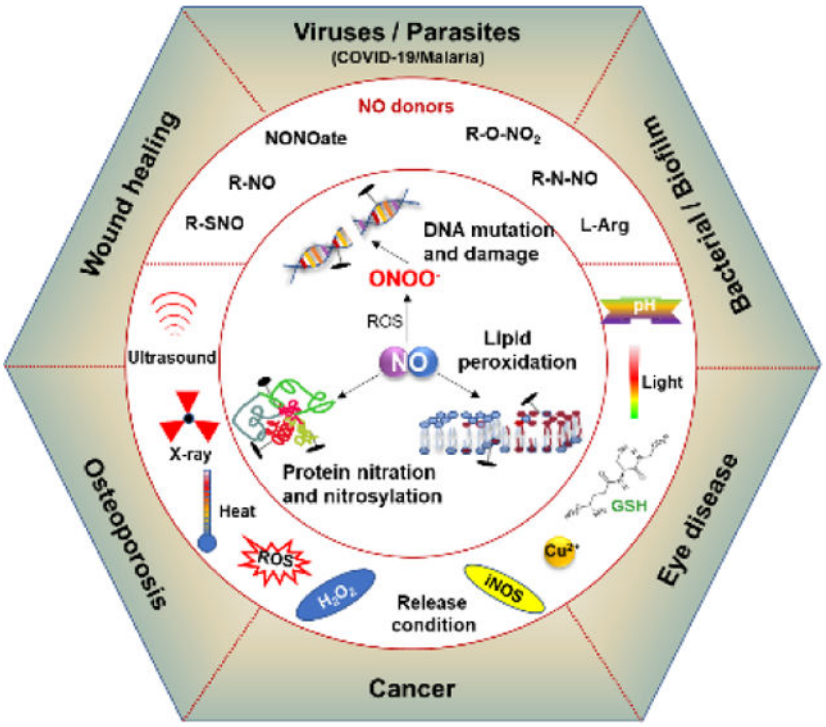

Keywords

Nitric oxide nanomedicine; Cancer; Bacterial; Biofilm; Wound healing; Glaucoma; Osteoporosis; Coronavirus; Biotechnology

INTRODUCTION

In 1982, nitric oxide (NO) was discovered by Furchgott, Ignarro, and Murad as a signalling molecule named endothelial-derived relaxing factor (EDRF).[1] Whereafter, this great discovery inaugurated extensive research on the key roles of NO in many physiological systems, earning the Nobel Prize in Physiology or Medicine for the three scientists in 1998.[2] L-Arginine (L-Arg) is the endogenous NO donor, under the catalysis of NO synthase (NOS) to produce the NO required by the body. In the human body, various biological processes such as vasodilation, platelet aggregation, immune response, and neurotransmission are related to NO.[3–6] Due to its indispensable role in physiology, defects in nitric oxide biosynthesis are related to many disease states. Despite forty years of extensive research, the complicated mechanism of NO in the human body remains uncovered. Fortunately, the strategies for the delivery of exogenous NO have been used in many life-saving biomedical applications. Inhaled NO is an FDA-approved treatment for clinical pulmonary hypertension.[7,8] The direct inhalation of NO cannot yet therapy other diseases due to critical concern for its *in vivo* distribution and high reactivity. Thus, the design syntheses of NO donors have become more efficient at delivering NO to specific disease lesions, thereby expanding NO applications. Organic nitrates ($RONO_2$s) (e.g., glyceryl trinitrate and isosorbide mononitrate) are widely used clinically to treat diseases including angina, heart failure, anal fissures, and pulmonary hypertension. Still, they are

common side effects, such as the risk of hypotension, headaches, and evolving tolerance (Table 1).[9] Nitrosothiols (RSNOs) (e.g., S-nitrosoglutathione (GSNO), S-nitrosocysteine, S-nitrosoalbumin, and Snitroso-N-acetylpenicillamine (SNAP)) can be antiplatelet agents, vasodilators, or cell cytoprotective agents for reduction of oxidative stresses. In addition, NONOates have therapeutic efficacy in pulmonary hypertension, arterial smooth muscles, and traumatic brain injury.[10] However, low molecular weight species of NO donors have had limited clinical application in other diseases owing to the rapid systemic clearance.[11]

The efficacy of NO-based therapeutics largely depends on the concentration profile of NO in the disease region vs. the general body. At low concentrations, NO interacts with transition metal-containing proteins, such as those carrying heme groups or metal regulatory transcription factors, to regulate various biological processes and the progression of diseases. In addition to such direct effects on biomolecules, NO can generate biologically active intermediates and reactive nitrogen species (RNS) at high concentrations, such as nitrogen dioxide (NO_2·). NO is further oxidized by NO_2· to form dinitrogen trioxide (N_2O_3) and rapidly decomposes into NO^+, which nitrates electrophilic compounds (e.g., thiols, phenols, secondary amines) and causes deamination of DNA bases. NO can also react with reactive oxygen species (ROS) to generate peroxynitrite ($ONOO^-$), which can modulate protein function by nitration. More importantly, these RNS can directly kill invading microbe and malignant cells.[12] However, when exposed to excessive levels of ROS and RNS, normal cells also experience damaging stresses that are oxidative (hydroxylation, lipid peroxidation, DNA strand breaks) and nitrosative (nitration, nitrosylation, DNA deamination). These stresses can damage DNA/RNA, proteins (e.g., heme groups), lipids, and other molecules, leading to impaired cellular functions, enhanced inflammatory reactions, inhibition of mitochondrial respiration, cell apoptosis, and genotoxicity. Therefore, controlling these parameters (e.g., delivery sites, concentration, and release rate) of NO remains critical in the development of advanced NO therapeutics.[13] Toxic side effects will increase when the NO drugs cannot be specifically applied to the disease lesion where self-tolerance may also develop. To solve this main challenge, nano-delivery systems of NO donors provide possibilities for specific targeting and control release of NO.[14] For example, NO at the micromolar level can directly affect nitric/oxide mitochondria or DNA for cancer therapy. NO at the Picomolar lever contributes to the angiogenesis of cell proliferation. In addition, since the half-life of NO is extremely short (less than 5 seconds), the delivery of NO must be highly targeted and selective, and the distance of NO donors to reactants is limited to about 100 microns.[15] More importantly, researchers have developed a series of activable precision NO delivery systems based on the endogenous (pH, glutathione (GSH), H_2O_2, enzyme) and exogenous (light, heat, X-ray, ultrasound) stimulus for the disease treatment.[16] Therefore, developing multifunctional NO delivery systems is significant for disease treatment.

This review discusses primary NO-treatable diseases such as cancer, anti-bacterial/biofilm, wound healing, eye diseases, and osteoporosis. The strategies of design synthesis of nano-sized NO-delivery platforms and their therapeutic mechanism are introduced in detail (Scheme 1). We also evaluate the potential challenges of NO nanomedicine in clinical translation. Nowadays, the COVID-19 pandemic has affected our lives all over the globe. The NO has been considered a promising therapeutic gas currently undergoing COVID-19 clinical trials, due to its capability of replication inhibition of the DNA and RNA viruses,

including coronaviruses.[17,18] Thus, we especially highlight potential NO drug applications for COVID-19. We also note more broadly that NO nanomedicine may have important roles in fighting other forms of infections including parasitic malaria.

CANCER

Cancer remains to be the second worst disease in the world by the fatality rate.[19] The current primary treatment modalities for clinical cancer include chemotherapy, surgery, and radiotherapy. Newer therapeutic modalities for cancer include phototherapy, ultrasound therapy, gas therapy, immunotherapy, and starvation therapy. However, these treatments still have drawbacks and limitations. For example, surgery is difficult to remove the small residual tumors and tumour cells scattered in the blood vessels and lymphatics, which easily induce tumor recurrence and further metastasis. Failure of chemotherapy mainly follows the development of drug resistance by the cancer cells. Hypoxia tumor environment also hampers the therapeutic efficacy of radiotherapy, sonodynamic and photodynamic. NO has an anti-cancer effect within the concentration range of 1 μm to mm by oxidation and nitrosative stress with few adverse effects.[20] Fabrication of NO prodrug achieves on-demand release of NO in the tumor microenvironment (TME) not only can inhibit the expression of mammalian HIF-1α, base-excision DNA repair enzyme and multidrug transporter P-glycoprotein (P-gp), but also normalize tumor blood vessels, even react with other ROS to generate highly reactive $ONOO^-$ to sensitize chemotherapy, radiotherapy, phototherapy,[21] and chemodynamic therapy.[22] But NO concentration higher than 1 mM may cause NO poisoning.[23] Picomolar NO has anti-apoptotic effects and promotes angiogenesis, thereby increasing nutrient delivery and promoting tumor growth.[24] This section covers the recent advanced development of NO-based nanomedicine for tumor therapy (Table 2).

NO enhances tumor chemotherapy

NO inhibits P-gp to reverse multi-drug resistance (MDR)—Modern chemotherapy has achieved a huge positive impact on pain relief for cancer patients and lifetime extension, but further improvements are necessary to overcome multi-drug resistance (MDR). Recently, several works related to NO) are the potential function to overcome MDR have been reported.[25] Chen et al. enlisted the mechanism by which NO could reverse the chemotherapy resistance (Figure. 1A).[26] NO could suppress DNA repair, reduce detoxification capacity, inhibit the activation of HIF and NF-kB, and enhance the nuclear transport of drugs.[27,28] In addition, the overexpression of the drug efflux P-gp to continuously pump the chemo drug outside of cancer cells broadly hinders cancer chemotherapy.[29,30] Sung et al. reported a pH-responsive NO-generating hollow microsphere (HM) system to overcome the resistance of MCF-7 breast cancer cells to the anticancer agent irinotecan (CPT-11) by inhibiting the P-gp expression of cancer cells (Figure. 1B).[31] The HM simultaneously carries CPT-11 and a NO-donor (EDTA NONOate), in acidic tumor tissue, acidic protons infiltrate HMs and generate NO bubbles from the encapsulated NONOate, triggering CPT-11 release and inhibit P-gp expression to enhance chemotherapy.

NO is reactive with superoxide ($O_2^{\cdot -}$) to generate more highly reactive $ONOO^-$.[32] Hu et al. designed cocktail polyprodrug nanoparticles (CPNs) that, in response to reductive cytosolic,

can release NO and generate $ONOO^-$ to kill cisplatin-resistant cancers (Figure. 1C).[33] Inside cancer cells, CPNs are degraded so that the released cisplatin activates nicotinamide adenine dinucleotide phosphate oxidase (NOXs) to catalyze oxygen to $O_2^{\cdot -}$, which further reacts with *in-situ* released NO to produce $ONOO^-$. *In vitro* and *in vivo* analyses demonstrate that CPNs can efficiently inhibit P-gp expression to overcome cisplatin resistance and enhance therapy efficiency for resistant cancer.

Dong et al. reported a general approach to the integration of heat-sensitive NO donors, chemotherapeutic DOX, and photothermal conversion attributes into polypeptide nanocomposite (PNOC-PDA/DOX) for overcoming MDR (Figure 1D).[34] Under NIR irradiation, PNOC-PDA/DOX induces photothermal therapy(PTT), NO, and chemotherapy (PTT-NO-CT) synergistic triple therapy, which produced a superior synergistic effect of NO release characteristics, light-to-heat conversion and chemotherapy on MDR reversal and killing MCF-7/ADR cells in *vitro*, and the P-gp expression level was down-regulated to about half. Notably, after tail-vein injection of the nanocomposites followed by single near-infrared laser irradiation, triple-modality therapy of mild PTT, NO therapy, and chemotherapy achieves complete ablation of MCF-7/ADR tumors without tumor recurrence and skin damage in a month.

NO promotes tumor environment normalization and enhances tumor chemotherapy—The abnormal neovessels in TME contribute to metastasis, immunosuppression, and other aspects of malignant progression, leading to resistance to chemotherapy and cancer immunotherapy.[35–37] Regulating TME by normalizing tumorous vascular functions is becoming a promising treatment method to combine with other traditional therapeutics to enhance overall anti-cancer efficacy.[38,39] NO can normalize tumor vasculature by regulating angiogenesis and homeostasis.[40,41] However, useful NO delivery schemes must overcome the limitation of a short half-life and the inability to sustain the release. Chen et al. developed a nano-scale carrier NanoNO that can continuously release NO into hepatocellular carcinoma (Figure 2A).[42] Low-concentration NO treatment normalized tumor vessels, promoted tumor tissue uptake of chemotherapeutic drugs, and improved therapy effectiveness against primary tumors and metastases through tumor necrosis factors and apoptosis. In addition, low-dose NO from NanoNO reprogrammed the TME to improve the immune efficacy of cancer vaccine immunotherapy, providing a concept for NO-based cancer therapy.

The poor permeability of nanoparticles in solid tumors is considered the main factor limiting the clinical applications of nanomedicine.[43,44] Nanoparticles can accumulate at the tumor site through the enhanced penetration and retention (EPR) effect.[45,46] However, it is difficult to deliver nanoparticles into tumor parenchyma with a dense interstitial matrix containing collagen and hyaluronan. Fang et al. designed a collagen depletion strategy based on NO-active endogenous matrix metalloproteinases (MMP-1 MMP-2) to deliver chemotherapeutic into solid tumors. The NO-releasing nanoparticles (N@MSN and DN@MSN) were created by loading mesoporous silica nanoparticles (MSN) with NO donor S-nitrosothiol and DOX (Figure 2B).[47] The formation of $ONOO^-$ is the key to the activation of MMP, causing a nearly 2-fold increase of 3-nitrotyrosine, indicating the generation of $ONOO^-$, and up to a 3.5-fold increase of MMP-1 and −2 in tumors. Notably, nanoparticles (N@MSN and

DN@MSN) significantly reduced collagen I expression and degraded collagen in the tumor TEM, leading to the enhanced penetration of chemotherapeutic DOX and antitumor efficacy without toxic side effects.

NO enhances tumor radiotherapy—Radiotherapy is conventionally used for 50–60% of tumor patients.[48,49] However, selectively enhancing the radiation damage to tumor tissues over healthy tissues remains a challenge.[50] Radiosensitizers are promising in targeting tumor tissue by producing free radicals and accelerating DNA damage locally.[51] Zhao et al. reported a multifunctional nano-radiosensitizer by loading UV-responsive NO donors Roussin's black salt into scintillating nanoparticles (SCNPs) (Figure 3A).[52] Upon X-ray irradiation, the nanocomposite can simultaneously produce NO and $O_2^{\cdot -}$, due to high X-ray-absorbing properties and the radioluminescence of SCNPs. NO and $O_2^{\cdot -}$ react further to form a more toxic $ONOO^-$ for sensitizing tumor radiotherapy by damaging DNA, inhibiting DNA-repair enzyme, and reversing hypoxia-associated radiotherapy resistance. T-SCNPs + X-ray significantly up-regulated the production of a marker of radiotherapy, Phospho-Histone H2A.[53] In most cases, poly (ADP-ribose) polymerase (PARP) can promote the repair of damaged DNA by ionizing radiation.[54] These results suggested that $ONOO^-$ can inhibit PARP expression by directly targeting zinc-finger motifs on PARP proteins, increasing the radiation-induced DNA damage by suppressing the PARP-related DNA repair process that decreases the efficiency of radiotherapy. Importantly, RBS-T-SCNPs under X-ray irradiation produce $ONOO^-$, leading to nitrification of PARP protein and ultimately promoting cell death. In addition, Shi et al. also proved that NO reduced the expression level of HIF-1α and enhanced the radiotherapy of hypoxic cancer (Figure 3B).[55]

NO enhances tumor phototherapy

NO enhances photodynamic tumor therapy—Photodynamic therapy (PDT) uses a photosensitizer and light energy to generate ROS to kill disease cells (Table 3).[56] PDT is highly biocompatible, highly spatiotemporal selective, and minimally invasive. Under the irradiation of suitable wavelength, the photosensitizer can absorb photons and activate from the ground state to an unstable excited singlet state that quickly transitions into a relatively stable triplet excited state through the intersystem crossing. Excited triplet-state photosensitizers can then transfer electrons to oxygen and other substances to form free radicals, such as $O_2^{\bullet -}$, hydroxyl radical (OH•), and hydroperoxyl radical ($HO_2^{\bullet}$) (Type-I process),[57] or directly transfer energy to oxygen molecules (the ground state is the triplet state) to form singlet oxygen ($^1O_2$) (Type-II process). Thus, Oxygen is the critical factor in photodynamic therapy relying on these ROS. Unfortunately, the hypoxic environment of cancer tissues decreases the concentration of oxygen and ROS production in PDT.[58,59] Interestingly, NO can provide synergistic therapeutic efficacy to other treatment modalities via the following three mechanisms. Firstly, NO and ROS can interact to yield $ONOO^-$, which is more highly reactive and induces oxidation of DNA and proteins,[60] thereby sensitizing radiotherapy, PDT, and chemodynamic therapy (CDT). Secondly, NO inhibits the expression of P-glycoprotein (P-gp) and DNA repair enzymes, thereby improving the therapeutic effect of chemotherapy and radiotherapy. Finally, NO can suppress hypoxia-inducible factor-1α (HIF-1α), thereby reversing the hypoxic TME for the enhancement of PDT and radiotherapy.[61] NO can reverse hypoxia by inhibiting cell respiration and

metabolism by competitively binding to the oxygen-binding site of mitochondria.[62–64] Zhang et al. designed a PDT-specific O_2 economizer by loading a NO donor and a photosensitizer into poly (D, L-lactide-*co*-glycolide) for PDT of hypoxia tumors (Figure 4A).[65] NO donor release NO in the tumor's reduction environment to inhibit cell respiration, allowing more O_2 in tumor cells and profound enhancement of PDT.[22] This O_2 restoration stops hypoxia-induced tumor resistance to PDT interventions. In addition, NO can inhibit HIF-α expression to enhance PDT efficacy.[66]

More importantly, Type-I PDT can generate $O_2^{\bullet-}$, which further reacts with nitric oxide to generate more toxic $ONOO^-$ to improve the PDT of hypoxia tumors.[67–70] Wang et al. reported an organic molecule, DANO, which possesses a functional π-conjugated donor-acceptor (D-A) backbone, an *N*-nitrosamine substituent, and two amphiphilic triphenylphosphines (TPP) ligands (Figure 4B).[71] The DANO can specifically target to mitochondria of tumor cells. Under LED light irradiation, it can simultaneously produce hydrogen radicals ($H^\bullet$), $O_2^{\bullet-}$, and $^1O_2$ through the dual PDT process. In addition, the DANO releases NO in response to the glutathione (GSH), which further reacts with $O_2^{\bullet-}$ to generate $ONOO^-$. This cascade reaction by NO and $H^\bullet$ can effectively improve the photodynamic therapy of hypoxia tumors.

NO enhances tumor photothermal therapy—Photothermal therapy (PTT) is an extension of the PDT, converting light energy into heat through photothermal agents (PTA).[72,73] To completely ablate the tumor, it usually was heated to more than 50 °C by high-power lasers, thus severely damaging normal tissues.[74,75] Zhao et al. reported multifunctional nanoparticles composited from bismuth sulfide (Bi_2S_3) and thermal-responsive NO donor (bis-*N*-nitroso compounds, BNN) for NO-sensitized mild PTT (Figure 5A).[76] Upon near-infrared (NIR) irradiation, Bi_2S_3 can absorb light energy and transform it into heat to increase the temperature of the tumor site and realize mild PTT, and simultaneously trigger-releasing of NO that could not only damage the mild PTT-induced autophagic of tumor cells in situ but also can directly kill surrounding cells by NO. In the meantime, Liu et al. also designed NIR light-controlled and organelles-targeted NO delivery nanoplatform for enhancing PTT.[77,78] NIR-II (1000–1700 nm) laser possesses lower photon scattering, tissue absorption, and deeper penetration for tissue; thus, it is better spatial resolution and is more suitable for the treatment of deep tissues diseases, compared to the NIR-I (650–950 nm).[79] Liu et al. further presented NIR-II responsive hydrogel angiogenesis inhibition agents (WB@hydrogel) based on NO-releasing donors (Figure 5B).[80] The wild-type p53 protein was activated by NO generation, to alternate pro-angiogenic to anti-angiogenic TEM. This method completely inhibited tumor growth and achieve an anti-recurrence purpose.

NO sensitizes tumor photoacoustic therapy—High-intensity focused ultrasound (HIFU) is being used to treat disease by itself or in combination with other therapies. Chen et al. demonstrated ultrasound could activate H_2O_2 to generate more reactivity ROS for oxidizing L-Arg to generate NO for suppressing one of the most aggressive and lethal cancers.[81] Recently, pulsed laser-triggered ultrasound wave for disease treatment has received widespread attention, which is utilized the probe's PA effects (shockwave) to target

selectively disease tissue with minimal regular cell damage and therapy resistance.[82–85] Wang et al. constructed a multi-functional nanocapsule (NO-NCPs) by loading a NO donor, EDTA NONOate into an acid-responsive NIR-absorbing polymer (Figure 6).[86] Upon entering tumor cells by lysosome-mediated endocytosis, NO-NCPs release NO responsively to the acidic environment. Pulsed laser irradiation generates photoacoustic (PA) cavitation and splits water into $H^{\bullet}$ and OH•, in which $H^{\bullet}$ further reacts with O_2 to generate hydroperoxyl radical ($HO_2^{\bullet}$) and then dissociating to form $O_2^{\bullet-}$. In addition, the photoacoustic effect accelerates NO-releasing, which recombines with in situ generated $O_2^{\bullet-}$ to produce $ONOO^-$, thereby significantly promoting mitochondrial depolarization, apoptosis-related proteins expression, and DNA fragmentation to initiate cancer cell death. PA signal of the NO-NCPs also can provide precise guidance for pulsed laser treatment during diagnosis and treatments. *In vivo* anti-tumor experiments demonstrated that NO-NCPs had superior tumor inhibition capability and even complete tumor ablation after treatment of 18 days. Precise control of ROS and RNS generation in tumor tissues was achieved and visualized by PA and fluorescence imaging.

NO enhances tumor chemodynamic therapy—Chemodynamic therapy (CDT) is a developing cancer treatment that utilizes advanced nanotechnology to catalytic hydrogen peroxide in TME into •OH through Fenton and Fenton-like reactions, inducing cell apoptosis and necrosis.[87,88] Ding et al. designed a nanoscale coordination polymer (Fe(II)-BNCP) that a glutathione(GSH)-sensitive NO donor (1,5-bis[(L-proline-1-yl)diazen-1-ium-1,2-diol-O^2-yl]-2,4-dinitrobenzene, BPDB) was co-coordinate to irons by precipitation and partial ion exchange process (Figure 7).[89] The NO of Fe (II)-BNCP was not leaked in the blood circulation, only the high concentration of GSH in cancer cells led to the specific release of NO, reducing the damage to normal tissues. An overproduction of H_2O_2 reacts with Fe^{2+} ions to generate •OH to realize the CDT of the tumor. In addition, the Haber-Weiss reaction of Fe^{2+} ions with H_2O_2 generates $O_2^{\bullet-}$, which can further react with NO to produce $ONOO^-$. The combined therapy effect of CDT and NO and biocompatibility of the Fe (II)-BNCP was proven in Heps xenograft ICR mouse models. In the meantime, Zhao et al. reported a versatile Cu^{2+} nanocomposite (UMNOCC-PEG) for luminescence (UCL), CT, and MRI trimodal imaging-guided synergistic CDT/PDT/NO therapy.[90] As a result, specifically generated ROS/RNS (NO, •OH, $ONOO^-$) to respond TME by the Fenton-like catalytic reaction to cause DNA damage, improving the therapeutic effect.

BACTERIA AND BACTERIAL BIOFILMS

Bacterial infections are a major threat to human health due to their high pathogenicity and fatality, causing increasing economic losses worldwide.[91] Although the emergence of antibiotics has effectively suppressed bacterial infections, the emergence of bacterial resistance has exacerbated the deterioration of the situation.[92] Developing a new generation of antimicrobial drugs and methods to combat bacterial infections is an urgent priority. NO is an excellent antibacterial candidate because of its critical role in the mammalian immune response to pathogens (Table 4).[12,93,94] More importantly, NO has a broad spectrum of activity, inducing oxidative and nitrosative damage to DNA, metabolic enzymes, microbial proteins, and membrane structures.[95,96] Chemical alteration of DNA by RNS

is the main mechanism of NO-mediated antimicrobial action, which is demonstrated by three mechanisms: 1, RNS directly reacts with DNA to inhibit the DNA repair capacity and increase the neration of genotoxic alkylating agents and H_2O_2. 2, N_2O_3 can deaminate cytosine, adenine, and guanine. 3, $ONOO^-$ and $NO_2\cdot$ cause DNA strand breaks and abasic sites. Schoenfisch et al. reported a variety of NO carriers based on macromolecules to combat bacterial infections.[97–100] NO can also sensitize PTT,[101] PDT, and CDT to bacteria and enhance their efficacy.[102,103] For example, Hu et al. synthesized NO/ formaldehyde (FA) -releasing polymer PEO-*b*-PNNBM (PNOFA) and self-assembled it into nanoparticles (Figure 8A).[104] The nanoparticle simultaneously released NO and FA under irradiation of visible light and could combat both Gram-negative and Gram-positive bacteria without side effects. Xue et al. constructed another nanocomposite by combining photothermal and NO release to achieve a more effective antibacterial effect (Figure 8B).[105]

Other gaseous signalling molecules (GSMs), including carbon monoxide (CO) and hydrogen sulfide (H_2S), have shown promising therapeutic potential.[106,107] Hu et al. synthesized a NO/CO-releasing donor by grafting the NO-releasing *N*-nitrosamine group[108] onto the CO donor 3-hydroxyflavone (3-HF) derivatives (Figure 8C).[109] The co-release NO and CO under irradiation of visible light showed excellent antibacterial effects on Gram-positive bacteria, with a combination index of 0.053. Moreover, their design efficiently eradicated methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

The formation of biofilm makes bacteria less susceptible to antibiotics.[110] Studies have shown that the dose of antibiotics used to kill bacteria in biofilms is 1,000 times higher than in the suspension of cells.[111] Interestingly, Schoenfisch et al. proved microbial cells could be killed effectively by NO-releasing silica nanoparticles inside *P. aeruginosa and E. coli* biofilms, *S. aureus, S. epidermidis* biofilms, and fungus *C. Albicans* biofilm.[112] Hu et al. reported amphiphiles polymer with NO-releasing property, poly(ethylene oxide)-b-polyCouNO (PEO-b-PCouNO), in which CouNO is a NO donor with a coumarin chromophore, featuring visible-light-triggered NO-release (Figure 9A).[113] The amphiphilic polymer could load the antibiotic ciprofloxacin (Cip) to achieve co-delivery of NO and Cip by self-assembly into nanoparticles. NO specifically generated in biofilm under light irradiation can efficiently eradicate the biofilm of *Pseudomonas aeruginosa,* and Cip release in lesions to further strengthen biofilm eradication. Light is a promising excitation source that can be precisely fixed to the treatment site without causing normal tissue damage due to its high spatiotemporal resolution. However, most photo-sensitive NO donors are responsive to UV light, which shows low penetration and high toxicity to tissues,[114] so Hu and co-workers developed a red-light responsive NO donor delivery micelle (Figure 9B).[115] The micelles could efficiently load Cip to collaborate with NO to combat *Pseudomonas aeruginosa (P. aeruginosa)* infections, completely eradicated bacteria, and promoted wound healing.

Phototherapy based on photosensitizers and photothermal agents has received more and more attention in antibacterial applications due to its spatiotemporal controllability, non-invasiveness, and avoidance of drug-resistant bacteria.[116–118] However, during phototherapy therapy, high local temperatures not only kill bacteria of the lesion tissues but also would destroy the normal cells. In addition, the uneven heat distribution in the biofilm

limits its ablation.[119] Therefore, the use of low-power laser-triggered phototherapy to eradicate biofilms remains an urgent problem. Cai et al. reported an NO/phototherapeutic nanoplatform (AI-MPDA) by mesoporous polydopamine (MPDA) to load L-arginine (L-Arg) and indocyanine green (ICG) to eliminate established biofilm (Figure 10A).[120] Under NIR irradiation, AI-MPDA can generate mild heat (≤45 °C) and ROS, catalyze L-Arg to release NO, and finally achieve severe destruction of the bacterial members. The multifunctional phototherapeutic platform could efficiently eliminate biofilm in a model of the abscess. Ji et al. designed a charge switchable supramolecular nanocarrier with loading NO and a photosensitizer to synergistic NO and PDT to eradicate MRSA formation biofilm (Figure 10B).[121]

NO can cooperate with phototherapy to combat biofilms; NO could react with $O_2^{\cdot -}$ to generate more reactive $ONOO^-$ to completely eradicate biofilm infection. Wu et al. designed a multifunctional titanium implant (Ti-RP/PCP/RSNO) for co-delivery of a hydrophilic and viscous hydrogel of poly (vinyl alcohol) modified chitosan, polydopamine, and a red phosphorus nanofilm (Figure 10C).[122] Under the irradiation of NIR light, NO and ROS were generated for eradicating MRSA biofilms. The results confirmed that synergistic phototherapy, immunotherapy, and NO therapy have excellent osteogenic and biofilm clearance effects.

WOUND HEALING

The wound-healing process is an integration of these overlapping stages: hemostasis, inflammation, proliferation, and tissue remodeling leading to wound resolution.[123,124] NO is a promising wound healing agent,[125,126] attributed to regulating various biological processes during wound healing, such as inflammatory response,[127] cell proliferation, angiogenesis, microbial elimination, and collagen formation (Table 5).[128,129] Shen et al. prepared the biocomposite mats by electrospinning S-nitrosated keratin (KSNO) with polyurethane (PU) and gelatine (Gel) (Figure 11A).[130] The mats released NO that promoted the proliferation of L929 murine fibroblasts and human umbilical vein endothelial cells (HUVECs), accelerated the cell adhesion and growth along the random arrangement of electrospun fibers as ECM-mimicking scaffolds for cells. These results showed that the NO-releasing mats could accelerate wound healing without stimulating inflammation. Liu et al. also proved NO released can accelerate the scarless repair of burned skin by inhibiting microorganisms and pro-vascularization activities.[131] NO can combine other antibacterial methods to accelerate wound healing.[132] For example, Cai et al. reported a ROS-responsive NO generation system (Ce6@Arg-ADP) for synergistic combat bacteria, eventually accelerating wound healing (Figure 11B).[133] NO is a vasodilator that stimulates the development of new blood vessels and improves collagen deposition. Yeh et al. reported a NO-loaded Prussian blue nanocube (PBNO) (Figure 11C).[134] Blood perfusion improved in a controllable fashion following multi-delivery PBNO colloids to the wound and NIR light irradiation, effectively enhancing the angiogenesis and collagen deposition. Bacterial infection is one of the most limitations of wound healing.[135]

Accelerating wound healing is critical for the diabetic.[136] Cu^{2+} generation in the lesion can develop wound healing.[137] Xu et al. designed synergistically released NO and Cu^{2+}

nanoplatforms to accelerate diabetic wound healing.[138] The prepared nanocomposites accelerated the diabetic wound healing, owing to NO releasing at the wound site promoting angiogenesis, collagen deposition, and endothelial cell growth without stimulating inflammation.[139]

EYE DISEASES

Glaucoma is a leading cause of blindness in over 70 million people worldwide.[140] Ocular hypertension is the primary risk factor, and reduction of intraocular pressure (IOP) is the most effective clinical method to prevent glaucoma vision loss.[141] NO could reduce outflow resistance and IOP in animal models and human patients by relaxing trabecular meshwork (TM) containing Schlemm's cells (Table 6).[142] Stevens et al. developed targeting the conventional efflux pathway NO nanoparticle to therapy for glaucoma by specifically controlling NO release in the lesion site (Figure 12A).[143] These results have shown that the as-prepared platform can target delivery of NO to the lesion tissue, and achieve a control NO-releasing. Therefore, endogenous stimuli-responsive NO nanomedicine is promising for glaucoma treatment. Chen et al. designed an endogenous NO nanotherapeutic (HOS-J_RL_O) by biodegradable hollow SiO_2 nanoparticles for efficient co-delivery of JS-K and L-Arg for inducing appreciable IOP reduction. This nanotherapeutic was dual stimuli-responsive in that releasing NO by hydrophobic JS-K in response to ascorbic acid, and by L-Arg catalyzed by endothelial NO synthase (Figure 12B).[144]

NO participates in the process of wound healing of the cornea.[145,146] Kim et al. designed a light-responsive gatekeeper (pH@MSN-CaP-NO) for spatiotemporal-controlled NO delivery (Figure 12C).[147] The developed gatekeeper system can store NO stably prior and can promote cornea wound healing. Polymersomes have attracted extensive attention to transport both hydrophilic and hydrophobic drugs.[148] Hu et al. constructed NO-releasing vesicles (BP Vesicles) via the self-assembly of NO donor-anchored amphiphiles polymer (Figure 12D).[149] The photo-mediated NO release increased cell migration and viability, synergizing the faster corneal healing process.

OSTEOPOROSIS

Osteoporosis can make bones more prone to sudden and unexpected fractures. NO can alleviate osteoporosis by promoting the proliferation and differentiation of osteoblasts.[150,151] Sung et al. formulated an injectable microparticle (MP) system to deliver NO donor (NONOate) by integrating phase-change materials capric acid (CA) and octadecane (Figure 13A).[152] The CA/OD MPs undergo a solid-to-liquid phase transition, resulting in leakage of the NONOate encapsulated inside. CA could provide an acid environment by deprotonating to promote NONOate decomposition to generate NO. Deprotonated CA captures the generation bubble to form stable micellar. This system can efficiently prevent NO bubbles from collapsing, prolong their half-life, exert a durable therapeutic function, and reverse ovariectomized-induced osteoporosis. Wang et al. developed a bone-targeting NIR photosensitizing NO-generating nanoplatform (UCPA) in response to NIR light (Figure 13B).[153] The UV-light responsive NO donor (BNN) could release NO due to the upconversion property of the nanoparticle to convert an

irradiating NIR light (808 nm) into UV/blue light. Experiments both in vitro and in vivo showed that UCPA has a good affinity for the bone to directly release NO in bone and reverse osteoporosis. To achieve these targeting and therapeutic properties, upconversion nanoparticles (UCNPs) were carefully designed first with a core–shell–shell structure: (1) a monodisperse spherical core of NaYF4:Yb/Tm with a diameter of ~26 nm from thermal decomposition, (2) a shell layer of ~2nm thickness containing Nd (NaYF4:Nd/Yb) to enable excitation by the deep penetrating 808 nm NIR light, (3) a further shell about 1 nm thickness of NaYF4 to enhance its upconversion luminescence (UCL) performance. Next these uniform UCNPs were coated with mesoporous silica (MSN) layer of ~15 nm thickness to make the surface hydrophilic and loadable of the NO donor BNN. And finally, the UCM surface was modified by an amino group to load the NO donor BNN and coated with the outer most layer of PAA-Ald, poly(acrylic acid) (PAA) covalently bond to Ald with a high bone affinity, to form the nanomedicine UCPA for effectively targeting to the bone. The NIR light can reach UCPA accumulated deep in the bone while avoiding the potential damage caused by the UV/blue light, so the release of NO could be precisely controlled to promote osteoblast differentiation and to reverse osteoporosis. Therefore, strategically designed smart NO nanoplatforms are promising in treating osteoporosis.

INFECTIOUS DISEASES: VIRUSES AND PARASITES

NO is utilized directly and through the immune system to eliminate many types of infectious agents without unduly harming the host cells and the hosts.[154] COVID-19, which immerged in 2019 and was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[155,156] is responsible for more than 6.5 million deaths according to the World Health Organization (WHO) globally. This pandemic also has resulted in the loss of individual livelihoods and a global economic depression due to prolonged shutdowns. Despite significant progress in clinical vaccines against COVID-19 and a much better understanding of SARS-CoV-2 and COVID-19 prevention and management, the emergence of new SARS-CoV-2 variants likely will overturn the major progress achieved so far in limiting the spread of the virus and its damage.[157] Notably, NO can inhibit the replication of several DNA and RNA viruses owing to its high reactivity.[158,159]

Application of NO in the therapy of COVID-19

SARS-CoV-2 is the latest of the RNA viruses to cause the ongoing pandemic, whereas the therapeutic potential of NO delivery systems against infectious is unlimited based on fundamental mechanisms (Figure 14A).[159] NO has been demonstrated to inhibit the replication of SARS-CoV-2 by two distinct mechanisms.[160] Firstly, NO or its derivatives cause a reduction in the palmitoylation of nascent expressed spike (S) protein which affects the fusion between the S protein and its cognate receptor, angiotensin-converting enzyme 2. Secondly, NO and its derivatives cause a reduction in viral RNA production in the early steps of viral replication, and this may attribute to an effect on one or both cysteine proteases encoded in Orf1a of SARS-CoV-2. But peroxynitrite does not affect the replication cycle of AARS-CoV-2.

Mirazimi et al. found that NO can effectively curb the replication of SARS-CoV-2 in a manner proportional to its concentration. This was achieved by suppressing the production of both viral proteins and RNA (Figure 14B)[161]. Moreover, inhaling NO has been shown to improve oxygen levels in patients with severe acute respiratory distress syndrome and decrease pulmonary vascular resistance. [162,163] Lundkvist et al. also explored NO's antiviral properties against SARS-CoV-2 *in vitro* and found that SNAP (NO donor) could successfully suppress the virus' replication in Vero E6 cells in a dose-dependent manner. Additionally, the authors observed that NO could decrease the activity of the SARS-CoV-2 protease by nitrosation of its active site cysteine. Although the virus was not fully eradicated at concentrations of 200 μM and 400 μM, SNAP treatment delayed the onset of the viral cytopathic effect in the treated cells, and the protective effect was positively correlated with the level of inhibition of virus replication. These findings provide a theoretical foundation for the potential use of NO in the treatment of COVID-19 in a clinical setting (Figure 14C).[164]

Tandon et al. conducted a phase III clinical trial to assess the efficacy of NO in eliminating SARS-CoV-2 RNA from the nasal passages.[165] The study involved 306 adults (aged 18 to 70) with mild symptomatic COVID-19, with a focus on patients at a high risk of illness progression. Participants self-administered NO through a nasal spray (NONS), using two sprays in each nostril (0.45 mL solution/dose) six times daily for 7 days. The results showed that the high-risk population, defined as unvaccinated individuals over 45 years of age or with one or more comorbidities, experienced a significant reduction in SARS-CoV-2 RNA burden of 93.7% at 24 hours and 99.0% at 48 hours with use of NONS. Inhaling NO was crucial for alleviating COVID-19 symptoms, especially in light of the shortage of ventilators, and was granted emergency authorization by the US FDA to save COVID-19 patients.[166] Furthermore, phase 2 clinical trials have been ongoing to evaluate NO for the specific treatment or prevention of COVID-19 (NCT04305457, NCT04306393, NCT04312243). Such approaches hold great promise, particularly for correcting nitric oxide deficiencies caused by infections.[167–169]

Guidelines for NO nanomedicines in infectious diseases

Beyond bacteria and viruses, the important role of NO is known in parasitic infections where malaria is the biggest human burden.[170] Interestingly several anti-malaria drugs including Hydroxychloroquine (HCQ) and Artemisinin-based combination therapies (ACTs) were front-runner candidate drugs to combat COVID-19 at least during its onset.[171,172] The mechanisms of action again all infectious agents include the direct killing of microbes and their growth inhibition via the immune system.[173,174] Strong evidence has been accumulated that NO has many beneficial effects on hosts' defense against parasites including malaria protozoans but also requires tight control to limit damage to the body's cells either by cytotoxicity or by inflammation (Figure 15).[175]

Fighting infectious diseases like COVID-19 and malaria requires faster and more dynamic application of NO gas or NO donor systems. Inhaled NO content is in the mM range, orders of magnitude higher than endogenously produced NO (μM–nM). However, such high NO concentrations (> 1 mm) may cause NO poisoning especially if utilized in

emergency rooms or intensive care units. Developing smart NO nanomedicine loaded with NO donors via FDA-approved liposomes or polymersomes, administered as a nasal spray or injection, facilitates the sustained release of NO in the lungs and other targeted organs for effective treatment under life-threatening situations of patients with COVID-19, severe malaria, and other dangerous infections. However, careful guidelines must be developed to ensure the safe and effective use of NO nanomedicine in this setting. (1) Determining the optimal amount of NO to effectively treat COVID-19: The optimal level of NO required to effectively treat COVID-19 is not yet known and will likely vary based on the severity of the illness. It is important to determine the minimum effective concentration of NO for the treatment of COVID-19 while minimizing potential toxicities. The concentrations and durations of NO undergoing clinical or preclinical trials of COVID-19 treatment are summarized in Table 7. (2) Delivery method and system: The delivery method and system for NO nanomedicine will depend on the severity of the illness and the stage of the disease. For example, inhaled NO may be appropriate for mild cases of COVID-19, while intravenous administration may be necessary for severe cases. (3) Potential toxicities: As with any therapeutic agent, it is important to minimize the risk of toxicity while delivering effective therapeutic concentrations of NO to the infection site. (4) Preclinical and clinical testing: Before NO nanomedicine can be used in humans to treat COVID-19, it must undergo rigorous preclinical testing and clinical trials to determine its safety and validate its efficacy. (5) Interactions with other therapies: It is important to consider the potential interactions between NO nanomedicines and other therapeutics used to treat COVID-19, such as antiviral drugs and immunomodulatory agents.

CHALLENGES IN NO NANOMEDICINE

The number of NO nanomedicines is rapidly increasing, but the efficiency of clinical translation is barely satisfactory. All NO nanomedicines face the same set of challenges. First, the safety issues of nanomedicine are the biggest for clinical application. The synthesis of nanocarriers is complex and uses many potentially hazardous chemicals that have yet to receive clinical backing for human use. Even the FDA-approved liposomes, which have been extensively studied, still face complex toxicity issues when combined with different clinical drugs. In addition, the physicochemical properties of nanomedicines, including dimension, shape, surface area, and aggregation, can impact biodistribution and interactions with cells and biomolecules at larger scales, adding to safety concerns. Second, NO is highly reactive and can damage healthy cells and tissues, thus carefully controlling the dosage to minimize its toxicity is crucial. Determining the minimum effective concentration of NO needed to treat the disease while minimizing potential toxicities must remain a key research and development focus. For example, Acute kidney injury (AKI) is a high-burden global disease partially caused by reactive oxygen/nitrogen species (RONS), so NO generating nanomedicines for disease therapy must prevent AKI and other side effects by various smart strategies such as co-development of NO scavengers. Finally, the optimal amount of NO for a specific disease varies with the disease state and severity. Thus, it is highly desirable to image the process of spatiotemporal controllable release of NO by the guidance of multi-model imaging (e.g., MRI, PET, CT, fluorescence imaging) from *in vitro* to *in vivo*, favoring the development of NO nanomedicines in the forms of multifunctional theranostics.

OUTLOOK AND SUMMARY

NO is powerful and broad-spectrum in biology and medicine, so its relevance and application are seemingly limitless, and we touch upon just a few additional examples in this outlook below. Vascular stent implantation has become the central therapy to treat cardiovascular diseases, owing to the immediate reopening of acute vessel closure.[176] But the long-term clinical success of stenting is limited by in-stent restenosis (i.e., thrombosis and intimal hyperplasia around the implants).[177] NO has antiplatelet aggregation and SMC inhibition capabilities.[178] Therefore, organic nitrates and nitrites have been used as cardiovascular therapeutic agents to improve the dilation of vascular smooth muscle.[179] Indeed, NO not only has been developed for decades for effective cardiovascular disease therapy but also to improve thromboresistance, anti-restenosis, and promote re-endothelialisation after stent implantation.[180–182] With active ongoing research on the biological mechanism of NO, scientists will surely report more and more NO nanomedicine candidates for the treatment of a variety of additional diseases.[183]

NO is powerful and broad-spectrum in medicine because its prime targets are sulfhydryl and iron which are central in the physiology and biochemistry of all life and because it is small and lipophilic few cells or microbes could block its entry. But the therapeutic effect of any NO-based drug is dependent on the concentration and duration of NO released.[6] Therefore, controlling NO concentration and release rate remains critical for developing helpful therapeutics. New biotechnology and nanomedicine have greatly improved the spatiotemporally controlled release of NO. Physically entrapping, adsorbing, or covalently linking small NO donors with liposomes, polymers, hydrogels, and inorganic/organic hybrid nanoparticles exhibits the following advantages: (1) Extended blood circulation time and enhanced permeability and retention in disease tissue, concurrent delivery of multiple drugs to the disease site for synergistic therapy, (3) the integration of diagnosis and treatment for precise disease therapy.

The development of multifunctional NO nanomedicines and further research on NO therapeutic mechanisms will provide theoretical guidance for clinical translation of next-generation NO drug delivery systems. Although NO's role in disease treatment and development will remain multi-facet and not wholly understood, NO therapy is an emerging research frontier and deserves much further exploration. In this review, we have detailed the significant recent progress in NO nanomedicines and their relevant biomedical mechanisms for the treatment of a variety of diseases such as cancer, bacterial biofilm, wound healing, eye disease, osteoporosis, and infectious diseases including COVID-19 and malaria. While NO nanomedicines still require much research and development to complete clinical translation, many NO nanomedicines will eventually become life-saving precision therapies.

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VOCABULARY

nitric oxide nanomedicine
the use of nanocarriers to deliver nitric oxide (NO) to specific areas of the body in a targeted and controlled manner

coronavirus
a virus class typified by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes the current COVID-19 pandemic disease in humans

wound healing
a process by which the body repairs damage to tissues caused by injury or disease, including three main phases of wound healing: inflammation, proliferation, and remodeling

glaucoma
a type of eye disease with high intraocular pressure, which can damage the optic nerve and lead to loss of vision

osteoporosis
a bone disease in which bones become weak and brittle due to loss of tissue, increasing the risk of fractures

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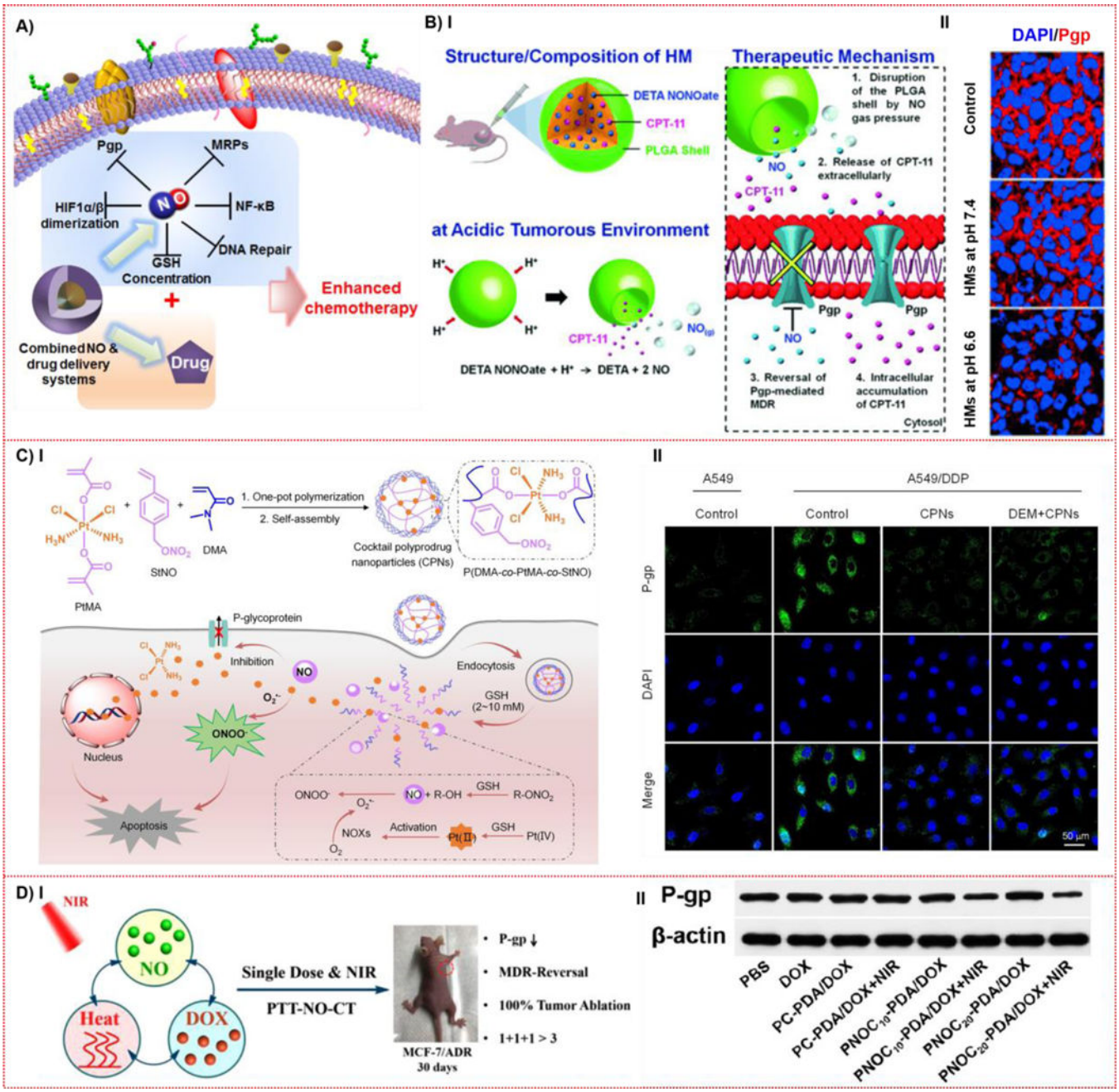


Figure 1.

NO inhibits P-gp expression to reverse MDR. A) Schematic mechanisms of nitric oxide (NO) against multidrug resistance (MDR). Reprinted with permission from ref 26. Copyright 2017 Elsevier. B) pH-responsive NO generating to reverse P-gp-mediated MDR. (I) Schematic composition of HMs and NO generating mechanism to responsive acid tumors environment. (II) Confocal images of P-gp expression levels after different treatments. Reprinted with permission from ref 31. Copyright 2015 WILEY-VCH. C) Polyprodrug nanoparticles (CPNs) using cisplatin and $ONOO^-$ to overwhelm cisplatin-resistant cancers. (I) Mechanism of CPNs to overcome cisplatin-resistant cancers. (II) P-gp expression level

for cells imaged after CPN and different treatments. Reprinted with permission from ref 33. Copyright 2020 Elsevier. D) Combined NO generation, mild photothermal, and chemotherapy to overcome MDR by PNOC-PDA/DOX. (I) Schematic mechanism. (II) Western blot detection of P-gp expression in MCF-7/ADR upon different treatments. Reprinted with permission from ref 34. Copyright 2019 American Chemical Society. P-glycoprotein 1 (permeability glycoprotein), P-gp; multidrug resistance protein 1, MDR1; Hypoxia-inducible factor, HIF-1; Photothermal Therapy, PTT.

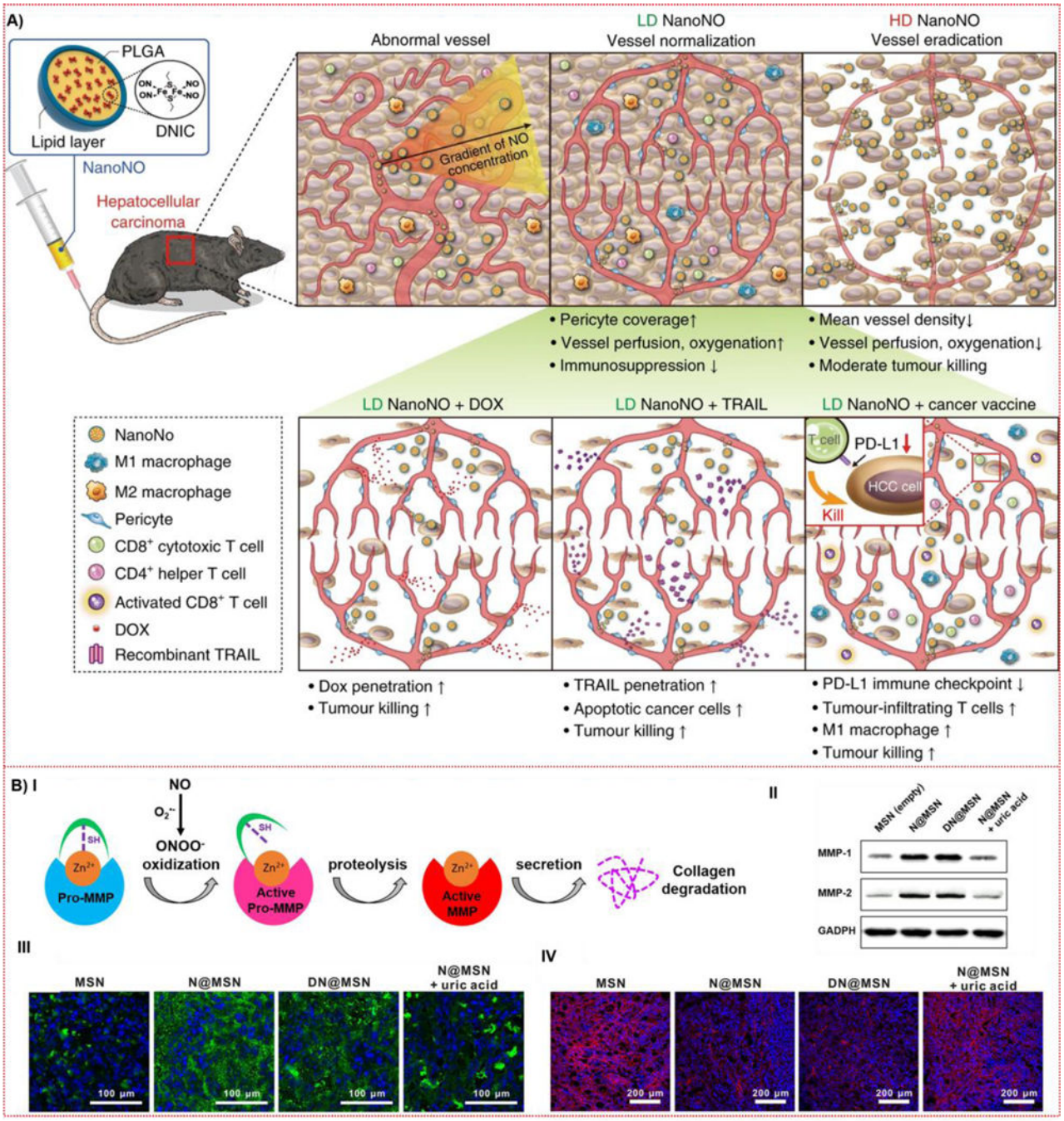


Figure 2.

NO promotes tumour environment normalization and enhances tumor chemotherapy. A) Schematic of the mechanism NanoNO to suppress hepatocellular carcinoma (HCC) progression in mice. The perivascular gradient produces nitric oxide (NO) and promotes the normalization of vessels and cancer suppression via apoptotic and programmed cell death ligand 1 (PD-L1) pathways in the tumor microenvironment (TME). Reprinted with permission from ref 42. Copyright 2019 Nature. B) NO inhibited collagen expression and improved chemotherapeutic penetration in tumors. (I) Mechanism of matrix

metalloproteinase aka matricin (MMP) production and collagen degradation induced by $ONOO^-$. (II) NO-generating nanoparticles increased the production of MMP-1 and MMP-2 shown by Western blots. (III) Confocal imaging for detecting collagenase activity under various treatments. (IV) immunofluorescent staining of Collagen I in tumors. Reprinted with permission from ref 47. Copyright 2019 American Chemical Society.

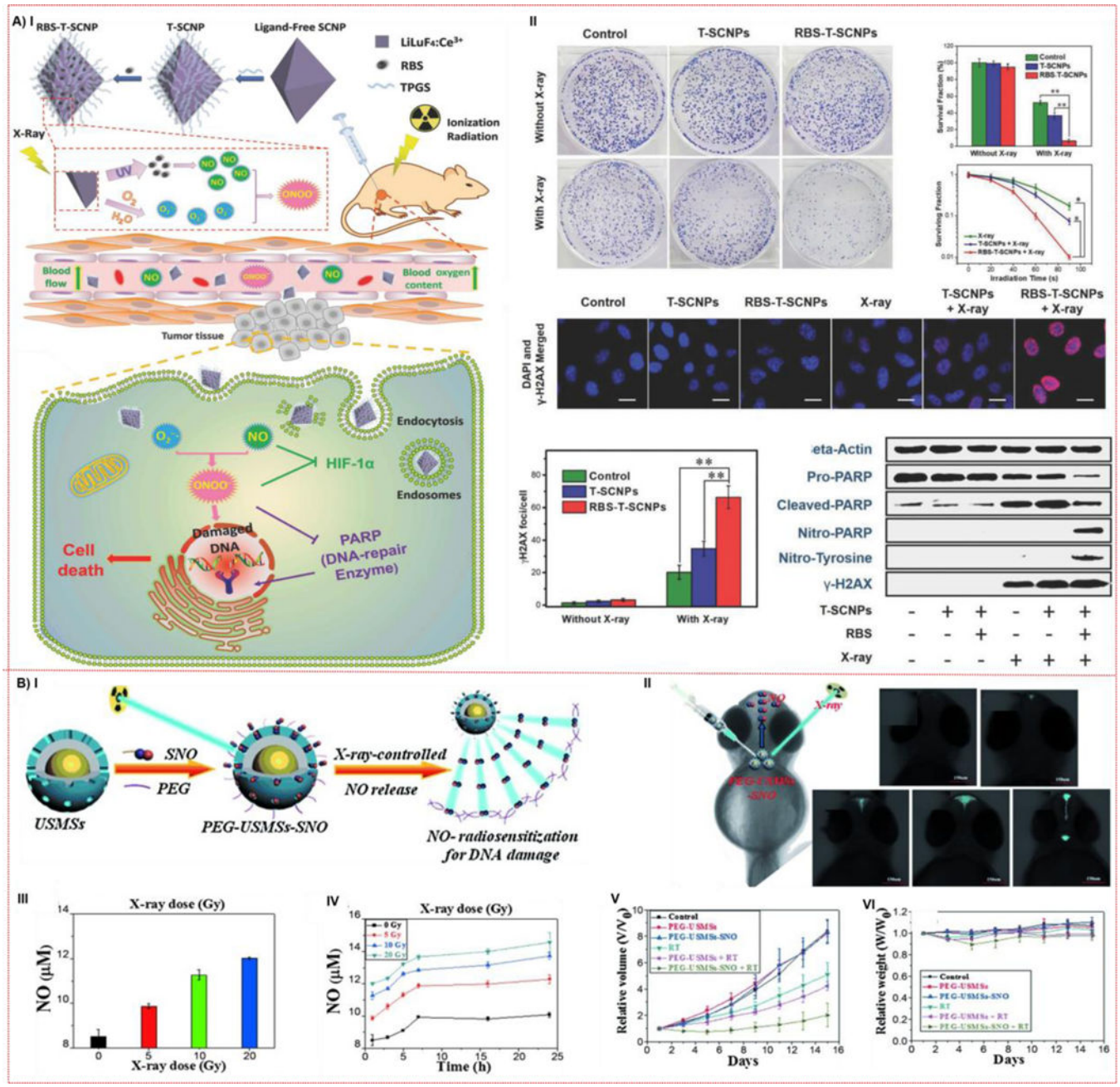


Figure 3.

NO enhances cancer radiotherapy. A) X-Ray-inducible $ONOO^-$ from nanosized scintillators of $LiLuF_4:Ce^{3+}$for radiosensitization. (I) Schematic illustration of RBS-T-SCNPs and the X-ray-controlled $ONOO^-$ generation for improving radiotherapy. (II) Detection of cell viability of A549 cells, expression of γ-H2AX, and Nitro-Tyrosine with various treatments (scale bar= 20 μm). Reprinted with permission from ref 52. Copyright 2018 WILEY-VCH. B) X-ray-triggered depth-independent on-demand NO-release for hypoxic radiosensitization. (I) Construction of PEG-USMSs-SNO. (II) X-ray-triggered NO release in zebrafish larvae from PEG-USMSs-SNO. (III) X-ray dose-dependent NO release from PEG-USMSs-SNO

in one hour. (IV) Cumulative NO release during the first day from PEG-USMSs-SNO after dose-dependent X-ray irradiation. (V) Relative tumor growth and (VI) weight change curve of mice with 4T1 tumors after indicated treatments. Reprinted with permission from ref 55. Copyright 2015 WILEY-VCH.

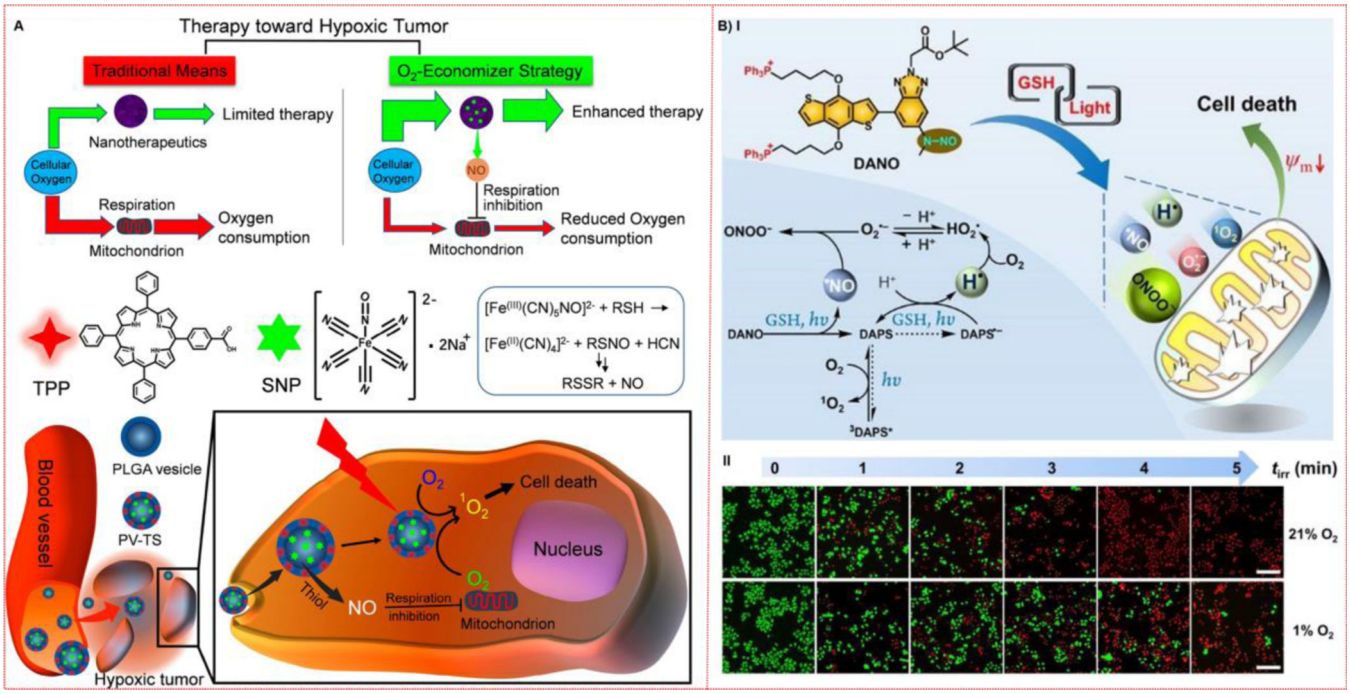


Figure 4.

NO enhances hypoxia tumor photodynamic therapy by inhibiting HIF-α expression and generation of $ONOO^-$. A) Schematic illustration of PDT-specific O_2 economizer used to inhibit cellular respiration to combat hypoxia tumor. Reprinted with permission from ref 65. Copyright 2019 American Chemical Society. B) A cascade reaction of NO and hydrogen radicals for anti-hypoxia PDT. (I) Schematic generation of the $H^•$, $O_2^{•-}/HO_2^•$, NO, $ONOO^-$, and $^1O_2$ from DANO and GSH upon light irradiation. (II) Cell viability images with DANO, calcein-AM, and PI staining under normoxic and hypoxic conditions with LED irradiation. Scale bars, 100 μm. Reprinted with permission from ref 71. Copyright 2021 American Chemical Society.

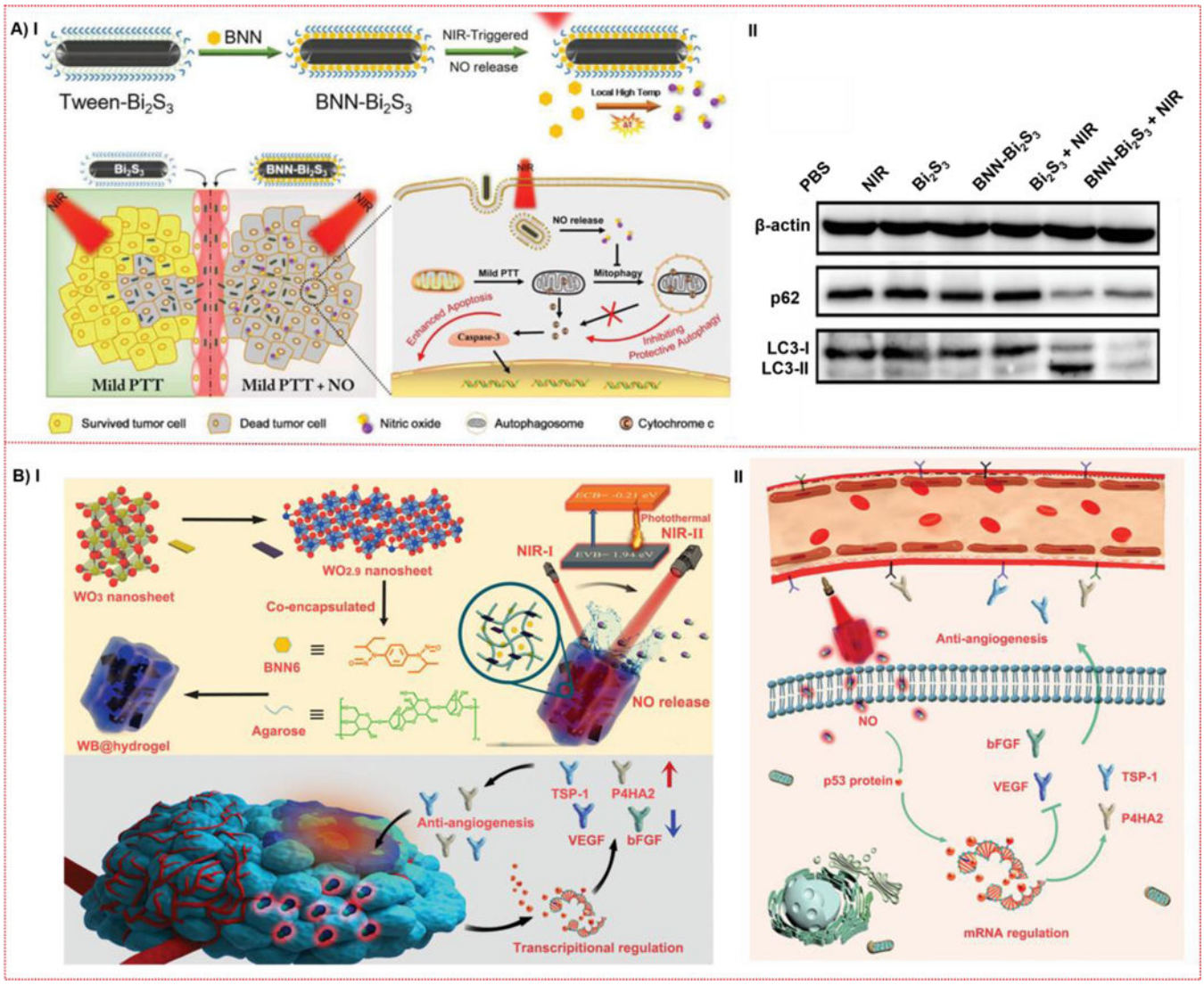


Figure 5.

NO enhances photothermal therapy for cancer. A) NIR light-triggered NO release for sensitizing mild photothermal therapy (PTT). (I) Schematic illustration of the synthesis of multifunctional BNN-Bi_2S_3 and NIR triggered NO and mild PTT in cancer therapy. (II) LC3-II, LC3-I, and p62 expression in BEL-7402 cells with different treatments by Western blot. Reprinted with permission from ref 76. Copyright 2018 WILEY-VCH. B) Schematic illustration of NIR-II -responsive NO-release anti-angiogenesis hydrogel. (I) Construction of WB@hydrogel and NIR-II laser-triggered anti-angiogenesis therapy of cancer. (II) Anti-angiogenesis mechanism of WB@hydrogel under laser irradiation. Reprinted with permission from ref 80, Copyright 2021 WILEY-VCH. Vascular endothelial growth factor, VEGF; Basic fibroblast growth factor, bFGF; Thrombospondins 1, TSP-1; Prolyl 4-hydroxylase subunit alpha-2, P4HA2.

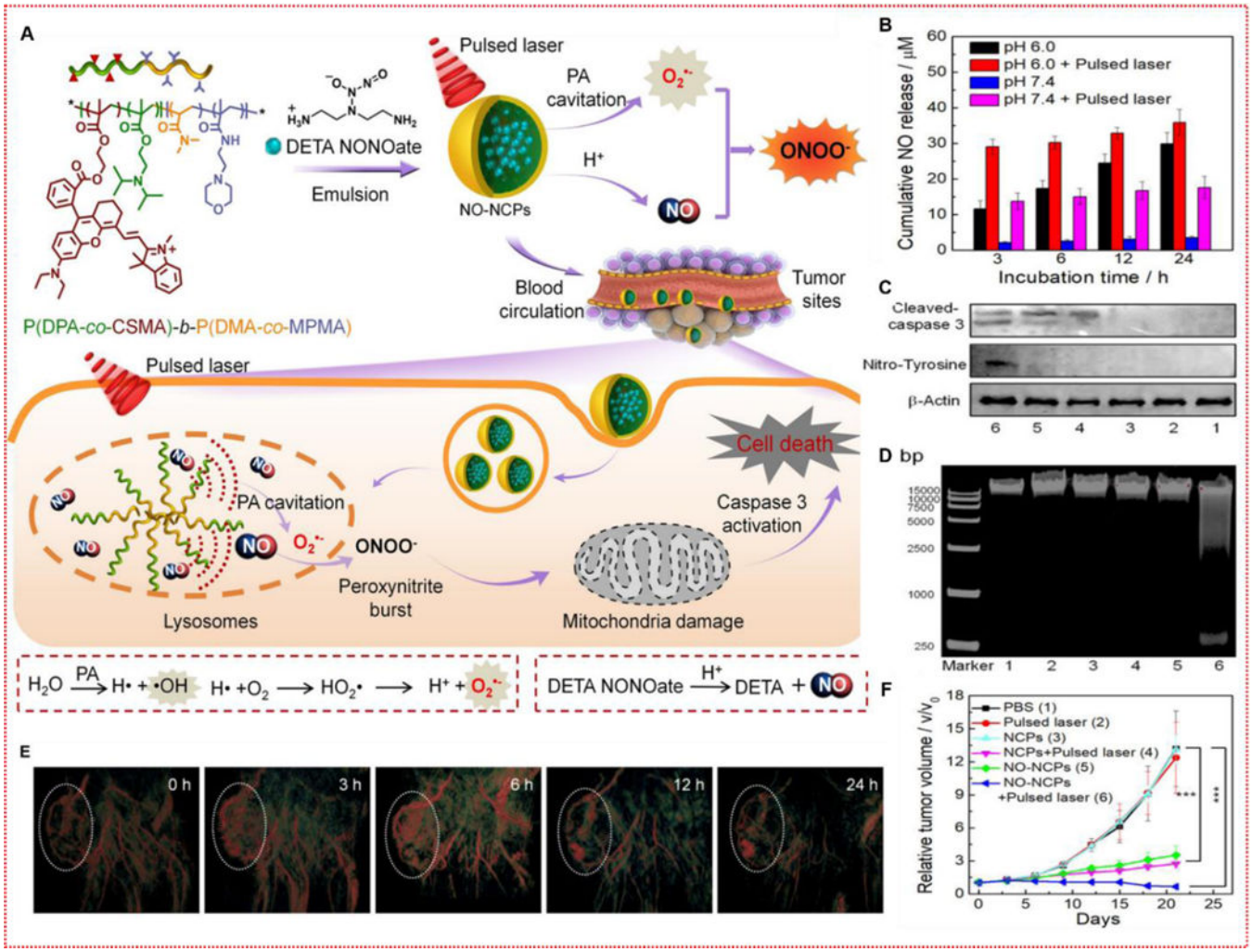


Figure 6.

NO sensitizes photoacoustic therapy by generating $ONOO^-$. A) Schematic illustration of photoacoustic (PA) cavitation-triggered $ONOO^-$ generation for cancer therapy. B) *In vitro* NO-releasing of NO-NCPs under different treatments. C) Western blotting analysis of apoptosis-related proteins (cleaved-caspase 3 and Nitro-Tyrosine proteins). D) Gel electrophoresis detected DNA fragmentation of EMT6 cells after different treatments. E) *In vivo* PA imaging of tumor-bearing mice following intravenous injection of NO-NCPs. F) Tumor response to various treatment processes. Reprinted with permission from ref 86. Copyright 2021 WILEY-VCH.

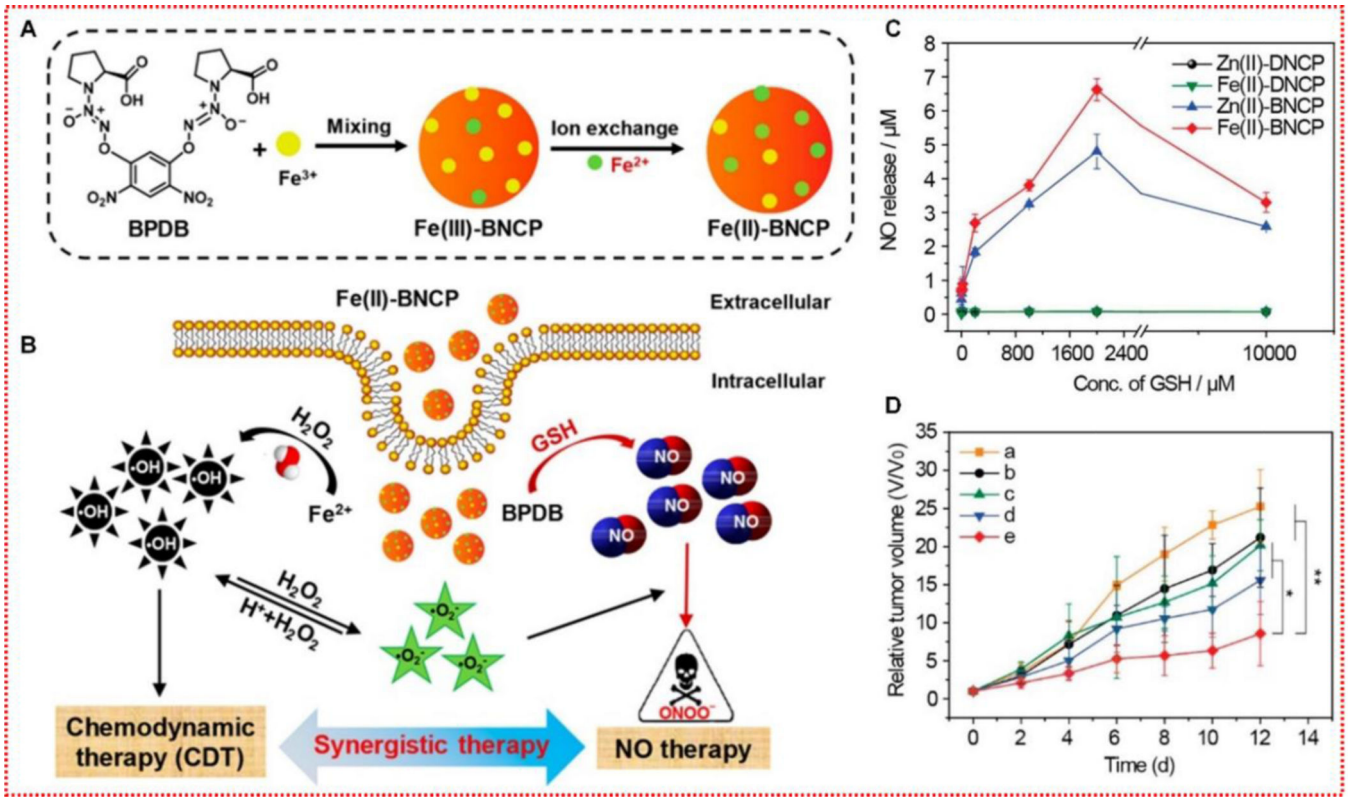


Figure 7.

NO enhances chemodynamic therapy for liver tumors. A) Illustration of Fe (III)-BNCP and Fe (II)-BNCP synthesis as nanoscale coordination polymers. B) The mechanism of NO-CDT synergistic therapy using Fe (II)-BNCP for tumor cells. C) NO release at different content of GSH. D) Tumor growth curves during various treatment processes: (a) saline, (b) Zn (II)-DNCP, (c) Fe (II)-DNCP, (d) Zn (II)-BNCP, and (e) Fe (II)-BNCP. Reprinted with permission from ref 89. Copyright 2019 American Chemical Society.

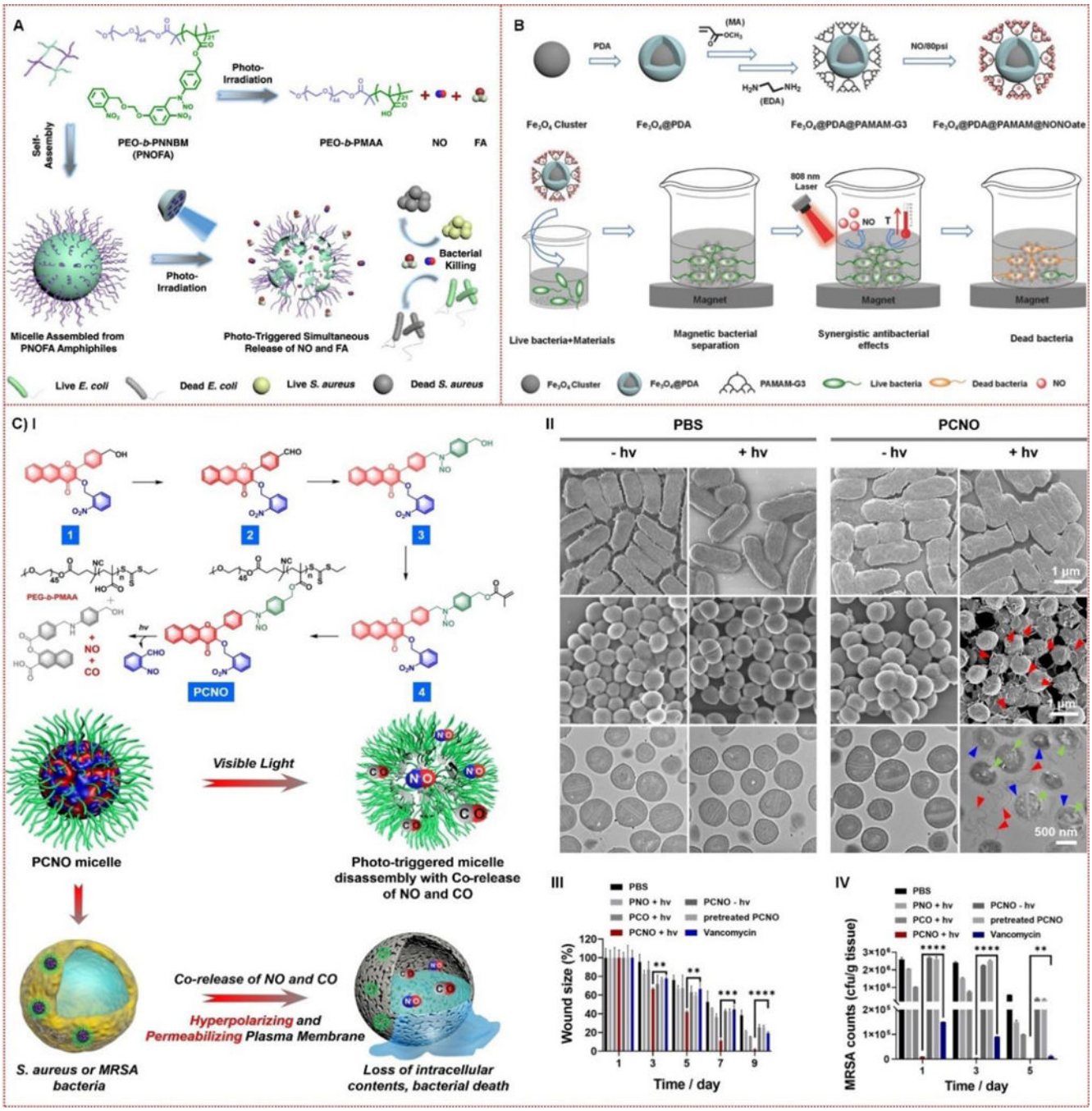


Figure 8.

NO for antibacterial applications. A) Illustration of visible light-triggered simultaneous release NO and formaldehyde as a broad-spectrum antibacterial. Reprinted with permission from ref 104. Copyright 2021 American Chemical Society. B) Synergistic photothermal and NO antibacterial research based on dendritic Fe_3O_4@Poly(dopamine)@PAMAM nanocomposite for NO-delivery. Reprinted with permission from ref 105. Copyright 2018 WILEY-VCH. C) Synergistic NO and carbon monoxide (CO) for combating methicillin-resistant Staphylococcus aureus (MRSA) infections. (I) Synthetic routes of PCNO diblock

copolymers and their mechanism for combating bacteria. (II) SEM images of *E. coli* (top) and *S. aureus* (bottom) incubated with PCNO micelles after irradiation (410 nm light). (III) Quantitative analysis of MRSA infection wound healing after receiving various treatments. (IV) Quantitative analysis of bacteria on days 1, 3, and 5 in wound tissues of MRSA-infected mice receiving different treatments. Reprinted with permission from ref 109. Copyright 2021 WILEY-VCH.

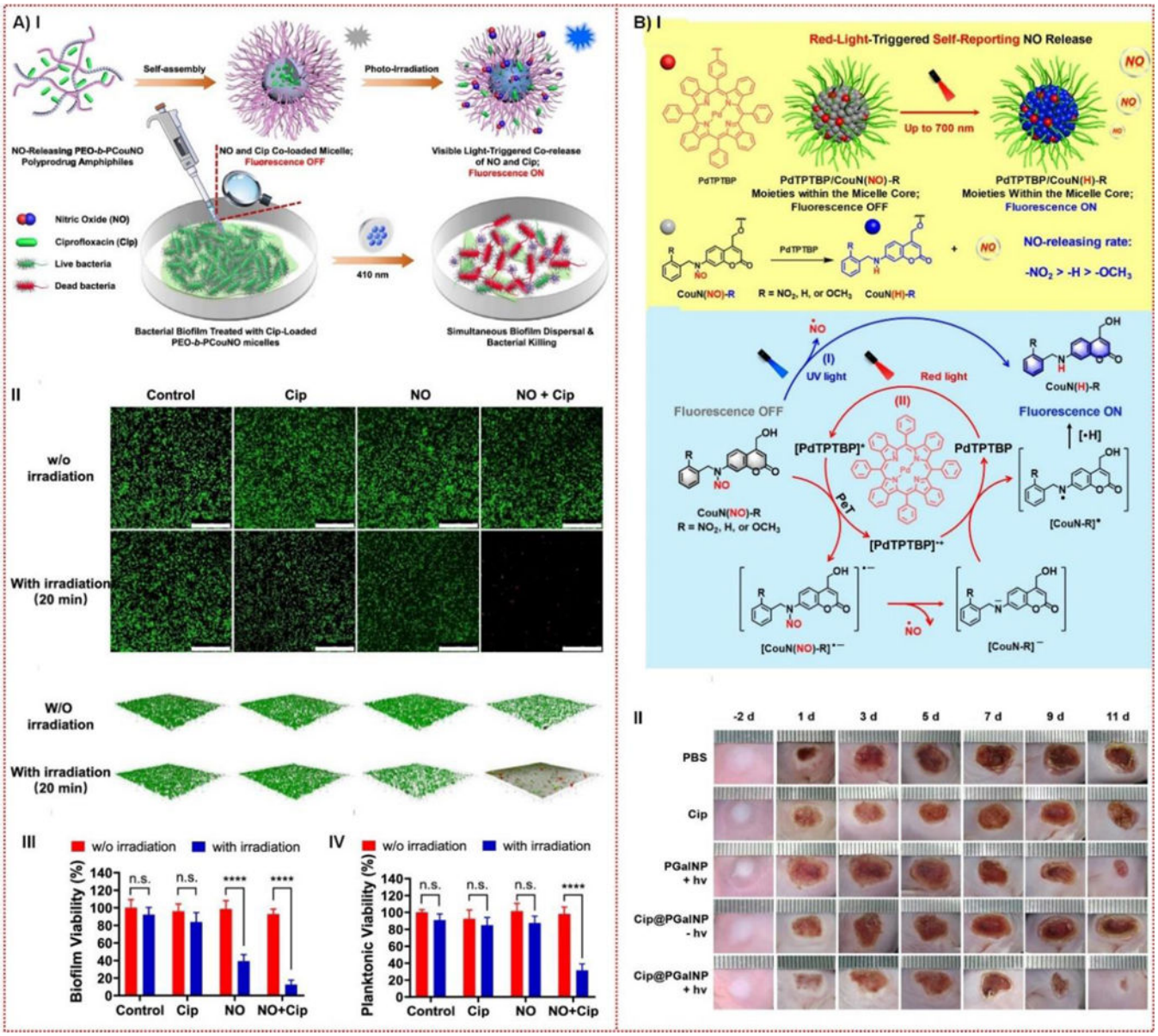


Figure 9.

NO for antibiofilm eradication. A) Visible-light-triggered NO releasing to eradicate biofilm. (I) Illustration of PEO-*b*-PCouNO nanoparticle preparation and synergistic therapeutic mechanism of NO and antibiotic against *P. aeruginosa* biofilm. (II) Two-dimensional and 3D confocal laser scanning microscopy (CLSM) images for detecting *P. aeruginosa* biofilms eradiation. (III) Quantitative analysis of biofilm viability. (IV) ATP assay for analysis of Planktonic bacteria. Reprinted with permission from ref 113. Copyright 2019 American Chemical Society. B) Red-light triggered NO release for efficient antibacterial treatment. (I) Illustration of the formulation of red-light triggered micelles and the NO-releasing mechanism of CouN(NO)-R derivatives responding to red light. (II) Representative images of the abscess during the treatment process *in vivo*. Reprinted with permission from ref 115. Copyright 2021 WILEY-VCH.

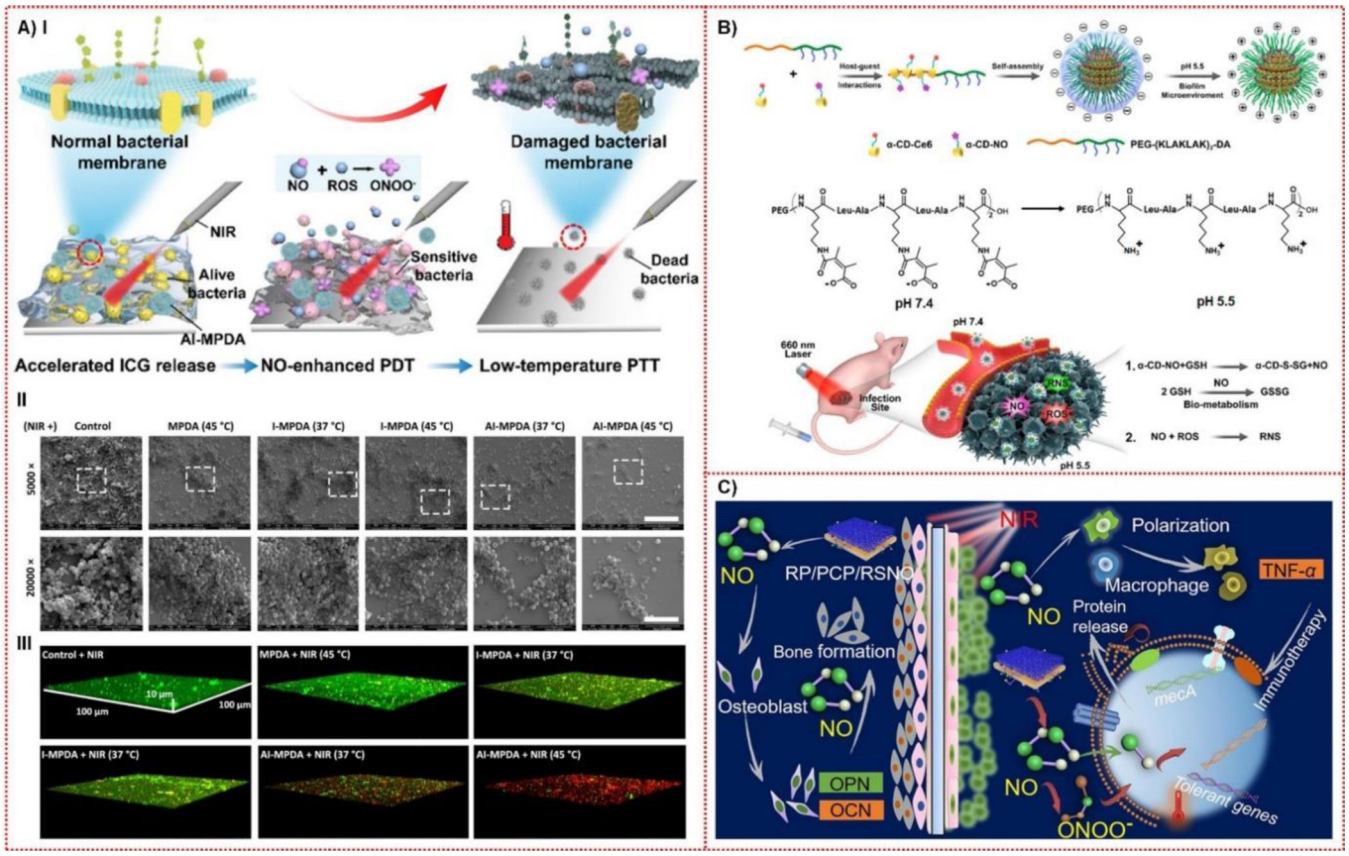


Figure 10.

NO enhances phototherapy against biofilms. A) NIR-mediated NO-enhanced photodynamic therapy (PDT) and mild photothermal therapy (PTT) for biofilm elimination. (I) Schematic illustration of the mechanism by which NIR triggers NO release to enhance PDT and PTT for biofilm ablation. (II) Scanning electron microscopy (SEM) images of biofilm after various treatments. (III) Live/dead stained 3D confocal laser scanning microscopy (CLSM) of biofilms challenged with other treatments. Reprinted with permission from ref 120. Copyright 2020 American Chemical Society. B) supramolecular nanocarriers with a switchable surface charge for synergistic NO and PDT destruction of biofilms. Reprinted with permission from ref 121. Copyright 2020 American Chemical Society. C) Illustration of the mechanism of MRSA biofilm eradication via NO-triggered gene downregulation. Reprinted with permission from ref 122. Copyright 2020 American Chemical Society.

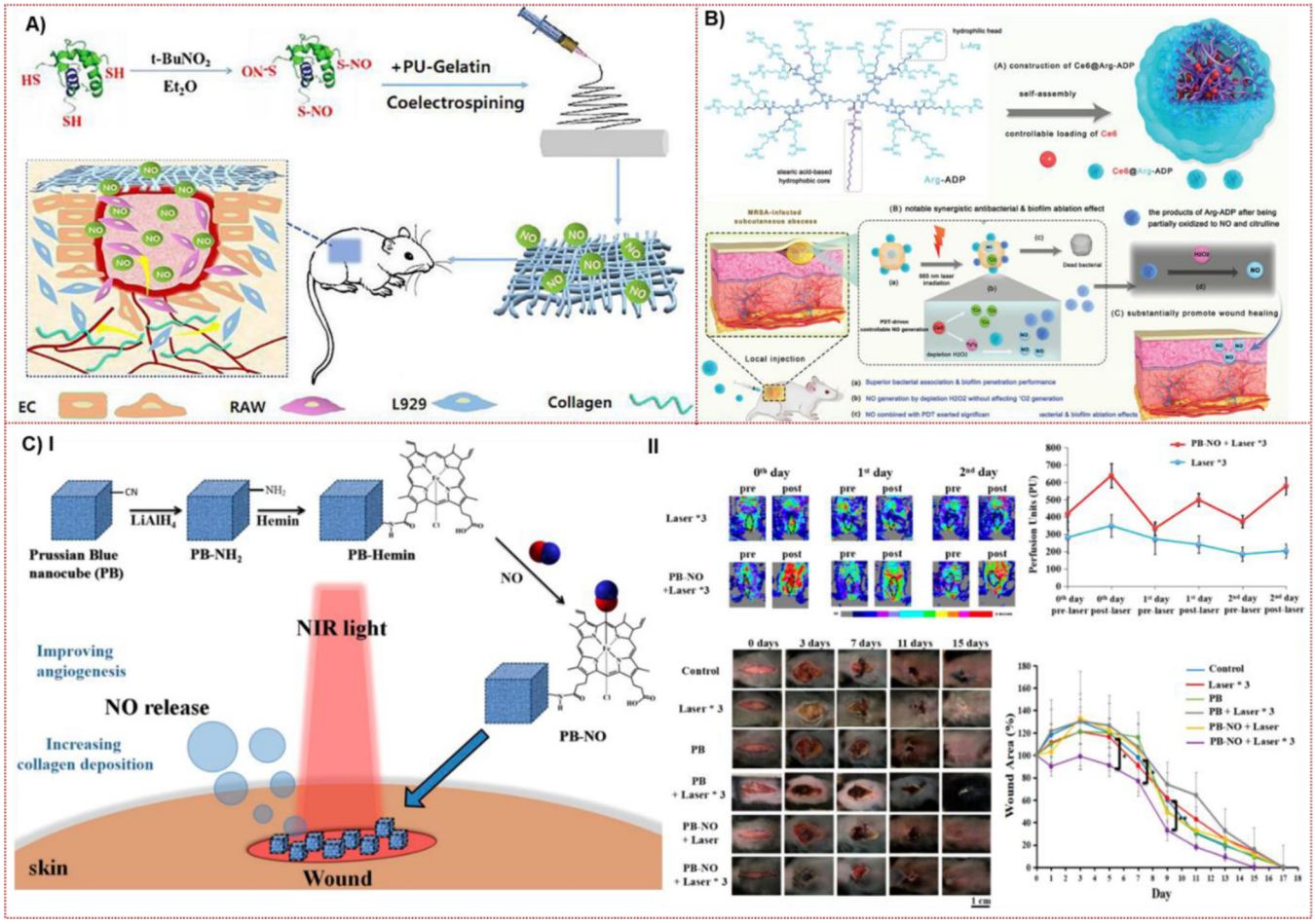


Figure 11.

NO accelerates wound healing. A) Keratin composite mats release NO based on S-nitrosated to accelerate wound healing. Reprinted with permission from ref 130. Copyright 2020 Elsevier. B) ROS-triggered NO-releasing for synergistically combat bacterial infection and accelerate wound healing based on L-Arg-enriched amphiphilic peptide. Reprinted with permission from ref 133. Copyright 2021 WILEY-VCH. C) Photon-mediated NO-releasing from hemin-derived colloids to promote angiogenesis, microcirculation, and collagen deposition during wound healing. (I) Illustration of a NO-carrying Prussian blue (PB-NO) nanocubes for NIR-responsive NO-release healing of incisional wounds. (II) *In vivo* assessment of NO release for incisional wound healing. Reprinted with permission from ref 134. Copyright 2019 American Chemical Society.

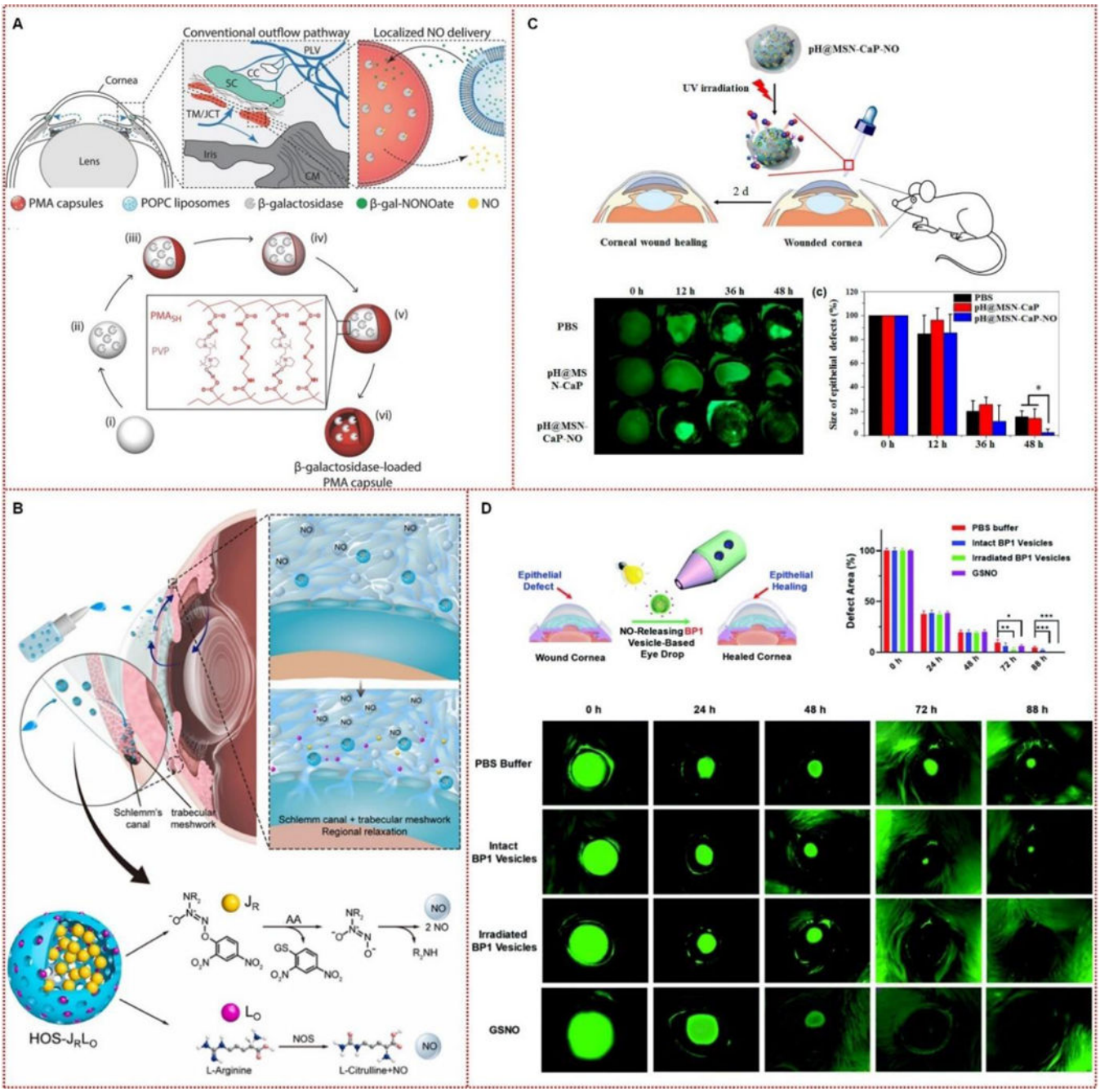


Figure 12.

NO for treatment of eye diseases. A) Localized and controlled delivery of NO for glaucoma therapy. Reprinted with permission from ref 143. Copyright 2017 WILEY-VCH. B) NO releasing in intraocular pressure (IOP) reduction pathway for precision glaucoma therapy. Reprinted with permission from ref 144. Copyright 2021 Elsevier. C) Smart NO delivery for corneal wound healing by light-induced acid generation from pH@MSN-CaP-NO. Reprinted with permission from ref 147. Copyright 2016 American Chemical Society. D) Light-triggered NO release from polymersomes for corneal wound healing. Reprinted with permission from ref 149. Copyright 2019 Royal Society of Chemical.

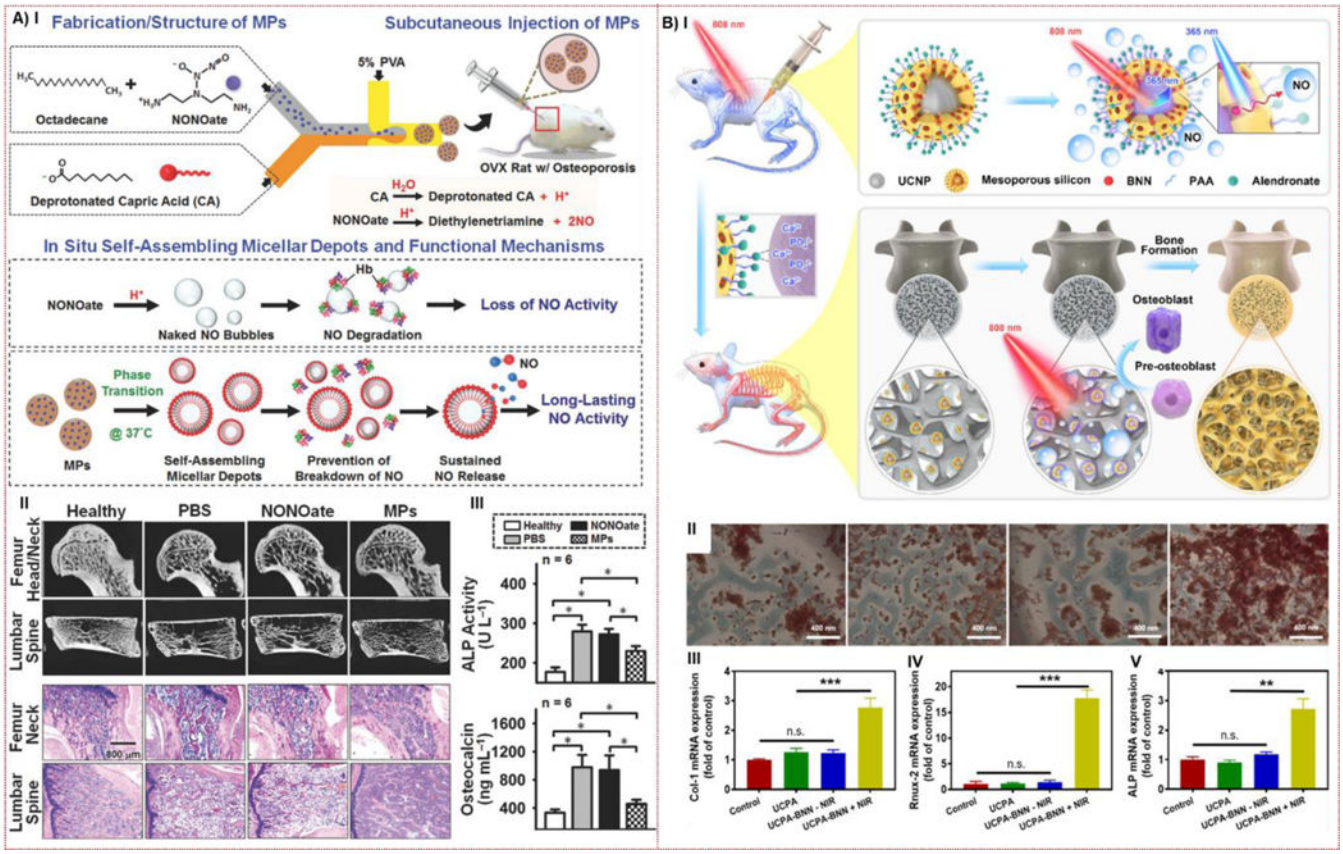


Figure 13.

Smart microparticles (MPs) release NO to reverse osteoporosis. A) After subcutaneous administration, MPs were converted into small micelles through a phase transition to generate NO to alleviate osteoporosis. (I) Illustration of fabrication, structure, and functional mechanism of MPs. (II) Micro-CT images and H&E staining images of bones from test rats under varying treatments. (III) Serum biomarker levels of alkaline phosphatase (ALP) and osteocalcin after multiple treatments. Reprinted with permission from ref 152. Copyright 2017 WILEY-VCH. B) NIR-induced NO therapy for osteoporosis mediated by upconversion nanoparticle (UCPA-BNN). (I) Schematic illustration of NIR-triggered NO therapy for Osteoporosis based on UCPN-BNN. (II) Alizarin red staining photos of calcium nodules after varying treatments. (III-V) The expression of Col-1, Runx2, and ALP of MC3T3-E1 cells after varying treatments. Reprinted with permission from ref 153. Copyright 2021 American Chemical Society.

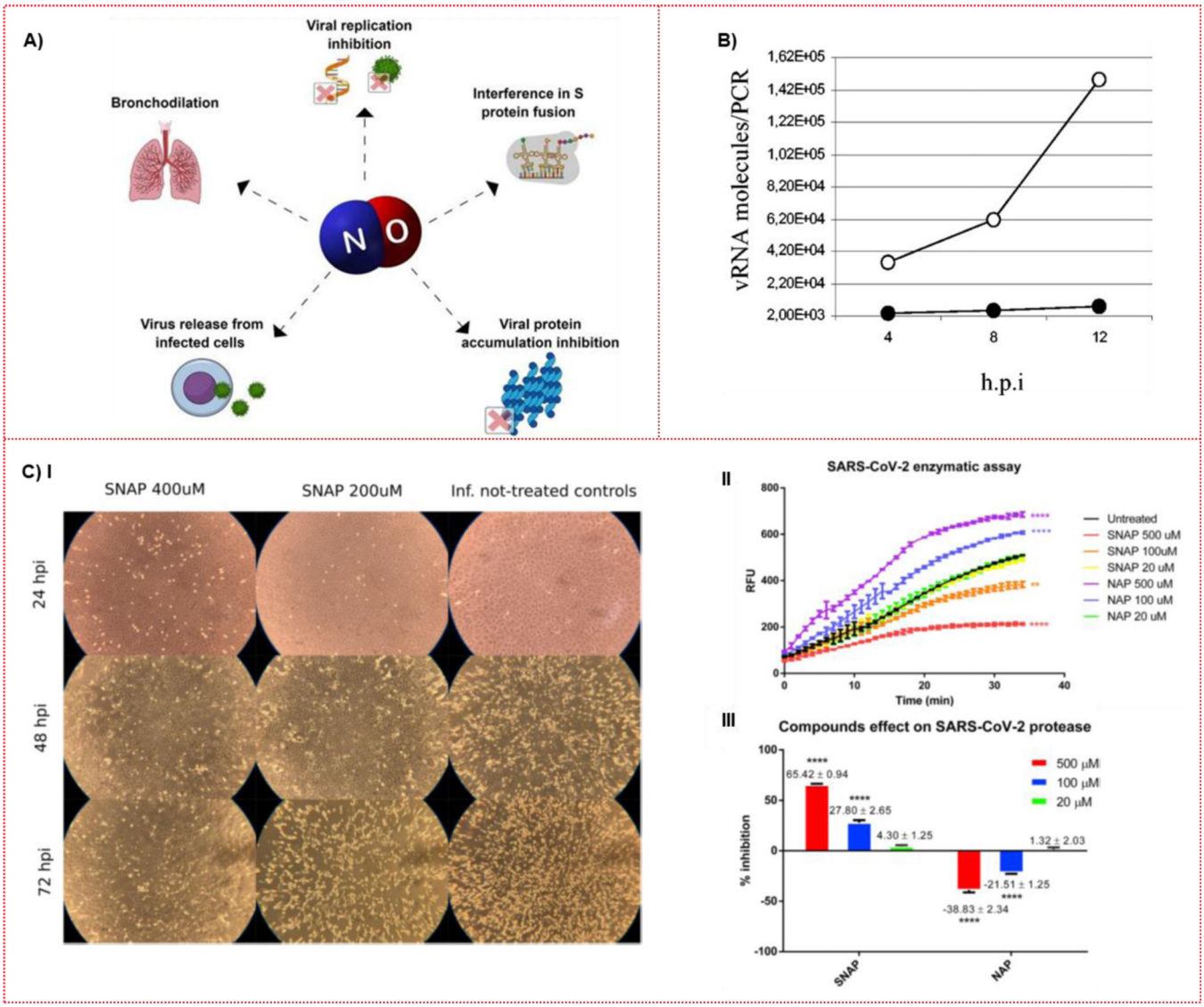


Figure 14.

Application of NO in the therapy of COVID-19. A) The mechanisms of nitric oxide (NO) antiviral. Reprinted with permission from ref 159. Copyright 2021 Elsevier. B) NO can efficiently inhibit viral RNA. Reprinted with permission from ref 161. Copyright 2005 American Society for Microbiology. C) Mitigation of the replication of SARS-CoV-2 by NO in vitro. (I) Comparison of the cytopathic effect development between cells treated with SNAP (a NO donor) and untreated controls. (II, III) Effect of NO generation on the activity of recombinant SARS-CoV-2 protease. Reprinted with permission from ref 164. Copyright 2020 Elsevier.

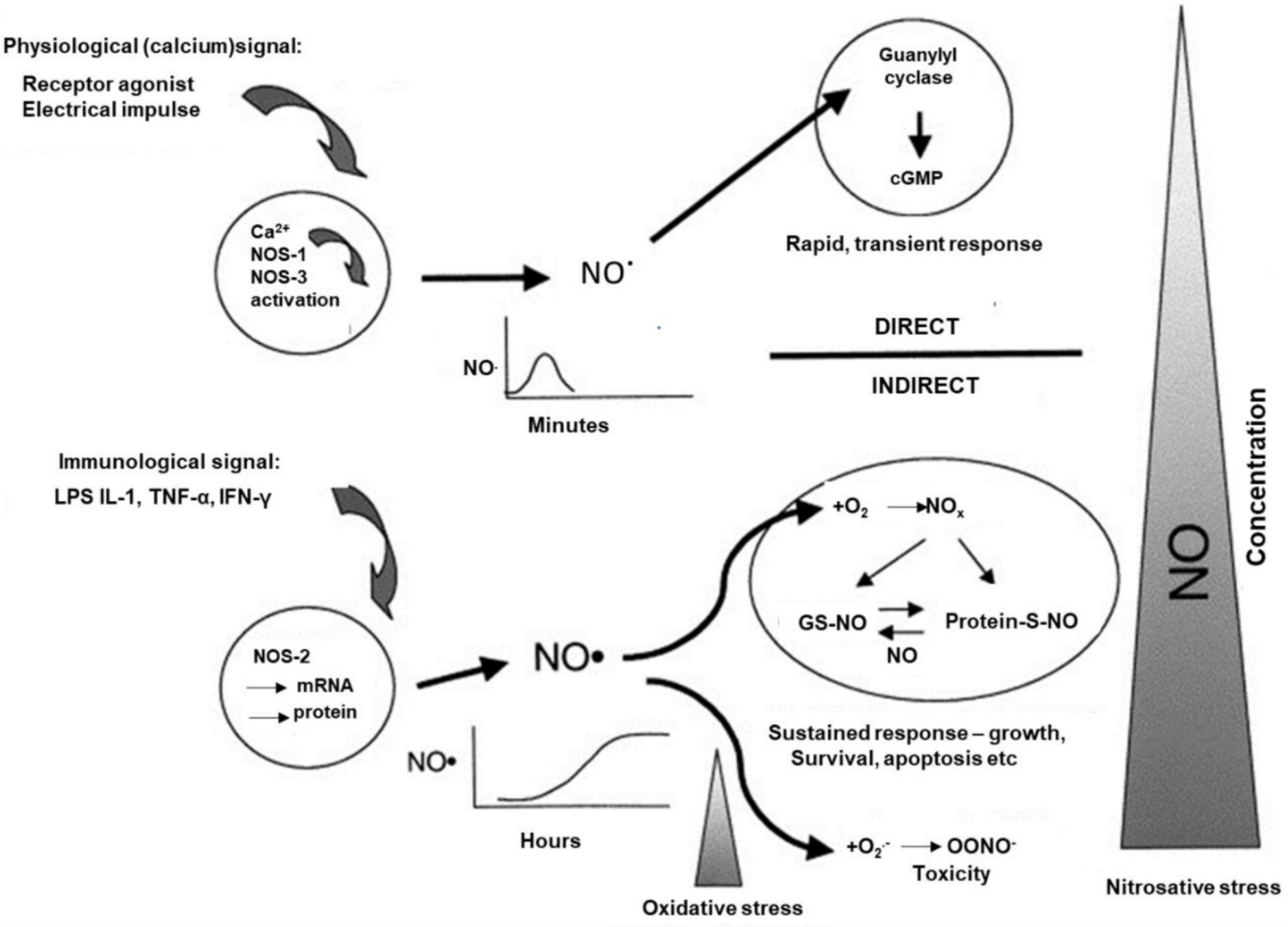
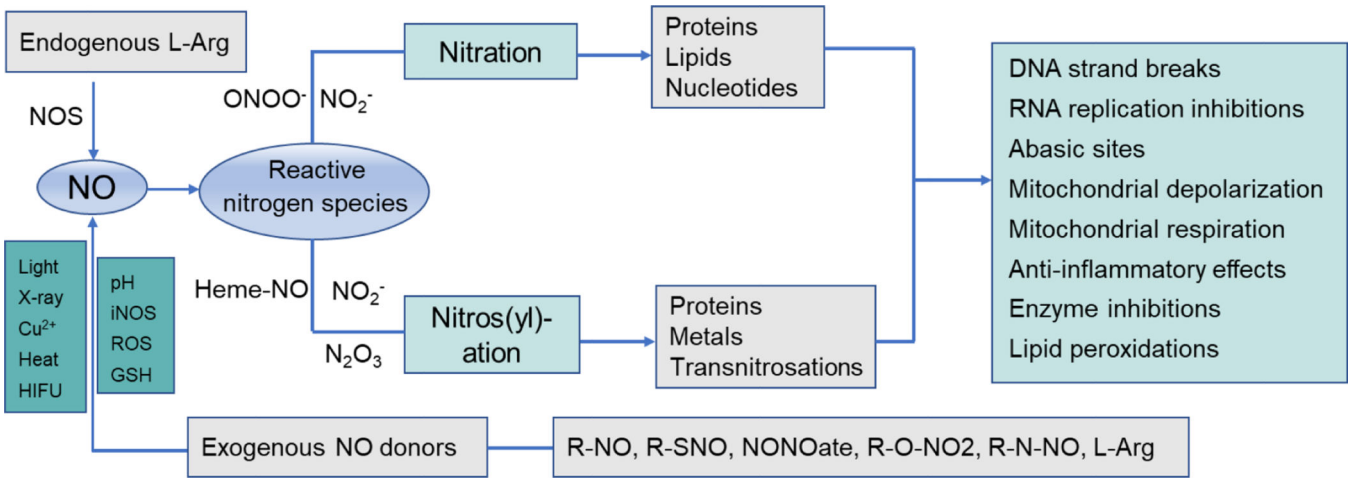


Figure 15.

Physiological and Immunological mechanism of NO action. Reprinted with permission from ref 175. Copyright 2001 Elsevier. Nitric oxide synthase enzymes, NOS; lipopolysaccharide, LPS; interleukin-1, IL-1; Tumor necrosis factor alpha, TNF-α; Interferon, IFN; messenger RNA, mRNA.



Scheme 1.

The treatment mechanisms of nitric oxide (NO) for various diseases. In addition to the direct effects of NO on biomolecules, NO reacts with oxygen or other reactive oxygen species (ROS) to generate reactive nitrogen species (RNS) to act on proteins, lipids, nucleosides, and metals as well as to induce transnitration, which can cause DNA strand breaks, abasic sites, enzyme activity inhibitions, mitochondrial depolarization, mitochondrial dysfunction, and DNA/RNA replication inhibitions. High-intensity focused ultrasound, HIFU; Glutathione, GSH.

Table 1.

Clinical NO Donors.

NO donor	Disease	Half-life	Working mechanism of NO	Side effects
Sodium nitroprusside	Hypertensive emergency, heart failure, decrease bleeding	< 2 minutes	NO stimulates intracellular cyclic guanosine monophosphate (cGMP) production.	low blood pressure, cyanide toxicity, methemoglobinemia
Glyceryl trinitrate	Angina pectoris, chronic heart failure	2 to 3 minutes	Relaxation of vascular smooth muscles, arteriolar and venous dilatation.	Headache, dizziness, lightheadedness, nausea, flushing, and burning/tingling under the tongue
Isosorbide dinitrate	Angina pectoris, heart failure, esophageal spasms	1 hour	Relaxation of vascular smooth muscle, dilatation of peripheral arteries and vein	Headache, dizziness, lightheadedness, nausea, and flushing
Pentaerythritol tetranitrate	Angina, heart conditions	4 to 5 hours	Increased cellular cGMP concentration in vascular smooth muscle.	Flushing, dizziness, nausea, headache, hypersensitivity, rash, fast heart rate, low blood pressure (hypotension),
Molsidomine	Angina pectoris, myocardial infarction	1 to 2 hours	Increased cGMP levels and decreased intracellular calcium ions in smooth muscle cells.	Headache, low blood pressure

Table 2.

NO Nanomedicines for Tumor Therapy[a]

Nanomedicine	NO donor	Release condition	Working mechanism of NO	Refs
RBS-T-UCNPs	Roussin's black salt (RBS)	808 nm laser irradiation	Sensitizing chemotherapy by reducing tumorigenic ability: inhibiting cancer stem-like cells and mammosphere formation ability, reducing $CD44^+$ / $CD24^-$ subsets.	184
α-CD-Ce6-NO NPs	α-CD-NO	GSH	Sensitizing PDT: depleting intracellular GSH, relieving hypoxia at tumor sites, and $ONOO^-$ generation to enhance ROS reactivity.	69
RBS-UCNPs	RBS	808 nm laser irradiation	Sensitizing chemotherapy: High NO concentration kills cancer cells; low NO concentration reduces P-gp level to overcome MDR.	30
NanoNO	DNIC $[Fe(\mu\text{-}SEt)_2(NO)_4]$	Physiological condition	Sensitizing chemotherapy: gradient NO generation efficiently reprograms tumor vasculature and microenvironments to improve chemotherapy	42
NMOF−SNO	R-SNO	808 nm laser irradiation	Sensitizing PTT: NO releasing to enhance PTT efficiency	185
DN@MSN	R-SNO	Natural release	Sensitizing chemotherapy: NO activating MMP-1 and MMP-2, promoting DOX delivery to more deep tumour tissues	47
Peptide-HMSN-LA	L-Arg	ROS	NO direct oxides proteins	81
photoNORM/UCNP	Metal-NO	794 nm laser irradiation	Low dose reduces HIF-1a, and high doses are cytotoxic	186
PTNGs	R-SNO	808 nm laser irradiation (Photothermal)	Sensitizing chemotherapy: NO reverses MDR by inhibiting Pgp expression	187
GCZ@M	nitrosoglutathione (GSNO)	Ultrasound irradiation	Sensitizing SDT: $ONOO^-$ generation, relieving tumour hypoxia	188
IDDHN	2-(Nitrooxy)acetic	808 nm laser irradiation (Photothermal)	Sensitizing chemotherapy: NO improves the EPR effect	189
L-Arg-HMON-GOx	L-Arg	H_2O_2	Starving-like/NO for synergistic cancer therapy	190
BNN-Bi_2S_3	Bis-*N*-nitroso compounds	808 nm laser irradiation	NO impairs the autophagic self-repairing ability of tumor cells in situ	76
PFTDPP-SNAP NPs	R-SNO	808 nm laser irradiation (Photothermal)	Sensitizing PTT: NO generation enhances PTT efficiency	191
Lip-SNAP	*S*-nitroso-*N*-acetylpenicillamine	GSH	NO induces stromal depletion for improved nanoparticle penetration	192
S–NO NPs	Aryl N-nitrosamine	808 nm laser irradiation (Photothermal)	NO release activates photothermal agent for synergistic tumor treatment	193
QM-NPQ@PDHN	NPQ	Glutathione S-transferases π	Specific, high-efficacy, and low-toxic patocellular carcinoma therapy	194
AL-SISIN-1	SISIN-1	Physiological conditions	Inhibiting tumour metastasis by inducing cytotoxicity preferentially on tumour cells in lymph nodes	195
iCPDN	R-SNO	GSH	Sensitizing chemoimmunotherapy: Reversing DOX resistance and enhancing antitumor immune responses by reprogramming the tumor microenvironments.	196
WB@hydrogel	BNN6	1064 nm laser irradiation (photothermal)	Anti-angiogenesis and tumor microenvironment reprogramming: activating wild type p53	80

Nanomedicine	NO donor	Release condition	Working mechanism of NO	Refs
			expression, alternating pro-angiogenic TME to anti-angiogenic TME.	
pPTX/pCD-pSNO	R-SNO	Redox conditions	Sensitizing chemoimmunotherapy: Enhancing dendritic cell activation, T cell expansion, cytotoxicity, and immunogenic cell death,	197
TPE-RSNO micelles	R-SNO	H_2O_2	Reducing P-gp expression, reversing MDR, RNS	198
FZ-SS-FZ@FA NPs	phenylsulfonylfuroxan	GSH	Upregulating p53 and cleaved caspase-3 proteins	199
Ce6/PDE5-i@FHMON-O_2	_	DE5-inhibited PDE5 pathway to upregulate eNOS	RNS helps ROS to evade the hypoxia-induced resistance to ROS-based antitumor	200
$NPS_{D\text{-}IR}$	NTC	GSH	Sensitizing chemotherapy: inhibiting Pgp expression to overcome MDR	25
PIH-NO	R-SNO	Ultrosound	$ONOO^-$ generation to enhance SDT, promote the maturation of dendritic cells, and increase immune cells infiltration	201
PtR/CPG	L-Arg	H_2O_2	Enhancing anticancer chemoimmunotherapy: NO can trigger immunogenic cell death to produce tumor-associated antigens	202
HFC/DTX/aPD1	L-Arg	The environment of cancer cells	Promoting anticancer chemoimmunotherapy	203
NO-DOX@PDA-TPGS-Gal	N,N′-di-sec-butyl-N,N′-dinitroso-1,4-phenylenediamine (BNN)	808 nm laser irradiation (photothermal)	Enhancing chemo−photothermal therapy: inhibiting P-gp -the related efflux of DOX	204
S1P/JS-K/Lipo	JS-K	Glutathione S-transferases	Promoting glioblastoma multiforme cell death	20
CMH-OBN	Benzofuroxan	GSH	$ONOO^-$ generation enhances PDT/PTT/ immunotherapy	205
Alb-PLP/NO NPs	Diazeniumdiolate	Physiological conditions	Enhancing tumor penetration and inhibiting melanoma.	206
P@BDOX/β-lapachone-NO-NPs	R-O-NO_2	GSH	Overcoming chemo-resistance and enhancing the efficacy of HIFU in combination with chemotherapy	207
$SPNA_{Pt/NO}$	R-O-NO	GSH	$ONOO^-$ generation down-regulates glutathione reductase (GR) and xeroderma pigmentosum group A	32
$_{LP}Fe_3O_4$ NPs	L-Arg	iNOS	NO enhances immune therapy	208
BPNs-Arg-GOx@MnO_2	L-Arg	H_2O_2	NO activates matrix metalloproteinases to degrade the dense extracellular matrix	209
UC-ZIF/BER	R-O-NO	NIR irradiation to UV by upconversion	NO turns on the ryanodine receptors for Ca^{2+} elevation to achieve Ca^{2+}-initiated cancer therapy	210
Artificial microbots (AMBs)	L-Arg	iNOS and ROS	Regulating vasodilation and invasion to promote drug release to solid tumors	211
HFLA-DOX	L-Arg	H_2O_2	Promoting deep drug penetration and reversal of MDR in cancer chemotherapy.	212
L-Arg@Ce6@P NPs	L-Arg	H_2O_2	Inhibiting mitochondrial respiration	213
HA@MOF/D-Arg	D-Arg	H_2O_2	Down-regulating HIF-1α to alleviate tumor hypoxia for sensitizing radiotherapy	214
ArgCCN	L-Arg	H_2O_2	High concentration NO induces cancer cell apoptosis	215
RBCm/PAAVSNO/ IR1061 + 1-MT NPs	R-S-NO	Heat and pH	NO normalizes tumor vessels	216
NO-NCPs	DETA NONOates	pH and photoacoustic	$ONOO^-$ generation to damage lysosome, mitochondria, and DNA	86

Nanomedicine	NO donor	Release condition	Working mechanism of NO	Refs
CuS-PEI/NO-TPP	Diazeniumdiolate	1064 nm laser irradiation (photothermal)	Inhibiting heat shock proteins expression	74
GMOF-LA	L-Arg	H_2O_2	NO sensitizes PDT	217
ZGO-Mn-RBS	Roussin's black salt	X-ray excitation	depth-independent NO-releasing strategy for gas-sensitized therapeutic applications.	218
Ptx@AlbSNO	R-SNO	GSH	Enhancing immune cell infiltration into tumor microenvironments.	219
BSA-IRLA@RVs-RGD	L-Arg	ROS	Inhibiting cancer-associated platelet activation and disrupting tumour vascular barriers	220
Au@SiO_2-SNO/PEG/TPP	R-SNO	808 nm laser irradiation (Photothermal)	Activating MMPs to break collagen fibers to enhance the cellular internalization	221
α-CD-DOX-NO-DA NPs	R-SNO	GSH	NO facilitates mitochondrial membrane permeabilization and downregulates ATP level and inhibits pgp to reverse MDR	222
Micellar NO@HMs	NONOate	pH	$ONOO^-$ generation sensitizes radiotherapy of hypoxia tumor	50
DM1-NO-NPs	R-SNO	X-ray irradiation	$ONOO^-$ causes DNA and lipid damage to sensitize radiotherapy.	223
SNO-HSA Dimer	R-SNO	Physiological conditions	NO augments the EPR effect to promote drugs to the tumors.	224
DPP-NF NPs	4-Nitro-3-Trifluoromethylaniline	660 nm laser irradiation.	NO directly damages DNA, and inhibits the expression of HIF-α to enhance PDT efficiency	225
Lyso-Ru-NO@FA@C-TiO_2	R-NO	808 nm light irradiation	Lysosome-targeted NO delivery to enhance PDT	226
PpRE@PEG-PpIX NPs	R-Fe$(NO)_2$	637 nm laser irradiation	Reversing MDR and overcoming hypoxia to enhance PTT.	227
Ce6-loaded NO-mannan	R-O-NO_2	GSH	NO prompts vessel-relaxing and hypoxia relief	228
N-GQDs@Ru-NO@Gal	R-NO	808 nm light irradiation	NO enhances PTT	229
CPNs	R-O-NO_2	GSH	$ONOO^-$ and NO inhibit Pgp expression to reverse MDR	33
L-Arg@PCN@Mem	L-Arg	ROS	NO overcomes hypoxia to sensitize PDT	70
P(IR/BNN6/AIPH)@Lip-RGD	BNN6	1064 nm laser irradiation (Photothermal)	Synergistic NO and alkyl radical action	230
Fe(II)-BNCP	BPDB	GSH	Synergistic NO and chemodynamic therapy	89
$_{AD}$Au@CuS YSNPs	L-Arg	ROS	Inhibiting P-gp expression to reverse MDR	29
IPO-NO	R-SNO	808 nm laser irradiation (Photothermal)	Low NO concentration increases the EPR effect and high concentration directly kills the tumors.	231
IMesNO/DOX@MCs	R-NO	HIFU irradiation	Accelerating drug accumulation in tumor	232
PV-TS	Sodium nitroprusside dihydrate	GSH	NO inhibits cellular respiration to relieve tumor hypoxia	65
NO-M@DOX	R-O-NO_2	GSH	NO reverses MDR to enhance chemotherapy	233
N-GQDs@Ru-Cl@TPP	R-NO	808 nm light illumination	NO enhances PTT	78
M@BPAG	L-Arg	H_2O_2	Reprogramming the tumour immune microenvironment and significant synergistic antitumor effect	234
AI-MPHA NCs	L-Arg	ROS	NO sensitizes PTT	235

Nanomedicine	NO donor	Release condition	Working mechanism of NO	Refs
PNOC-PDA/DOX	R-SNO	808 nm laser irradiation (photothermal)	NO reverses MDR to sensitize PTT and chemotherapy	34
RBS-T-SCNPs	Roussin's black salt	X-ray irradiation	$ONOO^-$-generation directly damages DNA and downregulates the DNA-repair enzyme	52
HMs	DETA NONOate	pH	NO inhibits P-gp expression to reverse CPT MDR.	31
PEG-USMSs-SNO	R-SNO	X-ray irradiation	NO sensitizes radiotherapy of hypoxia tumor	55
P-lapa-Fc	L-Arg	ROS	$ONOO^-$ generation enhances tumor therapy	64
UMNOCC-PEG	R-SNO	pH	RNS generation enhances PDT/CDT	90
mCuMNO	S-nitrosoglu-tathione	Cu^+	Interrupting the interaction between platelets and circulating tumor cells and enhancing CDT	236
T-$NP_{CA/NO}$	R-SNO	GSH	$ONOO^-$ promotes mitochondrial membrane permeabilization	237

[a] RBS-T-UCNPs, Roussin's black salt-upconversion nanoparticles; α-CD-Ce6-NONPs, α-cyclodextrin-chlorin e6-NO nanoparticles; NMOF-SNO, nanoscale metal-organic framework-*S*-Nitrosothiol; DN@MSN, doxorubicin-NO-Mesoporous silica nanoparticles; Peptide-HMSN-LA, Peptide-hollow mesoporous silica nanoparticles-L-Arg; photoNORM/UCNP, photochemical precursor of NO-upconversion nanoparticles; PTNGs, phototriggered NO nanogenerators; GCZ@M, GSNO/Ce6@ZIF-8@Cytomembrane; IDDHN, intelligent nanoparticle; L-Arg-HMON-Gox, L-Arg-hollow mesoporous organosilica nanoparticle-glucose oxidase; BNN-Bi_2S_3, bis-*N*-nitroso compounds-bismuth sulfide; PFTDPP-SNAP NPs, semiconducting polymer-s-nitrosothiol groups nanoparticles; Lip-SNAP, SNAP loaded liposomes; S–NO NPs, N-nitrosamine nanoparticles; QM-NPQ@PDHN, fluorogen QM-2-O^2-(2,4-dinitro-5-{[2-(β-d-galactopyranosyl olean-12-en-28-oate-3-yl)-oxy-2-oxoethyl] piperazine-1-yl}- phenyl) 1-(methylethanolamino)diazen-1-ium-1,2-dilate-PEGylated disulfide-doped hybrid nanocarriers; AL-SISIN-1, N-((2-pyridin-2-yldisulfanyl)ethoxyl)carbonyl-3-morpholinosydnonimine; iCPDN, poly(amidoamine)-Doxorubicin-NO; WB@hydrogel, $WO_{2.9}$-N,N′-di-sec-butyl-N,N′-dinitroso-1,4-phenylenediamine@hydrogen; BNN6, N,N′-di-sec-butyl-N,N′-dinitroso-1,4-phenylenediamine; pPTX/pCD-pSNO, polymerized paclitaxel-nitric oxide-incorporated polymerized β-cyclodextrin; TPE-RSNO micells, *S*-nitrosothiol-functionalized tetraphenylethene; FZ-SS-FZ@FA NPs, phenylsulfonylfuroxan nanoparticles; Ce6/PDE5-i@FHMON-O_2, photocleaved O_2-released nanoplatform; $NPS_{D\text{-}IR}$, IR-780-Doxorubicin NO nanoparticles; PIH-NO, perfluorodecalin-IR780-human serum albumin- NO; PtR/CPG, cis-platinum-L-arginine/ Cytosine-phosphorothioate-guanine; HFC/DTX/aPD1, heparin-folate-cy5.5/l-arginine/ docetaxel/anti-PD-1; S1P/JS-K/Lipo, sphingosine-1-phosphate/ O_2-(2,4-dinitrophenyl) 1-[(4-ethoxycarbonyl) piperazin-1-yl] diazen-1-ium-1,2-diolate/liposome; JS-K, O_2-(2,4-dinitrophenyl) 1-[(4-ethoxycarbonyl) piperazin-1-yl] diazen-1-ium-1,2-diolate; CMH-OBN, chlorin e6-melanin-hyaluronic acid nanoparticles-oxidized bletilla striata polysaccharide microcapsules; Alb-PLP/NO NPs, albumin-coated poly(lactic-*co*-glycolic acid) (PLGA)-conjugated linear polyethylenimine diazeniumdiolate (LP/NO) nanoparticles; P@BDOX/β-lapachone-NO-NPs, peptides (pHLIPs)-poly(ethylene glycol) and nitrated gluconic acid copolymers @Doxorubicin prodrug/β-lapachone-NO; $SPNA_{Pt/NO}$, supramolecular prodrug nanoassemblies-platinum(IV) prodrug/NO; $_{LP}Fe_3O_4$ NPs, L-arginine-poly(acrylic acid)-hollow iron oxide nanoparticles; BPNs-Arg-GOx@MnO_2, black phosphorus nanosheets-L-Arginine-glucose oxidase @MnO_2 nanosheets; UC-ZIF/BER, upconversion nanoparticles-zeolitic nitro-/nitrile-imidazole framework-82-berbamine; HFLA-DOX, doxorubicin-heparin/folic acid/L-arginine; L-Arg@Ce6@P NPs, L-arginine@ chlorin e6@ poly-lactic-co-glycolic acid nanoparticle; HA@MOF/D-Arg, hyaluronic acid@ metal-organic frameworks/D-arginine; ArgCCN, poly-L-arginine modified carbon-dots-doped graphitic carbon nitride nanomaterial; RBCm/PAAVSNO/IR1061 + 1-MT NPs, red blood cell membrane/ copolymer (poly(acrylamide-*co*-acrylonitrile-*co*-vinylimidazole)-S-nitrosothiols copolymer+1-methyl-tryptophan; NO-NCPs, NO-nanocapsules; Ptx@AlbSNO, paclitaxel@ NO donor-modified albumin; BSA-IRLA@RVs-RGD, BSA-L-Arginine-IR783@ red blood cells membrane derived vesicle-RGD; NO@HMs, NO-poly(lactic-co-glycolic acid) (PLGA) hollow microsphere; DPP-NF NPs, diketopyrrolopyrrole-4-nitro-3-trifluoromethylaniline nanoparticles; Lyso-Ru-NO@FA@C-TiO_2, Lysosome-Ru-NO@ folic acid@ carbon-doped titanium dioxide nanoparticles; N-GQDs@Ru-NO@Gal, N-doped graphene quantum dots@ Ru-NO@ galactose derivative; CPNs, cocktail polyprodrug nanoparticles; L-Arg@PCN@Mem, L-arginine@ porous coordination network@ cancer cell membrane; P(IR/BNN6/AIPH)@Lip-RGD, IR 1061/BNN6/alkyl radical initiator@Liposome-RGD; Fe(II)-BNCP, 1,5-bis[(l-proline-1-yl)diazen-1-ium-1,2-diol-O^2-yl]-2,4-dinitrobenzene nanoscale coordination polymer; $_{AD}$Au@CuS YSNPs, l-arginine/Dox-loaded gold@ copper sulfide yolk–shell nanoparticls; IPO-NO, IR780-paclitaxel-NO donor-S-nitrosated human serum albumin; IMesNO/DOX@MCs, 1,3-bis-(2,4,6-trimethylphenyl)imidazolylidene nitric oxide/ Doxorubicin@ Micelles; PV-TS, polymeric nanovesicles- tetraphenylporphyrin- sodium nitroprusside; NO-M@DOX, Nitric Oxide Donor-containing polycarbonate-based micelles@ Doxorubicin; N-GQDs@Ru-Cl@TPP, N-doped graphene quantum dots@ ruthenium nitrosyl@ triphenylphosphonium; M@BPAG, macrophage membrane@ black phosphorus nanosheets-L-arginine-glucose oxidase; AI-MPHA NCs, indocyanine green/L-arginine-mesoporous core–shell structure nano-composites; PNOC-PDA/DOX, poly(L-cysteine)$_{20}$-poly(ethylene oxide)$_{45}$-SNO-polydopamine/ Doxorubicin; RBS-T-SCNPs, Roussin's black salt- tocopheryl polyethylene glycol 1000 succinate-scintillating nanoparticles; HMs, hollow microsphere system; PEG-USMSs-SNO, PEG-upconversion nanotheranostic system- S-nitrosothiol; P-lapa-Fc, poly(ε-caprolactone) (PCL)-b-PArg-ferrocene; UMNOCC-

PEG, copper peroxide nanodots-chlorin e6-polyethylene glycol-silicon pores; mCuMNO, S-nitrosoglutathione-copper-based metal-organic framework; T-$NP_{CA/NO}$, cinnamaldehyde-NO nanoparticles.

Table 3.

The Basic Characteristics of ROS, NO, $ONOO^-$

Free radical	Half life	Migration distance	Main activities
Superoxide anion ($O_2^{\cdot -}$)	10^{-6} s	30 nm	Reacts with Fe-S proteins, dismutases to H_2O_2
Hydroxyl radical ($OH^{\cdot}$)	10^{-9} s	1 nm	Extremely reactive with DNA/RNA, lipids, and proteins
Hydrogen peroxide (H_2O_2)	Chemical stable	≥ 1 mm	Reacts with proteins, heme proteins, and DNA/RNA
Singlet oxygen ($^1O_2$)	10^{-6} s	30 nm	Oxidases lipids, proteins, and G residues on DNA/RNA
Nitric oxide (NO)	< 5 s	100 μm	Regulates a variety of biological processes, nitrosative proteins
Peroxynitrite ($ONOO^-$)	1.9 s	100 μm	Oxidizes and nitrifies DNA/RNA, proteins, and lipids.

Table 4.

NO Nanomedicines for Anti-Bacterial/Biofilm[a]

Nanomedicine	NO donor	Release condition	Working mechanism of NO	Refs
AuNC@NO	*N*-Hydroxy-*N*-nitrosamine NO donor	NIR irradiation (heat)	NO/PTT synergistically degrades MRSA biofilms	238
PGalNO	CouN(NO)-R	NIR irradiation	High concentration of NO kills bacteria	115
pH@MSN-CaP-NO	diazeniumdiolate	pH 5.0	NO promotes cornea wound healing	147
BP1 Vesicles	oNBN, pNBN, BN	UV 365 nm irradiation	NO promotes cell migration and viability	149
PU/PPEG-OH-MPS-NO	R-SNO	Physiological conditions.	NO has a broad-spectrum antibacterial property	239
PNOFA	R-N-NO	Visible light irradiation	NO has broad-spectrum antibacterial performance with low drug resistance	104
CoFe2O4@MnFe2O4 nanoparticles	R-SNO	Magnetothermal	Efficiently killing sessile bacteria by rapidly releasing nitric oxide (NO) inside biofilms	240
nbi/NO film	*N*-Diazeniumdiolate	Cu^{2+} to accelerate NO release	Nitrosative stress partly causes DNA deamination; Oxidative stress causes membrane destruction through lipid peroxidation, tyrosine nitrosation, and DNA cleavage	241
SNP@MOF@Au-Mal	Sodium nitroprusside	Photothermal	High concentration of NO and derivatives to combat bacteria	101
AI-MPDA	L-Arg	ROS	NO enhances PDT and mild PTT for biofilm elimination	120
α-CD-Ce6-NO-DA nanocarriers	R-SNO	GSH	NO greatly improves the PDT efficiency by releasing $ONOO^-$	121
PNO	NONOate	Physiological conditions	NO for synergistic eradication of bacterial biofilms	242
PNBNPs	*N*-Diazeniumdiolate	pH	High concentration of NO kills bacteria	243
PDA-NO HNP	NONOate	Physiological conditions	NO has a broad-spectrum antibacterial effect	244
UKON-2jNO	R-SNO	Sunlight	Highly reactive $ONOO^-$ enhances antibacterial effect	94
GEN-NO	NONOate	Physiological conditions	Synergistic NO and antibiotic for biofilm eradication	245
ZnTPyP@NO	R-NO	Sunlight irradiation	Highly reactive $ONOO^-$ generation enhances PDT	67
UCNP@PCN@LA-PVDF	L-Arg	ROS	Highly reactive $ONOO^-$ generation enhances PDT	103
PEO-b-PCouNO	R-N-NO	410 nm light irradiation	NO has a broad-spectrum antibacterial effect	113
Fe3O4@PDA@PAMAM@NONOate	NONOate	808 nm laser irradiation (Photothermal)	NO damages DNA and kills bacteria	105
TG-NO-B	R-SNO	808 nm laser irradiation (Photothermal)	Synergistic NO/PTT to overcome MDR Gram-negative bacteria and their biofilms	102
Ti-RP/PCP/RSNO	R-SNO	808 nm laser irradiation (Photothermal)	Upregulating *Opn* and *Ocn* genes and TNF-α	122
PdTPTBP/CouN(NO)-NO2	R-N-NO	Red light	NO eradiates C. acnes pathogens, with antibacterial, anti-inflammatory, and anti osteoclastogenesis effects.	246

Nanomedicine	NO donor	Release condition	Working mechanism of NO	Refs
B/MA-GSNO	R-SNO	Heat	Rapid NO releasing for antibacterial efficiency	247
DMAH	R-SNO	Heat	Destroying bacterial nitrogen and respiratory metabolisms	248

[a]AuNC@NO, nitric oxide (NO)-releasing gold nanocage; PGalNO; pH@MSN-CaP-NO, Ph@ mesoporous silica nanoparticles-calcium phosphate-NO; BP Vesicles, PEO_{45}-*b*-P*o*NBN_n; PU/PPEG-OH-MPS-NO, ozone-pretreated polyurethane-PPEG-OH-mercapto-silane-RSNO; PNOFA, PEO-*b*-PNNBM-NO-formaldehyde; nbi/NO film, branched polyethyleneimine-alginate-NO film; AI-MPDA,L-arginine-ICG-mesoporous polydopamine; PNO, NO-loaded polymer; PNBNPs, surface charge switchable nitric oxide (NO)-releasing nanoparticles; PDA-NO HNP, Polydopamine-NO hollow nanoparticle; UKON-2JNO, NO-Mesoporous organosilica; GEN-NO, gentamicin-NONOate; ZnTPyP@NO, zinc *meso*-tetra(4-pyridyl)porphyrin@NO; UCNP@PCN@LA-PVDF, upconversion nanoparticle-porphyrinic MOFs@ L-arginine-polyvinylidene fluoride; PEO-b-PCouNO, poly(ethylene oxide)-*b*-polyCouNO; TG-NO-B, S-nitrosothiols-thiolated graphene-4-mercaptophenylboronic acid; Ti-RP/PCP/RSNO, red phosphorus nanofilm deposited on a titanium implant; B/MA-GSNO, magnetothermal aerogel-*S*-nitrosoglutathione; DMAH, dual-mode antibacterial hydrogel.

Table 5.

NO Nanomedicines for Wound Healing[a]

Nanomedicine	NO donor	Release condition	Working mechanism of NO	Refs
SNP@UCM	Sodium nitroprusside	NIR irradiation	Promoting HIF-1α expression, VEGF secretion, and endothelial cell proliferation and migration.	249
PU/Gelatin/KSNO	R-SNO	Physiological conditions	Promoting cell proliferation and adhesion to accelerate wound healing	130
TP-Por CON	BNN6	635 nm irradiation (Photothermal)	NO/PTT/PDT synergistically kill Gram-positive/ negative bacteria via $ONOO^-$	250
pH@MSN-CaP-NO	diazeniumdiolate	pH 5.0	NO promotes cornea wound healing	147
BP1 Vesicles	oNBN, pNBN, BN	UV 365 nm irradiation	NO increases cell migration and viability	149
HA-NO	Diazeniumdiolate	Physiological conditions	NO as an antibacterial agent for promoting wound healing	98
GelMA/HA-DA/GO-βCD-BNN6	BNN6	808 nm laser irradiation (Photothermal)	Promoting new blood vessels and collagen deposition to accelerate wound healing	134
MoS_2-BNN6	BNN6	808 nm laser irradiation (Photothermal)	NO kills the bacteria by damaging DNA, promotes the formation of collagen fibers, and reduces inflammation during wound tissue reconstruction	251
Ch/PAs-Cu	R-SNO	Cu^{2+}	NO combats bacteria and accelerates wound healing	131
PB-NO	R-NO	808 nm laser irradiation (Photothermal)	Promoting new blood vessels and collagen deposition to accelerate wound healing	132
Arg-ADP	L-Arg	H_2O_2	NO/PDT synergistically overcomes bacterial infections and promotes wound healing	135
NO@HKUST1/PCL/Gel	NONOate	Physiological conditions	Promoting endothelial cell growth, significantly improving angiogenesis and collagen deposition, and reducing inflammatory effects in the wound	138
FBN/PEG	NONOate	Physiological conditions	NO enhances reepithelialisation, collagen deposition, and blood vessel formation	252
$_{Ah}CeO_2$ NPs	L-Arg	H_2O_2	NO promotes cellular proliferation	253
MA-HA-(MEDN)-NONOates	NONOate	Physiological conditions	Effectively promoting proliferation and migration of fibroblasts	254
CS-PAMAM/NONOate	NONOate	Physiological conditions	NO antibacterial to accelerate wound healing	255

[a] SNP@UCM, SNP@MOF-UCNP@ssPDA-Cy7/IR786s; PU/Gel/KSNO, polyurethane/gelatin/S-nitrosated keratin; TP-Por CON, porphyrin-based COF nanosheets; BP Vesicles, PEO_{45}-*b*-P*o*NBN_n Vesicles; HA-NO, hyaluronic acid-NO; GelMA/HA-DA/GO-βCD-BNN6, methacrylate-gelatin/hyaluronic acid-dopamine hydrogel/ graphene oxide-β-cyclodextrin-BNN6; Ch/PAs-Cu, chitin sponges-proanthocyanidins-Cu^{2+}; PB-NO, Prussian blue-NO; Arg-ADP, L-Arginine-rich amphiphilic dendritic peptide; NO@HKUST1/PCL/Gel, NO@ copper-based metal–organic framework/hydrophobic polycaprolactone/gelatin; FBN/PEG, Pluronic F127-branched polyethylenimine-1-substituted diazen-1-ium-1,2-diolates/ PEG; $_{Ah}CeO_2$ NPS, hollow CeO_2-L-arginine nanoparticles; MA-HA-(MEDN)-NONOates, methacrylate-hyaluronic acid-N-diazeniumdiolate; CS-PAMAM/NONOate, Polyamidoamine dendrimer-grafted chitosan/NONOate.

Table 6.

NO Nanomedicines for Eye Disease Therapy[a]

Nanomedicine	NO donor	Release condition	Working mechanism of NO	Refs
β-galactosidase-loaded PMA capsules	β-gal-NONOate	β-galactosidase	NO-mediated IOP-lowering therapeutics	143
HOS-J_RL_O	JS-K/L-Arginine	ascorbic acid/iNOS	HOS-J_RL_O generates more NO to induce a larger IOP reduction	144
PEG-PAspTETA-SNO	R-SNO	GSH	Alleviating high intraocular pressure in mice with glaucoma	256
pH@MSN-CaP-NO	diazeniumdiolate	pH 5.0	NO promotes cornea wound healing	147
BP1 Vesicles	NBN, pNBN, BN	UV 365 nm irradiation	NO stimulates cornea wound healing	149
BPEI-NO NPs	NONOate	Physiological conditions	NO improves ocular wound recovery	257

[a]HOS-J_RL_O, hollow mesoporous organosilica-JS-K-L-Arginine; PEG-PAspTETA-SNO, PEG-poly(2-acetamido-N-triethylenetetramine-3-nitrosothiol-3-methylbutanamide) aspartamide-S-nitrosothiols; BP Vesicles, PEO_{45}-*b*-P*o*NBN_n Vesicles; BPEI-NO NPs, silica nanoparticles-branched polyethylene imine-*N*-diazeniumdiolates.

Table 7.

NO for SARS-CoV-2 Infection and COVID-19

NO source	Dose	Duration	Follow-up / d	Indications/Results	Refs
Inhaled NO gas	20 PPM+2 L/min O_2 10 PPM+2 L/min O_2 10 PPM+2 L/min O_2	12–14 h/day	0–6 7–9 10–12	Improved Covid-19 patient symptoms and full recovery	258
SNAP	200 μM 400 μM	In vitro	-	Inhibited the replication cycle of SARS-CoV-2	162
NONS	2 sprays per nostril (0.45 mL / dose)	6 times daily	18	Accelerated virus clearance (153 patients)	165
SNAP	200 μM 400 μM	In vitro	-	Reduced SARS-CoV-2 protease activity	164