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Review

Light-induced nitric oxide release in the skin beyond UVA and blue light: Red & near-infrared wavelengths

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ABSTRACT

Nitric oxide (NO) is omnipresent in the body and synthesized by 3 isoenzymes (nNOS, eNOS and iNOS), all detected in human skin. NO can be stored in a pool of compounds readily converted to NO following skin irradiation by UVR and blue light. This non-enzymatic (without NOS involvement) photolytic reaction mobilizes cutaneous stores of NO derivatives to the bloodstream, lowering blood pressure. However, with the likelihood of skin deleterious effects caused by UVR/blue light, safer wavelengths in the red/near-infrared (NIR) spectrum are becoming potential contenders to release cutaneous NO, possibly via NOS temperature-dependent effects. The use of red/NIR light to mobilize NO stores from the body's largest organ (the skin) is auspicious. This review focuses on UVR, blue, red, and NIR spectra and their capacity to release NO in human skin. PubMed and Google Scholar were used as article databases to find relevant publications related to this particular field.

1. Introduction

1.1. Nitric oxide: the Ubiquitous jack of all trade

Nitric oxide (NO) is synthesized endogenously by Nitric Oxide Synthase (NOS), including three different types; two are expressed constitutively, and one is an inducible isozyme [1]. There are neuronal NOS (nNOS) along with endothelial (eNOS) and inducible NOS (iNOS). nNOS and eNOS have been discovered in their respective cell types and are constitutively expressed, as opposed to iNOS, which is inducibly expressed in a variety of human cells. The three NOSs have been detected in human skin [2], where NOS-dependent production of NO potentially occurring in all cell types driven by one or more of the three NOSs [3]. NOS isoenzymes are homodimeric proteins needing many cofactors to perform their catalytic activity, such as incorporating molecular oxygen to L-arginine to release NO and the formation of L-citrulline as an end-product. Those cofactors are nicotinamide adenine dinucleotide phosphate (NADPH), reduced flavins, heme-bound iron, and 6 (R) 5,6,7,8-tetrahydrobiopterin. Expression of nNOS has been identified in keratinocytes and melanocytes [4]. Mast cells located in the dermis also express nNOS [5]. Whereas eNOS can be observed in keratinocytes of the basal epidermal layer, dermal fibroblasts, endothelial cells, and eccrine glands. Generally, iNOS is not expressed in resting skin cells but may be induced following immune/inflammatory activation. In pro-inflammatory skin environments, keratinocytes, fibroblasts, Langerhans cells, endothelial cells, and mast cells may express iNOS [6]. Expressed NOS isoforms, like nNOS and eNOS, are activated by increasing calcium influx levels leading to the activation of the NOS-upstream activator, calmodulin [4]. iNOS is unique among the NOS family in that it is not regulated by calcium signals; instead, it is continuously active once expressed [7]. Also, iNOS generates the highest concentrations of NO, which is in nanomolar rather than picomolar, and this level of synthesis is sustained for hours or longer until the enzyme is cleared from the cells or tissues [7].

NO is a free radical with an unpaired electron in his highest orbital state. It behaves as a potential antioxidant agent by reducing other molecules and therefore inhibits lipid peroxidation [8]. However, NO is quickly inactivated by the superoxide anion (O_2^-) to form peroxynitrite

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($ONOO^-$), known as a potent oxidant [9]. As NO and O_2^- are simultaneously released by cells, the balance between these two radicals is decisive in the faith of NO towards lipid peroxidation. Hence, a higher NO/O_2^- ratio will favor lipid peroxidation inhibition, while ratios equal or lower to one will induce lipid peroxidation [8].

The short half-life of NO (gaseous state) could explain the sphere of influence of this biomolecule and its limited diffusion in the immediate microenvironment. It is currently understood that NO can be stored in an accessible pool of compounds easily converted to NO [10]. Some proteins and biomolecules react quickly with NO, resulting in S-, N-, O-, and C- nitroso compounds, such as S-nitroso-glutathione (GS-NO) or S-nitroso-albumin [11]. In addition, oxygen reacts quickly with NO, forming nitrite ($NO2^-$) and nitrate ($NO3^-$). These NO derivatives can be found in relatively high skin concentrations, and some are easily converted to NO (Fig. 1) [10,12]. In fact, S- and N- nitroso compounds (RS-NO and RN-NO), along with other NO derivatives, like nitrite and nitrate, are found in high concentrations in the skin [13]. Concentrations of nitrite and RS-NO reach up to 15 μM and 7 μM in healthy subjects' skin, respectively. This represents 25- and 360- times the concentration of these respective compounds found in the plasma [13].

Following skin irradiation by Ultraviolet A (UVA) light, some studies showed that cutaneous stores of NO derivatives could be mobilized to the bloodstream [14]. The authors showed that UVA increased circulating nitrite and reduced circulating nitrate [14]. NO was therefore made more available, with nitrite easily converted to NO by UV irradiation, a reaction called UV photolysis [15–17]. So, UVA irradiation of the skin freed up some of its large stores of NO derivatives, making NO available to promote vasodilation and other biological processes. In other words, human skin contains NO derivatives photodecomposed to NO following UVA irradiation, presumably independent of NOS involvement.

More recently, blue light has been shown to release NO [18,19] in the blood circulation from photolabile intracutaneous NO metabolites with corresponding cardiovascular benefits [20].

Longer wavelengths in the red and NIR spectra may also be used to release NO locally and systemically. Our group recently showed that red and NIR wavelengths could release NO from ex-vivo skin [21,22].

Low-intensity visible and NIR light is part of photobiomodulation (PBM). NO is one of the three PBM primary cellular effectors, namely ATP, ROS and NO. They can all be released by the mitochondria following photons' absorption by the main chromophore; Cytochrome C Oxidase. NOSs have also been linked to red/NIR light-induced NO release [23]. Despite established ultraviolet radiation (UVR) and blue light photolytic release of NO in the skin [15,24], light exposure in the red/NIR spectrum is a promising alternative using safer non-ionizing photons [21,25]. NO stores are prominent and mostly located in the epidermis, modulating local and remote systemic effects [20]. Finding new methods to mobilize such a substantial NO reservoir in the skin have broad implications in photomedicine.

Herein, we will describe the current knowledge on light-induced NO release in the skin using UVR and blue light. We will also introduce new modalities capable of releasing NO in the red and near-infrared spectra.

2. UVA-induced NO release

The UVA part (320–400 nm) of the UVR spectrum is the last frontier

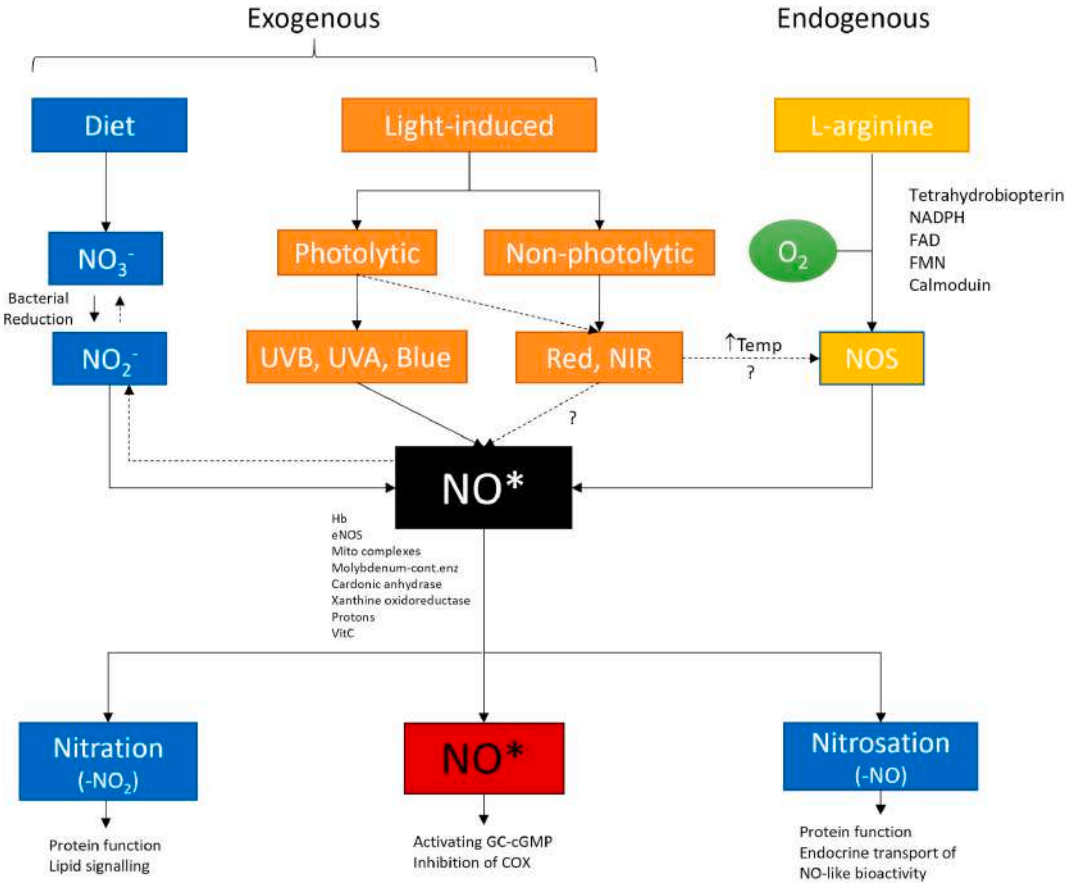

Fig. 1. Major pathways lead to NO formation in the skin primarily originating from exogenous and endogenous sources and subsequent nitration/nitrosation metabolic end reactions. Apart from dietary intake and endogenous stores of L-arginine, light-induced mobilization of NO is conceivable. Despite established NO release benefits via UVR and blue light, the use of longer wavelengths in the red/NIR spectrum remains to be determined. O2: oxygen, NO3: nitrate, NO2: nitrite, NOS: nitric oxide synthase, UVB: ultraviolet B, UVA: ultraviolet A, NIR: near-infrared, NO; nitric oxide.

of ionizing radiation prior to non-ionizing visible blue light at 400 nm (Fig. 2). Among several UVA-induced NO release studies [10,26–32], Liu et al. demonstrated that there is a photolytic process occurring following human skin irradiation. [14]. This report showed that most of the light-sensitive NO pool (fluorescence) was located in the upper epidermis and stratum corneum. Moreover, the reaction was unaffected by the NOS antagonist L-NMMA but entirely abrogated by the NO scavenger cPTIO, suggesting that UVA photolytic effect can significantly release NO non-enzymatically. Another study showed the implication of UVA radiation in upregulating iNOS expression [33]. The results showed a peak in iNOS expression 24-h post-UVA irradiation and a return to normal levels after 72 h. Furthermore, through epidermal growth factor (EGF) receptors, UVA induces a calcium influx in keratinocytes, which activates NOSs and the formation of ROS [11,34]. Similarly, UVA is also known to modulate a calcium influx in melanocytes via the retinal-dependent pathway [35]. Additionally, elevated NO levels are known to be pro-inflammatory, partially explaining the development of erythema and the tight connection between UVA-induced expression of iNOS along with its photolytic capacity to yield high levels of NO from skin NO derivatives [11,36]. On the other hand, it is important to note that UVA exposure may also lead to photoaging, melanoma (*e.g.,* lentigo maligna) and non-melanoma skin cancers (NMSCs) [37] even though bursts of UVA-induced NO release have shown protective effects against cellular oxidative stresses [38,39]. Nevertheless, safer light-based approaches to release NO would be preferable.

2.1. Key absorption spectra

It has been acknowledged that UV light liberates NO via photodecomposition of NO derivatives, a process called photolysis, especially photolabile molecules such as nitrite and S-Nitrosothiols (RS-NOs).

UVA can release NO radicals from the cutaneous nitrite reservoir. This nitrite photolytic reaction results in the release of NO and indirectly to the nitrosylation of surrounding biomolecules through the formation of important by-products, like nitrogen dioxide radicals ($NO_2^{\cdot}$) and N_2O_3 [11]. Compared to NO itself, N_2O_3 is very efficient at nitrosating thiols to RS-NO. It is hypothesized that the formation of N_2O_3 plays a major role in forming RS-NOs (i.e. S-nitroso-albumin), making them more abundant in bloodstream circulation [40]. Besides, photolysis of nitrite is always followed by the release of harmful hydroxyl radicals ($OH^{\cdot}$) [41].

UVA photolysis of Nitrite [11]:

$$NO_2^- + h\nu \rightarrow NO^{\cdot} + O^{\cdot -}$$

$$O^{\cdot -} + H_2O \leftrightarrow {}^{\cdot}OH + {}^{-}OH \ (pK_a = 11.9)$$

$$NO_2^- + {}^{\cdot}OH \rightarrow NO_2^{\cdot} + OH^-$$

$$NO_2^{\cdot} + NO^{\cdot} \rightarrow N_2O_3$$

$h\nu$ = light energy
νstands for frequency (Hz)
h is Plank's constant (6.626 x 10^{-34} J s)

Thereby, UVA photons release NO directly by disrupting the Nitrogen–Oxygen bond with a transition state energy of + 87.4 kcal mol^{-1} [11]. For example, at 320 nm, the radiation energy (i.e. $h\nu$) delivered is +89.35 kcal mol^{-1}, easily releasing NO from nitrite stores. Interestingly, the nitrite absorption spectrum falls within the UVA spectral band (Fig. 3) [42].

UVA photolysis of RS-NOs is also taking place in human skin, releasing NO radicals (Fig. 4). The required experimental transition state energy needed to decompose RS-NOs have been reported to range from +23 kcal mol^{-1} to +34 kcal mol^{-1} [19]. As such, UVA (320 nm–400 nm) is readily capable of releasing NO from thiol compounds with radiation energies ranging from +89.35 kcal mol^{-1} to +71.48 kcal mol^{-1}.

Regarding nitrate, although it is physiologically inert, it can be reduced to biologically active nitrite by bacteria in the oral cavity and the gut or reduced by local xanthine oxidoreductases (XOR) [27] (Fig. 1). Although its peak absorption (303 nm) corresponds to UVB emission spectra [45], UV light (UVB + UVA) has limited ability to photodecompose and release NO. [14,46]. Paunel et al. showed that neither nitrate nor N-nitroso compounds (RN-NO) are involved in the

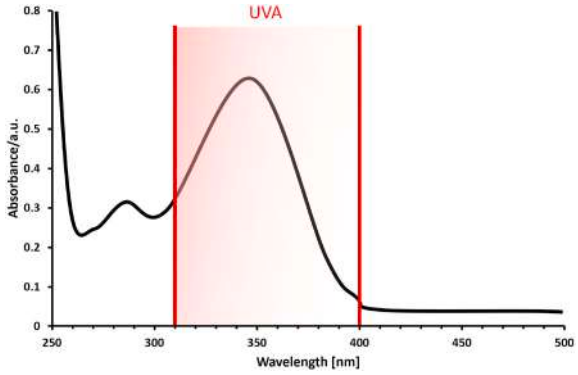

Fig. 3. Nitrite absorption peak in the UVA spectra with practically no absorption above 400 nm. As for S-nitrosothiols (RS-NOs), photodecomposition occurs primarily between 290 nm and 390 nm [43]. It is known that visible light above 500 nm can easily reach the reticular dermis. This context induces significant decomposition of RS-NOs needing lower energy levels to release NO [44].

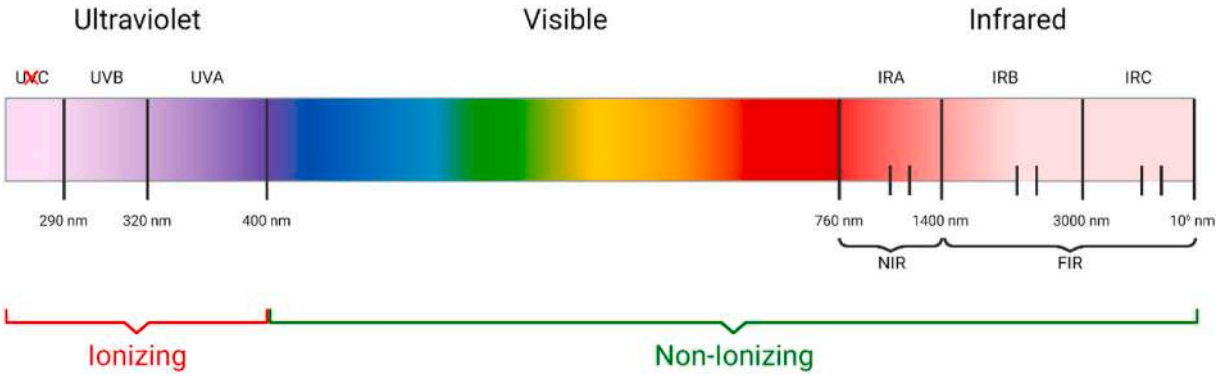

Fig. 2. Electromagnetic Spectrum (EMS) solar spectrum composition. It is worth mentioning that UVC is blocked by the ozone layer. UVC: ultraviolet C, UVB: ultraviolet B, UVA: ultraviolet A, IRA: infrared A, IRB: infrared B, IRC: infrared C, NIR: Near Infrared, and FIR: Far infrared. This figure was sketched using BioRender.com.

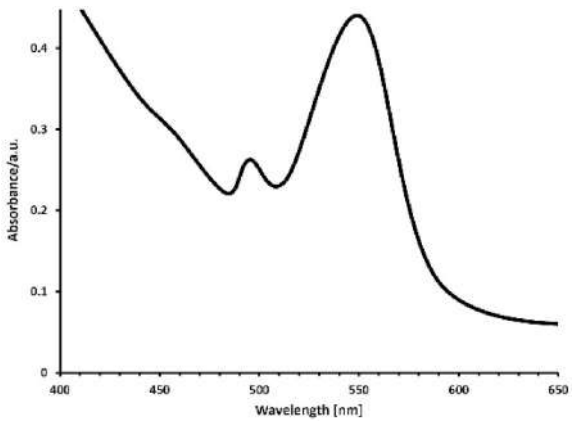

Fig. 4. Absorption spectra of a prominent RS-NO, S-nitroso-N-acetylcysteine (SNAC) [44]. Note the second absorption peak at 550 nm.

non-enzymatic UVA-induced NO release [13]. However, in vitro studies reported nitrate absorption peaks at 630 & 660 nm [47], making it theoretically possible for red light to interact with nitrate for NO release.

It is noteworthy to mention that photodecomposition of nitrite yields lower NO release content compared to RS-NO [18]. However, nitrite photodecomposition is more sustained over time. RS-NO photodecomposition results in much higher NO release content since less energy is necessary to decompose RS-NOs. Nonetheless, the reaction is short-lived, and photodecomposition causes a rapid depletion of RS-NOs in the skin (i.e. photobleaching) [13].

3. Blue light-induced NO release

Visible light represents approximately 50% of solar rays reaching the earth's surface. Other visible light sources are lasers, LEDs and flash lamps [48]. Blue light is the first segment of visible light on the EMS starting at 400 nm (Fig. 2).

Blue light cutaneous effects are still under debate in the medical literature and appear to be dose-dependent and perhaps even more precisely intensity-dependent. Many studies using blue light with low energy and short exposure time showed promising results in treating some inflammatory skin disorders like psoriasis and atopic dermatitis [49,50]. The hypothesis outlines the potential of blue wavelengths to reduce proliferation and increase differentiation of keratinocytes along with their potential to downregulate the modulation of immune cells [19]. However, numerous studies reported that by using longer exposure time combined with moderately low intensity (i.e. similar to the sun's intensity), blue light might increase the amount of DNA damage [51,52], cell and tissue death [53], skin hyperpigmentation [54], skin barrier damage [54,55], premature photoaging [52,56,57], and carcinogenesis [51,52]. Prolonged hyperpigmentation has been described even at low irradiance (intensity 30 mW/cm^2), much like in photobiomodulation applications [58].

Blue light irradiation modulates cellular behavior by generating ROS and NO bursts. When they both rise by further blue light exposure, skin cells undergo apoptosis [19]. Accordingly, many studies have shown that blue light decreases proliferation and inhibits cellular growth [59–61], possibly due to the absorption of blue photons by porphyrin-containing enzymes and flavins, resulting in the production of ROS bursts [62,63]. The enzymatic-induced NO release following blue light exposure seems possible via the absorption capacity of flavins needed as cofactors for NOS catalytic activities. This assumption has only been mentioned in one study [64].

Some work has been done using blue light capable of releasing photolabile NO non-enzymatically [18] the same way ultraviolet does [30]. As mentioned above, the energy needed to decompose RS-NO is relatively low, ranging from +23 kcal mol^{-1} to +34 kcal mol^{-1}. Accordingly, blue light (400 nm–500 nm) radiation energies, covering +71.48 kcal mol^{-1} to +57.18 kcal mol^{-1}, can easily photodecompose RS-NO molecules.

As for nitrite, the energy needed to decompose the N–O covalent bond is too high for blue light. Oplander et al. found that blue light-induced photodecomposition of nitrite needs the presence of cupric ion (Cu^{2+}) and is highly dependent on the reduction of the cupric ion to the cuprous form (Cu^{1+}) [18]. Briefly, copper salts and blue light catalyze the spin-forbidden formation of the intermediate triplet-nitrite ($^3NO_2^-$), which reduces the Cu^{2+} into Cu^{1+} via the unpaired-excited electron. Cu^{1+} will then catalyze the formation of NO via a nitrite molecule, and then water and cupric ion will be released as by-products [19].

Blue light photolysis of nitrite [19]:

$$Cu^{2+} + NO_2^- \rightarrow \left[Cu^{2+}NO_2^-\right] + hv \rightarrow \left[Cu^{2+3}NO_2^-\right]$$

$$\left[Cu^{2+3}NO_2^-\right] \rightarrow Cu^{1+} + NO_2$$

$$2\,NO_2 + H_2O \rightarrow NO_2^- + NO_3^- + 2\,H^+$$

$$Cu^{1+} + NO_2^- \rightarrow \left[Cu^{1+}NO_2^-\right] + H^+ \rightarrow Cu^{2+} + H_2O + NO$$

In biological environments, copper ions are soluble and mostly bound to specific proteins, like ceruloplasmin and albumin, or other copper-bound proteins [65]. Surprisingly, upon blue light absorption, copper-bound proteins lose their catalytic sites and cannot function properly [19]. As such, it is improbable that blue light-related photodecomposition of nitrite plays an important role in human skin [11]. However, there are relatively high nitrite and free copper levels at the skin surface (12 μM and 10 μM, respectively) [11]. Blue light might then decompose nitrite at the apical skin surface.

The resulting NO release following non-enzymatic photolysis is sufficient to induce a significant increase in local blood flow through vasodilatation or even reduce systemic blood pressure [66]. Thus, regarding the potency for intracutaneous NO generation from RS-NOs, blue light is comparable to UVA-induced effects. Still, blue-light-induced NO formation from nitrite has different mechanisms compared to UVA-induced nitrite decomposition [16] (see Fig. 7).

Regarding blue light's proximity to ionizing wavelengths in the UVA spectrum, it is elusive to set a limit at 400 nm securing the skin from ionizing hazards. Several authors now use blue light at 455 nm further away from this borderline to avoid potential overlapping effects and still generate comparable beneficial effects [11,67,68].

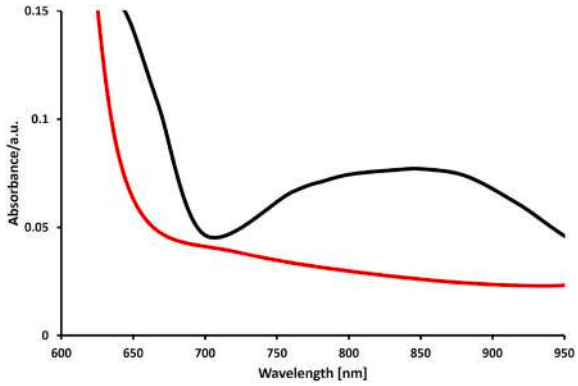

Fig. 5. Absorption spectra of Cytochrome C Oxidase in the oxidized state (Black) and reduced state (Red) in the visible and near-infrared spectra [101]. It shows higher peaks in the red and NIR at 670 nm and 850 nm, respectively. For instance, at 850 nm, oxidized Cytochrome C Oxidase shows ~8% of absorbance compared to ~3% for its reduced state.

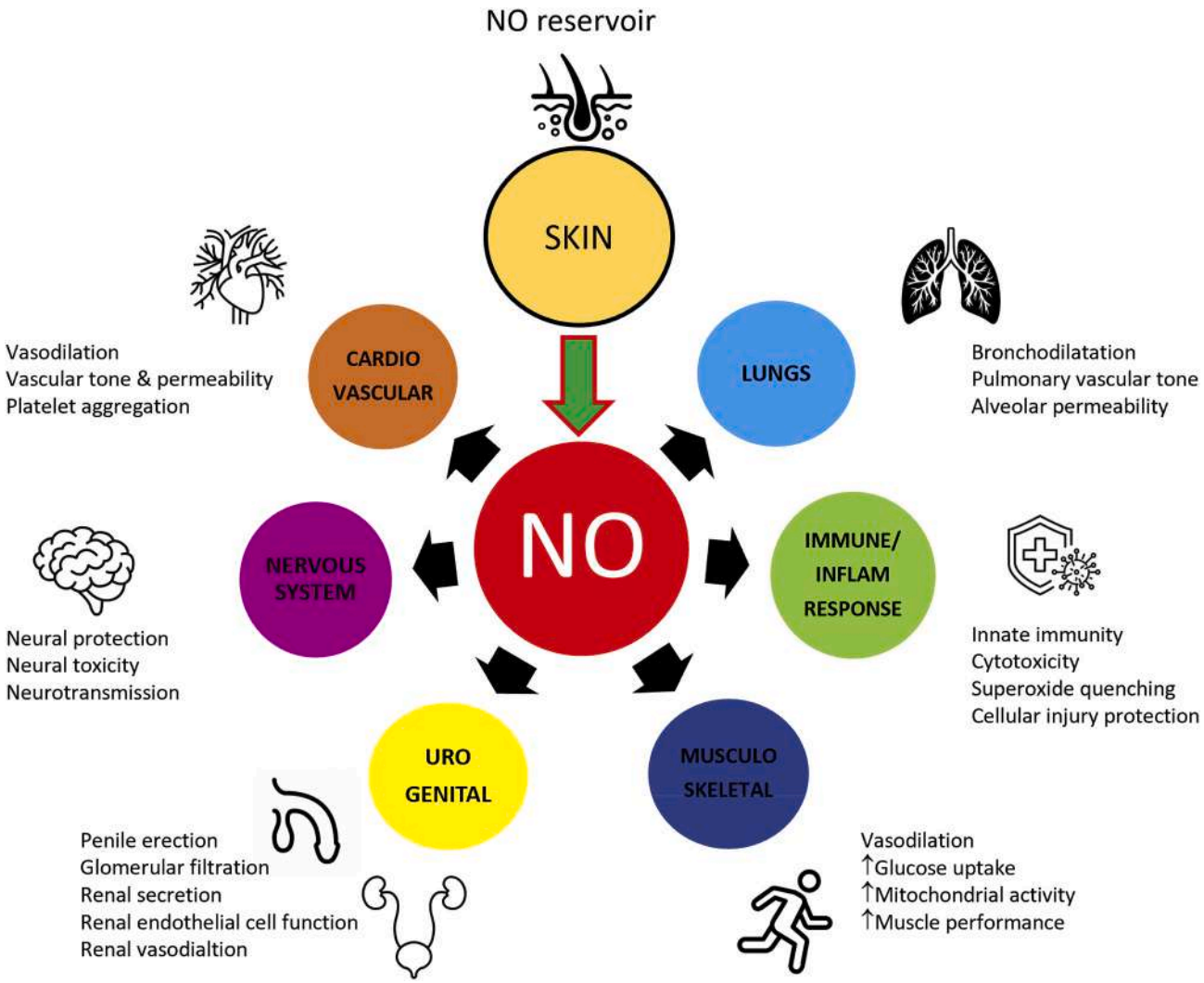

Fig. 6. Potential NO therapeutic applications throughout the human body.

4. Red/NIR light therapy: new contenders

Further away from UVA and blue light on the EMS and emitting non-ionizing photons, visible red light provides deeply penetrating wavelengths in tissues [69]. Red light is the most commonly used part of the visible spectrum, especially in light-based low-intensity skin applications (PBM) with known beneficial effects [70–73]. Apart from photodermatoses caused or exacerbated by visible light, such as solar urticaria, cutaneous porphyrias, and less commonly polymorphous light eruption and chronic actinic dermatitis [48], red light has an impressive safety profile in PBM [74]. Unlike blue light, red photons do not trigger cutaneous side effects like hyperpigmentation [70] but rather can even reduce it [75] when using conventional PBM parameters (i.e. intensity $<$ 50 mW/cm^2 and dose $<$ 50J/cm^2).

Infrared light (760 nm - 1 mm) constitutes approximately 45% of the solar radiation reaching the ground at sea level [76]. Shortest wavelength near-infrared photons (NIR or IR-A: 760–1400 nm) can penetrate the epidermis, dermis and subcutaneous tissue with numerous biological effects [76]. NIR used to have a bad reputation based on past studies using high-intensity artificial light sources (above the solar IR-A irradiance threshold) at high doses leading to detrimental effects (i.e. upregulation of matrix metalloproteinase-1) [77–86]. Although deleterious effects may occur at higher intensities that do not represent real-life daily sun exposure, mimicking sunlight NIR (at lower intensity: 30–35 mW/cm2) will rather trigger beneficial cutaneous effects [71,72,76,87–89]. It appears that intensity is more important than the total dose delivered, such as in sun exposure, to reach the therapeutic window of the biphasic dose curve [90], making the law of reciprocity inapplicable in photobiology [76,91].

The therapeutic benefits of red/NIR light therapy have been demonstrated in multiple studies [72,73,87,92]. Red/NIR light has been proposed to influence the photodissociation of NO from CCO, thereby allowing oxygen to reclaim its binding site on the binuclear center, formed of Cytochrome *a*3 and CuB [93], allowing ATP production process to resume [89]. For instance, as part of photobiomodulation therapy for cutaneous inflammatory lesions, CCO oxidized state has two absorption peaks at 660 nm and 850 nm (Fig. 5) corresponding to classical red and NIR PBM wavelengths. However, this intramitochondrial reaction is probably not sufficient to significantly impact cutaneous NO stores [92]. Another explanation relates to red/NIR capacity to generate bursts of ROS and trigger Ca^{2+} influx in skin cells [94,95]. Both are molecular events upstream of eNOS and nNOS activation through the modulation of calmodulin [96,97].

The efficacy of Red/NIR light to photodecompose NO derivatives has not been proven so far. Under Planck's equation (i.e., $E = h\nu$), red light at 660 nm and NIR at 850 nm have radiation energies of +43.32 kcal mol^{-1} and +33.64 kcal mol^{-1}, respectively. In theory, using these two absorption peaks of CCO, their radiation energies should decompose RS-NOs in the skin. Oplander et al. showed that green light was able to photodecompose RS-NOs at the same magnitude as blue light [18].

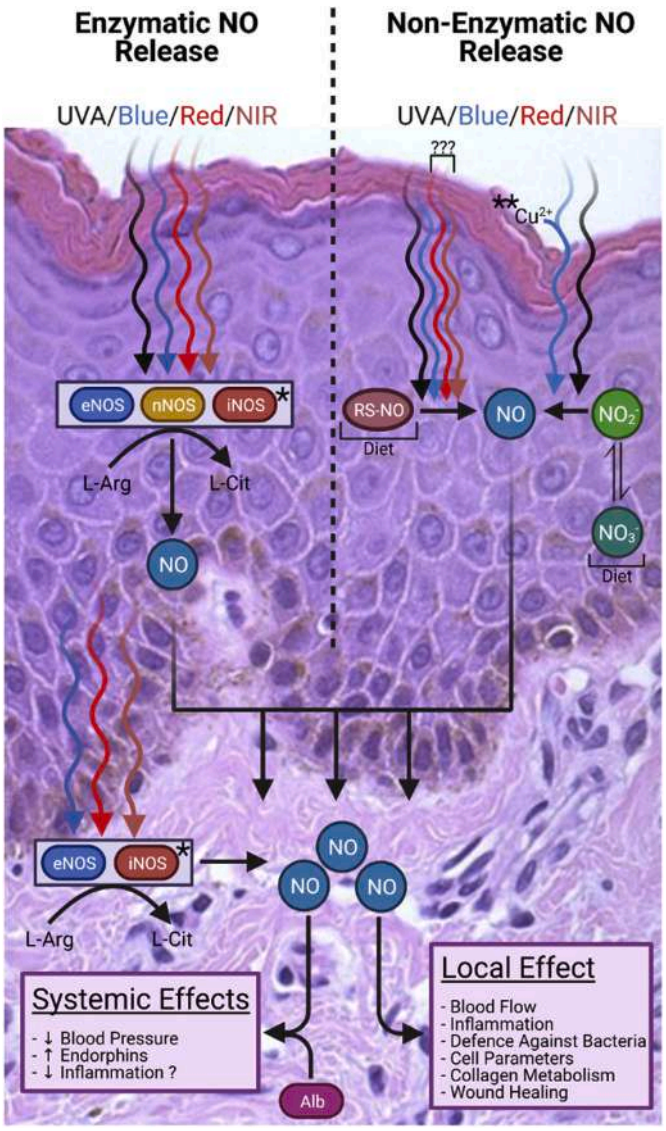

Fig. 7. Summary of proposed NO metabolism in the skin with enzymatic and non-enzymatic (photolytic) pathways occurring concomitantly, leading to local and systemic effects. The epidermal activity of NOS enzymes mainly involves eNOS and nNOS. Whereas dermal NOS activities essentially concern eNOS alone, except for mast cells that slightly express nNOS. *In specific conditions, iNOS activation is induced in both epidermal and dermal cells, but it is not constantly expressed compared to nNOS and eNOS. **Blue light-induced photodecompositon of nitrite is most likely taking place only at the surface of the skin (i.e., stratum corneum), where there is free copper and a relatively high concentration of nitrite. Albumin (Alb) is proposed as a transporter of very potent NO radicals throughout the body for systemic effects. Red and NIR-related photodecomposition of RS-NOs has not been proven yet but is plausible. Note that nitroso compound (NO_3^-, NO_2^-, and RS-NO) interactions can occur in the following skin cells: keratinocytes, melanocytes, fibroblasts, Langerhans cells, endothelial cells, immunocompetent cells and smooth muscle cells. eNOS: endothelial Nitric Oxide Synthase, nNOS: neuronal Nitric Oxide Synthase, iNOS: inducible Nitric Oxide Synthase, L-Arg: L-Arginine, L-Cit: L-Citrulline, Temp.: Temperature, NO: Nitric Oxide, NO3-: Nitrate, NO2-: Nitrite, RS-NO: S-Nitrosothiols, and Alb: Albumin. Figure created with BioRender.com.

However, many-fold higher irradiances were needed to achieve it. Hence, it is conceivable that red and NIR may photodecompose RS-NOs but not nitrite, needing much higher radiation energies (Fig. 7).

Lately, red and near-infrared wavelengths have been reported to release NO from human skin [25,98]. Rizzi et al. observed an increase in NO concentration by irradiating human keratinocytes at 980 nm [98]. NO rises were abrogated by treating these skin cells with the NOS inhibitor L-NAME, thereby proposing an enzymatic involvement of NIR-induced NO release. They proposed that NIR-induced heating may stabilize NOSs and their cofactors. Accordingly, a temperature-dependent increase in enzymatic activity via NOS would trigger inside-out heating upon the absorption of NIR photons by water in the dermis. A temperature rise can actually modulate NO metabolism in the skin. Part of the explanation relies upon heat shock protein 90 (HSP90) being thermally regulated. HSP90 exerts an allosteric modulation on NOS isozymes by promoting the binding of their cofactors and enhancing their affinity for calcium (for nNOS & eNOS) [99]. Also, HSP90 has shown the capacity to neutralize NOS isozymes' proteolytic degradation [100].

Whether it be via radiation alone (photolysis or non-enzymatic) or radiation heat (enzymatic via NOS), further investigation is needed to elucidate the true capabilities of red/NIR wavelengths.

5. Polymeric NO donors and light irradiation to treat the skin

As previously mentioned, NO is a free radical that interacts rapidly with surrounding molecules. Over the years, many studies were conducted to find ways to compensate for this high reactivity. Organic (e.g. amine, nitrate, etc.) and inorganic (e.g. silica) polymers known as polymeric NO donors have been newly synthesized as therapeutic tools [102]. Compared to endogenous NO donors, they provide physiological environment stability and/or extensive pharmacokinetics. Their objective is to find ways to deliver high and sustainable NO content for different applications, like treating a diabetic wound, killing resistant bacteria (biofilms), or cancer therapy [103,104]. In recent years, these polymeric NO donors were classified into six categories: N-diazeniumdiolates (NONOate), S-nitrosothiols (i.e. RSNOs), metal nitrosyls, organic nitrates, nitrobenzene derivatives, and N-nitrosoamine derivatives [103]. These categories are determined by their different chemical structures and post-modification NO-releasing triggers. Amongst all categories, four are releasing NO following light irradiation, such as SNOs, metal nitrosyls, nitrobenzene derivatives, and N-nitrosamine derivatives [103]. They all show distinct advantages and drawbacks. Generally, stable NO donor polymers require more energy to cleave their NO moiety. Hence, their absorption properties fall under more energetic ionizing wavelengths, such as UV and blue spectra [104,105]. Whereas less complex NO donors, like RSNOs or metal nitrosyls, show very unstable behaviour or cytotoxicity at physiological conditions (due to heavy metal ions), respectively [103]. However, they have absorption peaks at safer non-ionizing wavelengths [106,107]. Recent studies using novel polymeric NO donors focus on the use of non-ionizing wavelengths synergistically with more complex and stable nanomaterials [103]. Zhou et al. synthesized N-nitrosoamine derivatives named photoNOD-1 and photoNOD-2, capable of releasing NO following NIR radiation [108]. These polymers consist of a photoacoustic molecule (i.e. aza-BODIPY dye) appended with an aryl N-nitrosamine NO-donating moiety. They show chemostability to various biological stimuli and negligible cytotoxicity, before and after irradiation. Using NO donor biomaterials and non-ionizing light sources to treat various skin pathologies is a promising treatment strategy.

6. Therapeutic approaches

The physiological functions of NO in the human body are highly concentration-dependent. Higher concentrations have damaging effects, such as promoting apoptosis, like deamination of DNA bases, nitrosylation of important enzymes and receptor proteins, etc. Also, it can generate high levels of ROS. Whereas lower concentrations of NO serve as signalling purposes for angiogenesis (e.g. vasodilation) and reepithelialization, in addition to the promotion of an anti-inflammatory environment. Hence, at low levels, NO acts as an antioxidant by reducing potential oxidizing molecules, thereby neutralizing lipid

peroxidation.

Releasing low levels of NO can then provide clinical benefits locally and perhaps systemically to distant body sites.

6.1. NO local effects

Several findings indicate that the balance between NO and ROS during UVA exposure determines the cellular fate [109]. The current debate to characterize NO is still open. Intracellular NO concentration seems to depend on the cell's redox potential and NO's resting levels. Therefore, the photolysis of nitrite has a two-sided effect [110]. It combines the beneficial release of cutaneous NO with the harmful production of hydroxide (OH) and nitrogen dioxide (NO_2) radicals. In human skin cells, even supraphysiological NO concentrations were shown to protect cells from oxidative stress and UVA-induced apoptosis [111]. Indeed, the skin nitrite content and apical acidity provide a favorable environment to foster NO protective effects.

On the other hand, in other cell types (i.e. extra-cutaneous), NO had been shown to promote apoptosis even at "physiological" concentrations [11].

In order to facilitate cell protection and scavenging of OH or NO_2 radicals, promotion of NO should take place. This can be achieved by exogenously applied NO or antioxidants against UVA/nitrite-induced cell death (radical formation) [112]. In addition, low-intensity visible/NIR light-induced NO enhancement is now possible, as mentioned earlier.

The promotion of wound healing was among the first observed PBM benefits, now substantiated by well-designed controlled human studies. Low-intensity light treatment parameters can be tailored to account for pathophysiologic responses in the skin corresponding to the type of vulnerable wound at stake [113]. The effect of NO release by PBM wavelengths on local wound healing has been reported with supportive evidence [92].

Wound re-epithelialization is regulated by mediators such as NO. An in vitro study showed a rise in NO production in human keratinocytes using low-intensity NIR (980 nm) light that might be directly related to the re-epithelialization process [98]. Another study using a mouse model by Moriyama et al. measured iNOS gene expression modulated by several PBM wavelengths (635, 660, 690, and 905 nm) in CW (continuous wave) and pulsing modes. They found that animals younger than 15 weeks showed reduced iNOS expression, while older animals showed a rise in iNOS expression. Light intensity and time course of iNOS expression were found to depend on wavelengths and delivery modes [114].

Apart from wound healing purposes, a large number of local cutaneous inflammatory lesions have been successfully treated using visible and NIR wavelengths as part of PBM therapy, with no reported side effects [70]. It has shown promise in erosive mucositis (oncology) [115], radiodermatitis [116], inflammatory acne [48,117] and to accelerate healing after aggressive skin treatments [118,119].

The next challenge in the field will be to clarify the mechanism of action of other non-ionizing wavelengths to release NO from the vast S- and N-nitroso compounds epidermal reservoir.

6.2. NO systemic effects

NO reacts extremely rapidly with surrounding molecules, either proteins, biomolecules, or oxygen species. It has a half-life of a few second. Moreover, its diffusion rate is very high at D~ 3300 μm2 s-1 at 37 °C [11]. For instance, its diffusion rate is about 1,4-fold higher compared to O_2 or carbonic oxide (CO) [11]. Hence, it can easily penetrate the cell membranes and reach up to 500 μm in tissues. How can NO reach distant organs with systemic effects in the human body if it dissipates rapidly at the site of release? How can it be transported throughout the body?

Oplander et al. have conducted some studies to elucidate NO transportation mechanisms [18,66]. They found that it is mostly RS-NOs that transport NO systemically. Larger concentrations of RS-NOs were found in the blood plasma following UVA and blue light irradiation, especially S-nitroso-albumin. Albumin composed 50–60% of the human blood plasma [65]. This makes it readily available to be nitrosated by light-induced NO radicals. Albumin is formed of 585 amino acids organized in three homologous domains each having five or six disulfide bonds. Only its cysteine residue 34 has a free thiol group that can be nitrosated [120]. Like hemoglobin that transports oxygen throughout the body, albumin is now the presumed NO carrier in the blood circulation transporting and releasing NO into vascular networks leading to vasodilation away from the irradiation site [11].

Systemic arterial hypertension is a significant public health issue with several environmental stressors and a much higher risk of cardiovascular complications, including coronary artery disease, heart failure and sudden death [121], even in young adults [122]. Interestingly, mean systolic and diastolic pressures and the prevalence of hypertension vary throughout the world. Many data suggest a linear rise in blood pressure at increasing distances from the equator [123,124]. Interestingly, epidemiological studies show that lack of sun exposure has a considerable impact in northern countries, considering that a decrease in 10 mmHg of people's blood pressure translates into a fall of 5% risk in cardiovascular complications [122].

Similarly, blood pressure is higher in winter than in summer [125,126]. Daylight length and ambient temperature also correlate inversely with BP [127,128]. Recently, Weller et al. showed that in addition to environmental temperature, incident solar UV radiation is associated with lower blood pressure in a large and diverse cohort of chronic hemodialysis patients [123]. Apart from reduced vitamin D stores and increased parathyroid hormone secretion [129] as a possible explanation, there might be another supporting mechanism by which ambient EMR may affect blood pressure. In a seminal experiment (1961), Robert Furchgott et al. showed that light exposure could relax isolated arterial strips of rabbit aorta [130], paving the way to his 1998 Nobel prize explaining the impact of NO on endothelial cells.

Besides, endogenous photo-sensitive NO derivates may be influenced by dietary nitrate and nitrite intake [131]. Accordingly, dietary nitrate supplementation combined with UV exposure has been shown to increase nitric oxide (NO) metabolites, reduce blood pressure (BP) and enhance exercise performance [28]. Photobiomodulation at 904 nm (NIR) alone can also prevent exercise-induced skeletal muscle fatigue in young women in part due to systemic NO release [132].

Other applications using NO release mechanisms are reported in psychiatry and neurology, where the systemic effects of PBM may achieve neurorehabilitation [133]. Likewise, this application could be of great help in dermatology, especially in neurodermatitis and prurigo nodularis, where two components of these psycho-cutaneous diseases (behaviour and skin) are targeted. However, the systemic effects on mood are often subjective and not easy to measure [134].

Lastly, PBM's anti-inflammatory effects are well described and partly explained by releasing biologically active molecules like NO [72]. The effects of NO on biological tissues are complex and multifaceted [135]. Upon systemic release following large surface body exposure via light-emitting diode (LED) beds, NO can probably induce multiple site-specific beneficial effects to distant organs (Fig. 6), including the modulation of inflammation in remote unexposed areas.

6.3. Challenges

We did not find any reported side effects caused by NO release via light-induced mechanisms, excluding studies using exogenous NO donors. However, end-organ tissue response may be limited by the availability of endogenous nitrosated substrates in the skin or elsewhere. Hence the importance of dietary nitrate, as explained earlier. Most studies report that endogenous NO donors photorelease their NO moieties at physiological levels with beneficial effects [11,13,15,18,63,

66–68]. On the other hand, long-standing difficulties of releasing NO using light devices include low delivery efficiency, undesirable bio-distributions, and uncontrolled side effects [11,103]. The main challenge now is to optimize light parameters, with or without novel polymeric NO donors, to regulate critical parameters, such as the distribution coefficient and delivery rates of NO.

7. Conclusion

In this review, we have thoroughly discussed light-dependent NO regulation in the skin focusing on wavelengths capable of releasing NO photolytically or enzymatically. Ubiquitous NO can be stored in a pool of compounds easily converted to NO after skin exposure to UVA and blue light. Beyond this spectrum, red and near IR wavelengths are potential contenders to trigger NO release in the skin. The two-sided nature of NO effects in the skin likely provides fascinating protective effects.

NO-related compounds found in the skin are also described with their respective molecular mechanisms to release NO. Also, we provide a brief review on newly synthesized polymeric NO donors vis-a-vis endogenous NO compounds. Finally, we have reviewed novel NO-dependent applications in treating local skin pathologies and potential systemic effects on distant organs.

This review intends to provide a critical evaluation of the data available in the literature related to light-dependent NO regulation. We believe that the constant improvement in understanding the human NO metabolism, added to the continuous development of nano-polymeric NO donors, will open a promising therapeutic avenue in medicine.

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