

Review Article

Microbial photoinactivation by blue light: advances and therapeutic perspectives in infections caused by multidrug-resistant pathogens

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ABSTRACT

Blue light (400–470 nm) is emerging as a promising alternative to address the growing threat of antimicrobial resistance. Microbial inactivation by blue light is based on the production of reactive oxygen species (ROS), which are light-induced and mediated by photosensitizers, resulting in the destruction of microbial cells. The microbicidal efficacy of blue light against diverse pathogens has been demonstrated in *in vitro* and preclinical studies, achieving reductions in cell viability greater than 3 log₁₀ in multidrug-resistant bacteria. Furthermore, blue light has been reported to be harmless to host cells, which has spurred the development of clinical treatments, as well as protocols for food preservation and environmental disinfection. However, variability in parameters such as wavelength, dose, and endogenous chromophores limits standardization for clinical use. Therefore, future research will need to focus on optimizing its use in clinical practice, considering not only the effect on microorganisms but also on the exposed tissue. This review presents an up-to-date analysis of the mechanisms of action, experimental evidence, and clinical applications of blue light, emphasizing its potential as an alternative or adjunctive therapy in controlling infections caused by multidrug-resistant pathogens.

Keywords: Antimicrobial resistance, Blue light, Inactivation, ROS, Phototherapy, Pathogens

INTRODUCTION

The emergence and accelerated spread of antimicrobial resistance (AMR) is one of the most significant threats to global public health, compromising the achievements of modern medicine and reversing decades of progress in the control of infectious diseases.¹ Since the introduction of antibiotics, life expectancy and survival rates from lethal infections have greatly increased.² However, the report The Global Burden of Bacterial Antimicrobial Resistance (GBD), published in “The Lancet”, estimated that in 2021, 4.71 million deaths were associated with AMR.³ This figure, according to the World Health Organization (WHO), will rise to 10 million annual deaths by 2050, surpassing cancer as the leading cause of death worldwide.⁴ This situation is exacerbated by the sustained

decline in the efficacy of existing antibiotics and the scarcity of new antimicrobial molecules, which threatens to leave healthcare professionals and patients without effective therapeutic options for serious infections.¹

AMR, defined as the hereditary ability of microorganisms to resist high concentrations of antimicrobial drugs, is the product of both genetic mutations and the transfer of resistance determinants. It manifests through mechanisms such as the modification of molecular targets, enzymatic inactivation of antibiotics, and the activation of efflux pumps.⁵ Given the limited pharmacological innovation in antibiotics and the rapid spread of multidrug-resistant microorganisms, the search for and validation of alternative therapeutic strategies has become a priority for the WHO.^{3,6}

In this context, microbial photoinactivation, specifically through the use of blue light, has emerged as a promising alternative.⁷ This technology leverages mechanisms of oxidative damage mediated by reactive oxygen species (ROS) generated from endogenous photosensitizers, offering potent antimicrobial activity independent of conventional resistance mechanisms.⁸ Recent studies demonstrate that blue light is not only effective against multidrug-resistant Gram-positive and Gram-negative bacteria but also against fungi, viruses, and biofilms, without significant adverse effects on human tissue.^{9,10}

The integration of blue light photoinactivation into clinical practice could transform the current approach to infection control, enabling the local treatment of chronic infections in wounds, burns, and those associated with medical devices.^{6,8} Furthermore, it could serve as an effective tool for environmental decontamination in hospital settings, reducing the risk of dissemination of multidrug-resistant pathogens. This would limit the need for conventional antibiotics and contribute to curbing the escalation of AMR in the general population and within hospital environments.^{6,11}

Given the magnitude and urgency of the challenge posed by antimicrobial resistance, blue light photoinactivation emerges not only as a scientific innovation but also as a high-impact intervention for global public health. This review analyzes current evidence on the efficacy, mechanisms, and clinical applications of blue light, positioning it as a viable and necessary solution to confront the AMR crisis in the 21st century.

BLUE LIGHT: PHYSICAL FUNDAMENTALS AND BIOLOGICAL EXPOSURE

Blue light corresponds to a region of the visible electromagnetic spectrum located between 400 and 470 nm, characterized by its relatively high energy and a frequency of approximately 600-670 THz (Figure 1).¹² This portion of the spectrum is relevant both due to its ubiquity in natural sources (sunlight) and the increasing exposure from artificial sources, such as light-emitting diodes (LEDs), electronic devices, and modern lighting systems.¹³ The efficiency of blue LEDs in terms of energy conversion and emission has facilitated their integration into biomedical applications, including antimicrobial therapies.¹⁴

The limited penetrability of blue light into human tissues and its scattering determine both its antimicrobial efficacy and its safety profile. Differences in the size, shape, and density of tissue constituents modulate its absorption and dispersion, which are key aspects for optimizing therapeutic interventions based on blue light and minimizing collateral damage to healthy human cells (Figure 2).^{7,14,15} Tissue exposure to blue light can induce the formation of ROS, a phenomenon demonstrated in human fibroblasts with dose-dependent and antioxidant-reversible effects. However, recent preclinical evidence

indicates that under controlled parameters, adverse effects can be minimal or reversible.^{16,17}

Blue light can modulate diverse cellular responses, including the activation of intracellular signalling pathways related to oxidative metabolism, apoptosis, and cell proliferation. These effects, explored in preclinical studies and recent reviews, reinforce the growing interest in photo biomodulation for medical and biological applications beyond its antimicrobial effect.^{14,17}

MECHANISMS OF ACTION OF BLUE LIGHT AS AN ANTIMICROBIAL AGENT

The antimicrobial action of blue light depends on a delicate interplay of photochemical and biochemical interactions within the cellular microenvironment of the target organisms.⁹ This process requires the simultaneous participation of oxygen and endogenous chromophores, molecules capable of absorbing radiation within the blue light spectrum and converting that energy into biologically active chemical reactions.¹⁷

The main chromophores identified in bacteria and fungi include porphyrins and carotenoids, which possess conjugated bond systems that facilitate photon capture and subsequent electronic excitation.^{18,19} Following energy absorption, these molecules reach an excited singlet state and then, through intersystem crossing, transition to a longer-lived triplet state.²⁰ The triplet state, where energy transfer to molecular oxygen is favored, enables the generation of ROS such as singlet oxygen, superoxide anion, hydrogen peroxide, and the hydroxyl radical (Figure 3).²¹

The production of ROS is the primary mechanism of the microbicidal effect of blue light, as their accumulation causes the irreparable oxidation of fundamental components and the disruption of key biochemical functions. This includes the peroxidation of membrane lipids, oxidation of proteins, and fragmentation of genetic material, resulting in functional loss and cell death.^{20,22} Because these oxidative effects simultaneously affect multiple intracellular targets, the emergence of bacterial strains resistant to this type of photoinactivation has not been reported to date. This represents a significant advantage over conventional antimicrobials, which attack specific and selective targets.¹⁷

Notably, bacterial porphyrins (such as protoporphyrin IX and coproporphyrin III) act as extremely active sensitizers. The intracellular accumulation of these photosensitive chromogens enhances microbial vulnerability to blue light. It has been observed that the intensity of the damage varies according to the concentration and accessibility of these precursors and the specific cellular architecture of each target microorganism.^{18,21}

Aside from diffuse oxidative damage, recent studies have highlighted a complementary mechanism mediated by the

inhibition of antioxidant enzymes.²³ A paradigmatic example is the photoinactivation of catalase, a key enzyme in the decomposition of hydrogen peroxide in aerobic bacteria and yeasts such as *Candida albicans*. When catalase is inactivated by blue light, the cell is exposed to lethal concentrations of hydrogen peroxide and other ROS, increasing its sensitivity to both endogenous and exogenous oxidative agents and even promoting the action of the innate immune system.^{18,21,24} This effect is particularly relevant in the case of bacterial biofilms, which are organized microbial communities protected by an extracellular matrix that confers high resistance to antimicrobial agents and host defences.^{11,12,14}

The damage caused by ROS differs markedly between microorganisms and higher eukaryotic cells, such as human cells.²⁵ Although both cell types possess internal antioxidant mechanisms (such as catalases and peroxidases), bacteria demonstrate a more limited capacity

for detoxifying free radicals. Consequently, the damage induced by blue light is especially severe in bacteria, whose smaller size, lack of specialized organelles, and the simplicity of their membrane and repair systems limit their adaptation to massive oxidative stress.^{22,25}

It is worth mentioning that the antimicrobial efficiency of blue light is influenced not only by the genetic, structural, and metabolic factors of the microorganism but also by external conditions such as the specific wavelength used (with the 405-420 nm band being the most effective), the received irradiation dose, oxygen availability, and the presence of biofilms.^{6,11} These structures, despite their recognized resistance to classical control agents, can be permeabilized and destroyed by appropriately programmed blue light exposures, providing an emerging strategy suitable for clinical, environmental, and food decontamination alike.^{10,14-18}

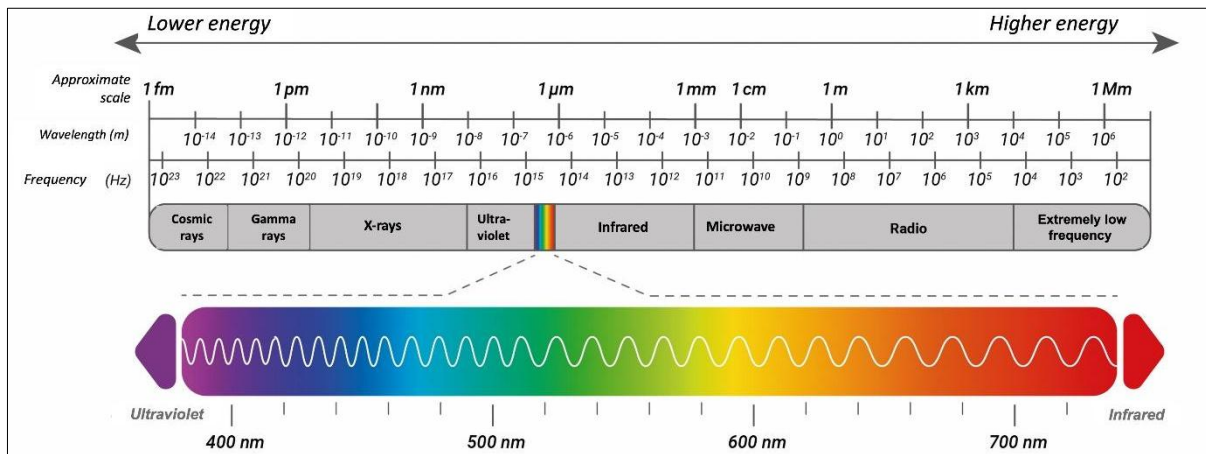


Figure 1: The electromagnetic spectrum, where the visible spectrum ranges in wavelength from 380 to 780 nm. As the wavelength increases, the frequency and energy of the quantum of light decreases.

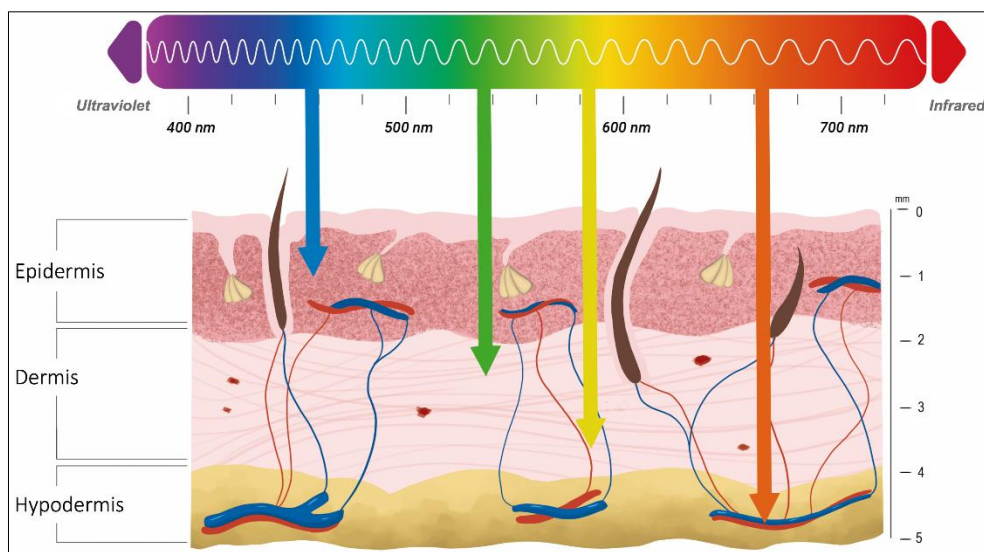


Figure 2: Comparison of the penetration depth of different light wavelengths into the skin. Note the shallow penetration of blue light; under normal conditions, its incidence on the skin does not extend beyond epidermal structures.

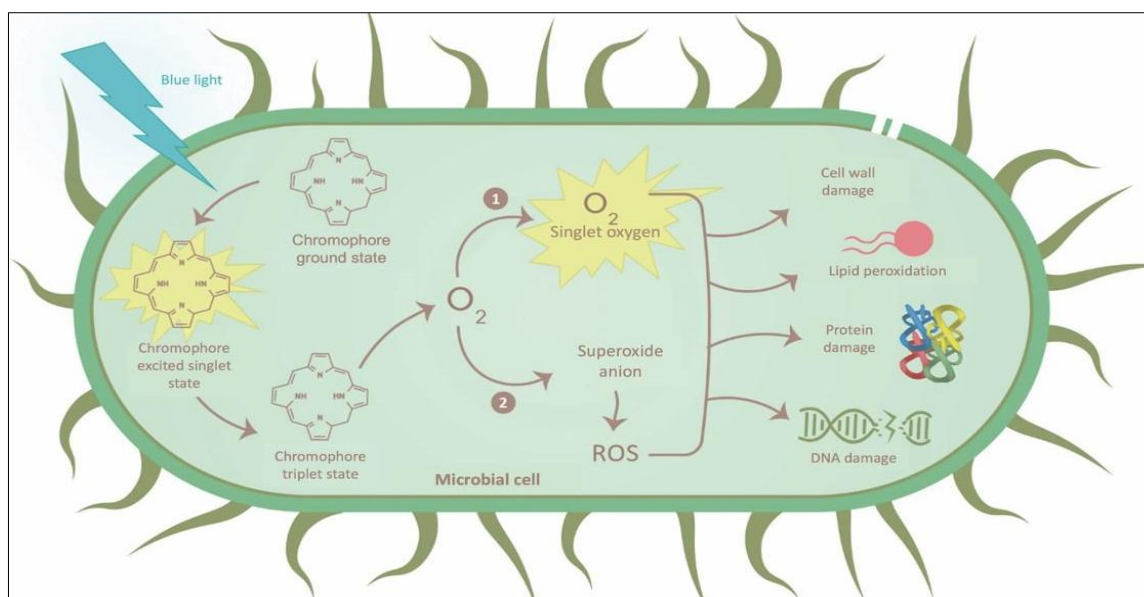


Figure 3: Graphical representation of the photochemical pathways of action of blue light as an antimicrobial agent (1) the triplet state of the excited chromophore collides with O_2 , leading to the formation of singlet oxygen, which causes damage to the bacterial cell; and (2) another pathway involves the triplet chromophore directly transferring an electron to O_2 , producing the superoxide anion and other ROS.

Table 1: Recently published in vitro studies confirming the antimicrobial activity of blue light against various bacterial species.

Bacteria	Wavelength (nm)	Irradiation dose (J/cm^2)	Reduction in cell viability (%)	Reference
<i>Cutibacterium acnes</i>	415	75	98	27
<i>E. coli</i> ESBL	395–414	68	99	28
Biofilm periodontal	455	12	48.2	29
<i>Listeria monocytogenes</i>	405, 420, 460	2, 672, 960, 800	99	30
<i>Mycobacterium smegmatis</i>	464	45	36.44	31
<i>Legionella rubrilucens</i>	450	300	99	32
<i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i>	470	284,90 y 603.44	75	33
<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>E. coli</i> and <i>P. aeruginosa</i>	393–413	133	99	34
<i>Staphylococcus aureus</i> MRSA, <i>Escherichia coli</i> , <i>Salmonella typhimurium</i> and <i>Listeria monocytogenes</i>	415	109,44	90	35
<i>Acinetobacter baumannii</i> , <i>Enterobacter cloacae</i> , <i>Stenotrophomonas maltophilia</i> , <i>Pseudomonas aeruginosa</i> , <i>E. coli</i> , <i>S. aureus</i> , <i>Enterococcus faecium</i> , <i>Klebsiella pneumoniae</i> and <i>Elizabethkingia meningoseptica</i>	390–410	54–108	70	36
<i>E. coli</i> O157:H7, <i>Listeria monocytogenes</i> , <i>P. aeruginosa</i> , <i>S. Typhimurium</i> and <i>S. aureus</i>	405	108-288	95-99	37

MRSA: methicillin-resistant; ESBL: extended-spectrum beta-lactamases

ANTIMICROBIAL EFFICACY OF BLUE LIGHT AND ITS CLINICAL APPLICATION IN INFECTIOUS PATHOLOGIES

Accumulated scientific evidence confirms that blue light in the 400–470 nm range exhibits marked antimicrobial activity against a broad spectrum of microorganisms,

including multidrug-resistant strains, fungi, viruses, and biofilm-forming organisms.⁶⁻¹⁰

Various reports have described a significant reduction in bacterial load under diverse experimental conditions, using different wavelengths, doses, and exposure times (Table 1).^{10,12-14,17-26}

Blue light has demonstrated bactericidal and fungicidal effectiveness against a wide range of pathogens relevant to infectious diseases.^{16,17} The literature reports reductions in microbial load exceeding 3–6 log₁₀ for highly important bacteria such as *Staphylococcus aureus* (including methicillin-resistant strains), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and other species belonging to the ESKAPE group, whose eradication is particularly challenging.⁸⁻¹³

Within the growing body of international evidence supporting the efficacy of blue light in inactivating multidrug-resistant microorganisms independent of their genetically determined resistance mechanisms the study conducted in Venezuela by El Hindawi, Varela-Rangel, and Araque stands out.^{10,17,19} This work is the first regional report to rigorously evaluate the photoinactivation of extensively drug-resistant (XDR) Gram-negative bacteria isolated from healthcare-associated infections (HAIs) in Venezuelan hospitals, a concerning issue for local and global public health. In this study, clinical multidrug-resistant strains of Enterobacterales and Pseudomonadales were exposed to blue light (405 nm) at irradiation doses between 86 and 126 J/cm², using a high-power LED unit designed by the same research team for antimicrobial applications. The results showed complete inactivation in 82.5% of the evaluated strains, regardless of their antibiotic resistance profile, thus demonstrating that blue light photoinactivation overcomes the barriers imposed by classical resistance mechanisms.^{10,13,17-19}

Although some tolerance was observed in a minority of isolates at higher doses, this finding emphasizes the importance of continuing to optimize irradiation protocols to ensure maximum efficacy and clinical reproducibility.¹⁰ The study not only provides robust in vitro evidence but also lays the experimental and technological groundwork for the future development of regional devices and clinical applications tailored to local epidemiological and healthcare particularities.

In vivo studies, such as those conducted in murine models and other experimental animals, have provided robust proof of the translational potential of blue light phototherapy for localized infections (38-40). Dai et al demonstrated that the application of 415 nm LED light significantly reduced the load of *S. aureus* and *P. aeruginosa* in wounds and burns, with reductions in cell viability of up to 3 log₁₀ units, even against hypervirulent strains.³⁹ Crucially, the treatment prevented progression to potentially lethal sepsis in the animal models, evidencing not only pathogen reduction but also an improved clinical prognosis marked by decreased inflammation and adequate tissue regeneration.³⁸ In this context, blue light phototherapy has shown encouraging results in infections that are typically refractory to conventional treatments, such as those associated with biofilms and those caused by intracellular or persistent pathogens. For example, in chronic skin ulcers superinfected by fungi and bacteria, where conventional antibiotic treatment is often

ineffective, photodynamic therapy with methylene blue as a photosensitizer has resulted in clinical and microbiological cure without significant adverse effects. The use of a photosensitive substance combined with a blue light irradiation process constitutes the principle of phototherapy or photon therapy, which is used as an alternative for treating skin and soft tissue infections, among other pathologies.

Furthermore, there are studies with initial clinical validations that reinforce the therapeutic potential of blue light phototherapy. A notable example is the selective eradication of *Helicobacter pylori* in the gastrointestinal tract via endoscopic photoexposure.⁴⁰ Morici et al achieved reductions in bacterial load between 91% and 99% in patients treated with blue light, specifically at 405 nm applied focally.⁴¹ Clinical evaluations were performed using quantitative biopsies. These results are especially promising for patients who have failed classic antibiotic treatment, thus highlighting the relevance of blue light as a next-generation clinical alternative.⁴¹

In dentistry, photodynamic therapy combines blue light with exogenous photosensitizing substances, such as methylene blue or toluidine blue, thereby potentiating the production of singlet oxygen and ROS, which destroy periodontal bacteria and other oral pathogens.⁴² Clinically, this phototherapy is used as adjuvant in the treatment of chronic periodontitis to eliminate resistant microorganisms, reduce inflammation, and improve the decontamination of periodontal pockets following scaling and root planning.⁴³ This technique is not only safe but also has the advantage of being less invasive, avoiding the excessive administration of antibiotics. Experimental and clinical studies have reported that blue light phototherapy is effective in eliminating oral biofilms and multidrug-resistant bacteria, which is important for controlling peri-implant and periodontal infections, which are often complex due to the presence of biofilms and antimicrobial resistance. This phototherapy is also being explored for treating abscesses, cold sores (*herpes labialis*), and promoting tissue regeneration in the oral cavity.⁴²⁻⁴⁴

Incipient clinical experience and implementation in surgical procedures also underscore the efficacy of blue light photoinactivation. As a result, it has begun to be employed as an adjuvant in intraoperative decontamination, in the treatment of infected skin surfaces, and for the asepsis of surgical instruments and medical environments, thanks to its rapid action, high selectivity, and safety profile in human tissues.^{6,7,11}

Likewise, the use of blue light is being successfully explored in the food, pharmaceutical, and cosmetic industries, as well as in the disinfection of surfaces, reinforcing its versatility and applicability in both intra-hospital and industrial settings.^{25,41}

In general terms, the robustness of the therapeutic potential of blue light phototherapy in the field of infectious diseases

is supported by: its broad efficacy *in vitro* and *in vivo* against critical and multidrug-resistant pathogens, the demonstrated safety and tolerance in animal models and controlled clinical exposures, the development of clinically acceptable devices and interfaces for focused applications, and the possibility of integration as an alternative or adjuvant therapy in antibiotic-refractory patients, with direct implications for surgeries, wound treatment, mucous membrane infections, and hospital decontamination.^{6-15,21,39,43,45}

FUTURE PERSPECTIVES

Blue light phototherapy is emerging as an effective and promising therapeutic alternative to address antimicrobial resistance. Future studies will focus on optimizing application parameters and developing portable devices for clinical and environmental use. A particularly relevant line of research will be the integration of blue light phototherapy with conventional antibiotics and immunomodulatory therapies, which could potentiate the action of antimicrobial agents. The future development of blue light phototherapy will depend on multidisciplinary integration between engineering, microbiology, and medical practice, as well as large-scale clinical validation to enable its safe and effective implementation across various healthcare settings.

CONCLUSION

Blue light is acquiring strategic relevance not only as a curative therapy but also as a tool for the prevention and control of healthcare-associated and community-acquired infections. Its capacity for decontaminating surfaces and environments, coupled with its low probability of inducing resistance, could transform infection control policies in healthcare facilities and public spaces. This makes it an essential complement during outbreaks caused by multidrug-resistant microorganisms. In this context, blue light is a therapeutic option with disruptive potential in the management of infectious diseases, especially in light of the global crisis caused by antimicrobial resistance.

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