Journal of Photochemistry and Photobiology 8 (2021) 100064

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology

journal homepage: www.sciencedirect.com/journal/journal-of-photochemistry-and-photobiology

The role of UV and blue light in photo-eradication of microorganisms

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ARTICLE INFO

Keyeords:
History of photobiology
Photo-disinfection
Antimicrobial therapy
Photobiomodulation
UV and blue light

ABSTRACT

Photo-eradication of microorganisms with UV and blue light has been around since the 1870s. Research to further the development and deployment of germicidal UV and violet-blue light has been on the rise since COVID-19 pandemic. This paper traces the evolution of UV and violet-blue light, presents suggested ways to exploit two leading germicidal light technologies—far UV and pulsed blue light (PBL)—in the ongoing quest to effectively stem the spread of pandemic diseases. An effective way to overcome or minimize the spread of disease is to inactivate and reduce the number of viral particles both in the environment and in accessible parts of patients. This can be achieved by irradiating spaces, infected air, and the general environment with PBL or far UV, and by similarly disinfecting supplies, tools, and equipment. Irradiating the oronasal cavity of infected patients with PBL could clear the virus and kill oral opportunistic bacteria that worsen coronavirus infections. The advantages and disadvantages of the two-leading photo-disinfection light technologies are discussed.

Introduction

Since the advent of COVID-19, Ultraviolet (UV) and violet-blue light have gained immense attention as sustainable non-chemical and non-pharmaceutical antimicrobials [1-9]. Germicidal UV has been around for more than 100 years, but in contrast to its waning application in the public domain, light in the adjoining spectral range—approximately 405 nm to 450 nm, generally referred to as blue light—has been gaining widespread acclaim as an alternative to UV, especially in patient care situations where safety from the adverse effects of UV is a major concern [10-12]. Before the foray into the use of blue light for germicidal purposes, UV was the gold standard for photo-disinfection. It remains an effective germicidal, but the relatively high cost of UV devices, its potentially harmful effects on humans, and its propensity to damage devices made of plastics and poly-carbon remains a serious concern [13-16]. Blue Light Emitting Diodes (blue LEDs), in contrast to UV, are innocuous, ubiquitous, and less expensive, and have similar germicidal effects against several microorganisms [17-31]. This makes blue light an attractive alternative to UV for widespread commercial development and deployment as an antiviral.

Recently, far UV—in the spectral range of 205 - 225 nm—has been proposed as an antimicrobial against viruses and other microorganisms [1,4-9], with the suggestion that it may be safe for public use [9]. Development and deployment of commercial UV products is underway [1,2,9,32], and the COVID-19 pandemic has inspired research on several areas of application of blue light and far UV as effective antimicrobials with germicidal applications in medicine and industry. The purpose of this paper is to: (1) review the evolution of both technologies, (2) explore the relative value of each technology, (3) offer suggested ways to exploit the advantages of each technology in the ongoing quest for effective but safe germicidal light-based technologies against viruses, bacteria, fungi, and other microorganisms, and (4) highlight the emergence of newer light technologies with the potential to inactivate most microorganisms without compromising safety.

The electromagnetic spectrum of radiation

The entire range of electromagnetic radiation, also known as the Light Spectrum, represents a continuum of waves or light particles, *i.e.*, photons—vibrating and twirling as they are propagated, and which for

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https://doi.org/10.1016/j.jpap.2021.100064
Received 1 April 2021; Received in revised form 2 August 2021; Accepted 9 September 2021
Available online 10 September 2021

simplicity and convenience of study are grouped as shown in Fig. 1. There are good reasons to assume that each end of the spectrum approaches infinity, since it seems illogical that the range of radiation is limited to what is detectable by available instrumentation. The photons in each region of the electromagnetic spectrum (EMS) differ in vibration frequency and photobiological reactivity, consequently, their effects on organic and inorganic matter also differ considerably. For example, the shorter wavelengths, *i.e.*, gamma rays, and X-rays tend to ionize matter, and while UV is deleterious to living things, the longer wavelengths such as radio waves are relatively innocuous [33].

In general, ultraviolet radiation lies between 10 nm on the X-ray side and about 380 nm on the visible light side of the spectrum; some authorities extend the shorter wavelength range to 4 nm [33]. While physicists tend to divide UV rays into four regions for convenience of study, *i.e.*, extreme UV (below 100 nm), far UV (100–200 nm), middle UV (200–300 nm), and near UV (300–380 nm), three categories are generally designated based on UV interactions with biological materials [33]. These include: (1) UV-C with wavelength ranging from 100 nm to 280 nm, (2) UV-B which ranges from 280 nm to 315 nm, and (3) UV-A which encompass 315 nm to 380 nm range. The latter classification and terminology will be used in the rest of this paper. UV-C exerts the most damaging effect on DNA compared to UV-B and UV-A. UV-B photons are of lower energy compared to UV-C, and are known to cause sunburns and skin tan, as well as basal and squamous cell carcinomas [34]. In turn UV-A photons are of lower energy relative to UV-C and UV-B. Prolonged exposure to UV-A is associated with accelerated aging, wrinkles, and skin cancer, notably melanomas [34].

Visible light and infrared radiation, which fall in between ionizing radiation and microwave, are harmless compared to the shorter wavelengths and have been the focus of clinical research and application for the past century. Moreover, visible light and infrared light have been shown to be of clinical value in patient care, for pain relief, tissue repair, microbial eradication, or a combination of all three depending on wavelength, dose, and treatment protocol [35-41]. To stay focused on the purpose of this paper, we will limit our discussion to those wavelengths within the UV and visible blue light ranges.

The development of UV and its germicidal effect

The existence of invisible radiation at either end of the EMS was unknown to humanity for a considerable period. All that changed in 1800 when Frederich William Herschel placed a thermometer in the invisible zone just beyond the red end of visually detectable light and unexpectedly observed a rise in temperature [42,43]. He accurately hypothesized that there were invisible rays beyond red light, and that those rays caused the thermometer to rise. Before this breakthrough, it was thought that radiation did not exist beyond what the eye could see. Herschel's finding prompted an examination of the opposite end of the visible spectrum, *i.e.*, the "invisible zone" below the violet end of visible light. Thus, in 1801, Johann Wilheim Ritter made a startling discovery when he showed that silver chloride, which decomposes in the presence of light, was more rapidly decomposed within the "dark" zone at the violet end of the light spectrum [44]. Like Herschel's detection of infrared radiation, Ritter's finding revealed the presence of rays beyond the violet end of visible light. Since these two discoveries, further studies have shown that, indeed, the range of light visible to the naked eye is minuscule relative to the spectrum of wavelengths below the violet spectral range or above the red spectrum, Fig. 1B.

Following the discovery of UV, attention focused on the development of light-based sterilization and disinfection devices. Although the belief that UV could be germicidal was held as early as 1845, confirmation of its antimicrobial effect came more than 30 years later [45-47]. The breakthrough occurred when in a series of papers published in 1877 and 1878, Downes and Blunt showed that sunlight inhibited the growth of microbes in test tubes containing Pasteur's solution [48], and that bacteria were more inhibited than fungi [48,49]. Further studies revealed that the violet-blue region of sunlight was indeed more antimicrobial than predominantly yellow and red light, and that bacterial inhibition depended on wavelength, treatment intensity and duration [50,51]. While it may seem intuitive today that the key factors in partial or total inactivation of microbes depend on (1) wavelength (λ) and (2) irradiation dose (J cm^{-2}), it was quite revolutionary in those days, and it should not come as a surprise that these early results have been hailed as some of the most influential discoveries in the history of photobiology [46,47].

Downes and Blunt's finding that the antimicrobial effect of solar

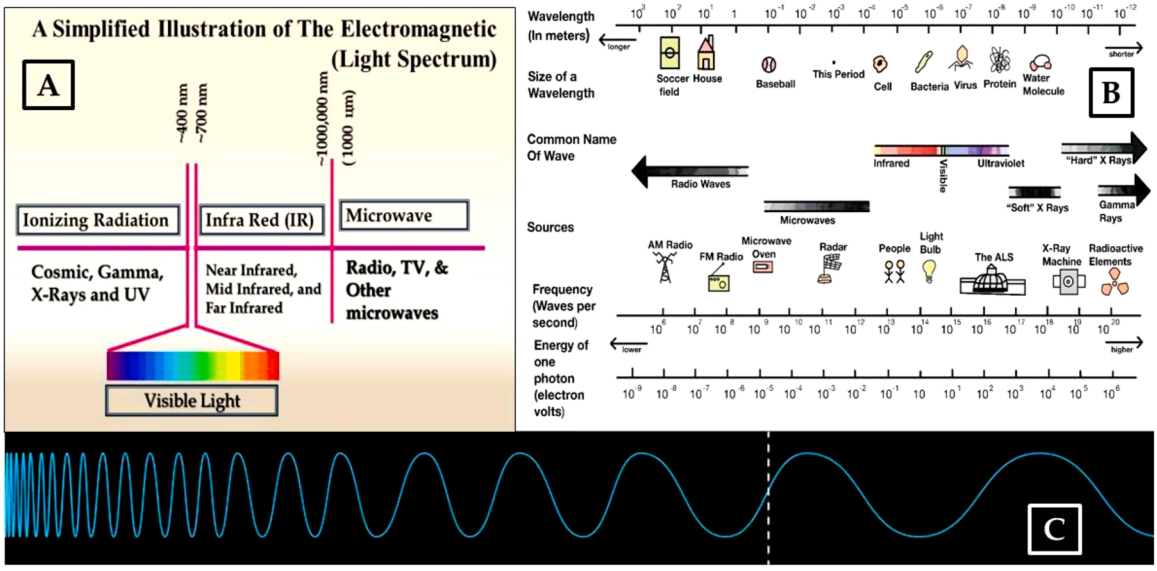

Fig. 1. The electromagnetic spectrum. [A] A simple illustration showing the major categories of radiation, ionizing radiation (< 400 nm approximately), visible light and its rainbow of colors, (400 – 700 nm, approximately), infrared light (700 – 1000,000 nm, approximately) and microwaves (>1000,000 nm). [B] An image detailing the approximate sizes of each wave category, common sources of such waves, and the related frequency and photon energy of each wave category. This picture was redrawn using a publicly available version from the website of US National Aeronautics and Space Administration (NASA). [C] A simple illustration showing that the wavelengths differ progressively from one region of the spectrum to another.

radiation (100 nm – 1 mm) was wavelength dependent further propelled research into the germicidal action of UV. This focus on the germ-killing effect of UV was greatly influenced by the discovery that microorganisms were responsible for deadly diseases, including anthrax, cholera, diarrhea, diphtheria, dysentery, tuberculosis, typhoid, typhus, and others [52,53]. As shown in Table 1, significant progress was made over the 50-year interval between 1880 and 1930 through the courageous efforts of many who braved deadly germs and the harmful effects of UV to advance our understanding [48-67].

For example, Duclaux showed in 1885 that susceptibility to solar photo-inhibition differed from one microbe to another [57], and this triggered efforts to quantify the sensitivity of various microorganisms to sunlight and the relative effects of different wavelengths on microbes [58,63–66,84–90; Table 1]. During this period (1885–1914), Tuberculosis bacillus was shown to be susceptible to sunlight, and this discovery led to using UV to combat tuberculosis, and the development and deployment of UV lamps [52]. Geisler confirmed that UV emitted by sunlight and electric lamps was more lethal to microbes than the longer wavelengths of light [63]. And while Buchner [84] found infrared radiation to be an insignificant contributor to the germicidal effect of sunlight, Ward [64-66] showed that violet-blue and UV-A wavelengths were severely deleterious to bacteria. Working with arc lamps, Bang [85, 86] as well as Barnard and Morgan [87] focused on the germicidal effect of arc lamps; they showed peak bactericidal effectiveness in the UV-B range, between 226.5 nm and 328.7 nm, while Hertel [88,89] compared the relative effects of UV and the visible spectrum by quantifying their intensities in arc lamp emissions. These series of studies [63-89] clearly showed that the UV-C wavelengths were the most lethal to viruses and other microorganisms, followed by UV-B, UV-A, and violet-blue light; subsequent research endeavors showed UV to also be mutagenic [90].

In summary, these early studies revealed that wavelengths in the UV and violet-blue ranges are lethal to various microorganisms, implying that any of these wavelengths could be effective in eradicating viruses. As early as 1930 Fredrick Gates showed that UV, the visible spectrum, and the infrared ranges are all lethal against *S. aureus*; however, while the effect is photochemical in the UV and violet-blue ranges, it is progressively photothermal beyond the blue wavelengths [68-70]. What this means is that a virus could be inactivated photochemically with wavelengths below 480 nm approximately, but to kill the virus with longer wavelengths, one must rely on irradiances that can heat and inactivate the virus, and this might make such wavelengths unsafe for humans. Gates further showed that the notion that the shorter the wavelength the more the bactericidal effect, is an oversimplification of the true antimicrobial effect of light, and that light absorption played a major role in its overall effect.

As reports, showing UV to be antimicrobial against microorganisms mounted, its use as a water disinfectant spread from Marseille, France in 1910 [91] to Austria, Switzerland, and other parts of Europe where light-based water disinfecting equipment were rapidly developed and deployed [91]. By 1985, about 1500 water treatment plants were in operation in Europe [92]. That number jumped to 6000 plants in 2001, following the discovery in 1998 that protozoa, such as cryptosporidium and Giardia were susceptible to UV rays. Widespread use of UV water treatment plants also spread in North America [92].

In summary, solar radiation and artificial sources of UV and visible light have been used as disinfectants for hundreds of years. Indeed, records show that the ancient Egyptians also used the full spectrum of solar radiation to disinfect and heal chronic wounds and ulcers as far back as 5000 BCE [93,94]. Moreover, UV lamps have been used for patient care for several decades [94,95], due to its germicidal effects against viruses, bacteria, fungi, and other microorganisms.

The evolution of germicidal light in the visible spectrum

Whereas UV application has been studied for about 150 years,

Table 1
Milestones in the historical development of germicidal UV.

Date/ Period	Author(s)	Discovery or Key Findings
1877	Downes and Blunt[48–51]	They showed that sun rays inhibited microbial growth, and that the extent of inhibition differed from one microbe to another. Moreover, they showed that the effect is wavelength dependent, and that the higher the dose the more the inactivation.
1881	John Tyndall[54,55]	Confirmed previous results and suggested that the effect of sunlight was more of bacterial suppression than bactericidal action.
1882	James Jamieson[56]	Raised the concern that the effect of sunlight may be photothermal in nature, not photochemical.
1885	Émile Duclaux*[57–59]	Found sunlight to be more potent in the summer than in early spring; showed significant variability in the antimicrobial response of spores to sunlight.
1885	Saturnin Arloing[60]	Showed that *Bacillus anthracis* was susceptible to inactivation by sunlight after only two-hour exposure. Also, he demonstrated that the inactivated *Bacilli* conferred immunity.
1886–1889	Arthur Downes and Thomas Blunt[61]	Showed that even at relatively low temperatures, sunlight still inhibited bacterial growth, thus disproving the claim that temperature was responsible for the bactericidal effect of sunlight.
1890	T. Janowski[62]	Explored the effect of temperature and various colors of visible light on *Typhus bacilli.* He showed that in both diffuse or direct sunlight, bacterial growth occurred about five times faster in yellow and black solutions compared to violet, blue or fuchsin*** solutions.
1892	Theodor Geisler[63]	Demonstrated for the first time that besides red light, all regions of the solar spectrum (including UV, visible light and infrared) are deleterious to bacteria.
1892 to 1895	H. Marshal Ward[64–66]	Showed bacteria to be highly sensitive to variations in wavelength; provided clear cut evidence that the most bactericidal rays were UV, and violet-blue wavelengths.
1896 to 1901	Niels Ryberg Finsen**[67]	Developed a light source** that was successful in curing patients with skin tuberculosis and other ailments. He treated 804 patients with skin tuberculosis and similar microbial infections with the lamp, achieving 83% cure rate. He received the Nobel Prize for this work in 1903. The Finsen lamp became popular.
1929–1930	Fredrick Gates[68–70]	Showed that the notion that the shorter the wavelength the more the bactericidal effect is indeed an oversimplification, and that light absorption plays a role in its overall effect. He published the first bactericidal action spectrum which showed that 260 – 270 nm is more bactericidal in the UV ranges. Further, he showed that UV and the visible spectrum are all bactericidal against *S. aureus*; however, the effect is photochemical in the UV and violet-blue ranges, and progressively photothermal beyond the blue wavelengths.
1933 to 1972, 1935, 1937	William F. Wells[71,] Wells & Faird[72,] Wells et al.[73]	Proposed the notion of airborne infection via “droplet nuclei;” and showed that dried droplets contain infectious microbes that can be airborne. They showed that UV effectively inactivates airborne microorganisms, and that UV disinfection of the upper areas of a room prevented the spread of measles. Other investigators could not replicate their findings, as a

(*continued on next page*)

Table 1 (*continued*)

Date/ Period	Author(s)	Discovery or Key Findings
		result, this method of room disinfection lost favor.
1956–1962	Riley et al.[74–76]	Further showed that germs can be airborne by exposing guinea pigs to air originating from an occupied tuberculosis ward. While the guinea pigs that received the infectious air became infected; those exposed to infected air that was purified with UV did not, thereby demonstrating the concept of air purification with UV.
1969–1975	Riley et al.[77–83]	Confirmed that UV is less effective at high humidity, and that mixing irradiated upper room air with air in the lower portion of a room is necessary for effective disinfection. They demonstrated reduction of tuberculosis infection using upper room UV irradiation.

*Duclaux was a former student of Louis Pasteur, and he became the Director of the Pasteur Institute following the death of Louis Pasteur.
**Finsen won the Nobel Prize in Medicine in 1903; further analysis of his lamp system now show that they produced violet-blue rays predominantly, not UV as the Nobel Laureate thought (see reference number 98).
***Fuchsin solution or rosaniline hydrochloride is a magenta dye; it partially allows the transmission of violet rays.

research aimed at uncovering the germ-killing effect of violet or blue light is relatively new. This delay may be ascribed to the rapid commercialization and popularity of what was presumed to be "UV", generated from quartz, mercury vapor and other lamp sources. Such lamps were used to treat acne, psoriasis, syphilis, leprosy, and pellagra, among other diseases [95-97]. The popularity of the Finsen Lamp, which won Niels Ryberg Finsen the Nobel Prize in Medicine in 1903 further extolled the use of "artificial UV" sources to treat diseases well into the second half of the 20th century. This practice of disease treatment was changed by the availability of potent antibiotics, due to their efficacy and ease of use [95,97]. As a result, the use of germicidal UV irradiation began to wane. We now know that the Finsen Lamp indeed generated light in the violet-blue spectrum, even though Finsen assumed that his light source produced UV [98].

Two concurrent developments encouraged investigators to closely examine the germicidal action of light in the violet-blue spectrum. The first was the growing awareness of the dangers of UV, its carcinogenic propensity, and the potential to foster skin wrinkles and dermatological diseases [99,100]. The second is the development of lasers in the late 50 s and the early 60 s, followed by the rapid evolution of less expensive light technologies, including LEDs in the 1970s. These developments gave rise to photodynamic therapy (PDT) for the treatment of cancer [101,102] and photodynamic inactivation (PDI) of microorganisms [103-110]. Advances in LED technology now enable interchangeable use of lasers and LEDs for PDT and PDI.

Photodynamic inactivation of microorganisms

Photodynamic inactivation is quite prominent as a light-based treatment for microbial eradication. In the rest of this paper, we will refer to PDT and PDI operationally as the use of light-based inactivation of malignancies and microorganisms respectively, even though the literature shows that both terms have been used interchangeably. PDT and PDI combine a nontoxic exogenous photosensitizer or dye with an appropriate wavelength of harmless light in the visible spectrum. The approach relies on the susceptibility of microbes to photo-inactivation in the presence of three entities: (1) oxygen, (2) a photosensitizer able to transform light energy into some lethal downstream product (s), and (3) light of the right wavelength matched with the absorption spectrum of the photosensitizer. The absorption of light rapidly excites the photosensitizer into a higher energy state, triggering a Type I or Type II photoreaction [111-114]. In Type I reaction, the excited photosensitizer releases its excess energy—in the form of an electron—to other biomolecules, giving rise to free radicals, such as superoxide anions and downstream production of cytotoxic hydrogen peroxide. In Type II reaction, the photosensitizer reacts with molecular oxygen to form singlet oxygen. The two types of reaction ultimately result in the formation of harmful reactive oxygen species (ROS), which in sufficient amounts either destroys microorganisms or malignancies as the case may be [111-124]; for a comprehensive review, see Bacellar et al. [125], Malik et al. [126], Costa et al. [127], and Yin et al. [128].

This principle enables PDT for cancer treatment; in this case, a nontoxic photosensitizer—known to accumulate preferentially in malignant tissue for a longer duration than in normal cells—is excited into a higher energy state with an appropriate wavelength of light, thereby triggering one or both types of reaction and downstream production of cancer cell-killing ROS. For PDI, the principle is the same, but the photosensitizing dye, such as methylene Blue, Rose Bengal, hypericine, xanthenes, etc., has a different molecular conformation; each dye is selectively matched with a wavelength that can trigger ROS in sufficient amount to inactivate the target microorganism; moreover, the influence of the treatment parameter cannot be overstated [116,121,122, 125-128]. The rest of this paper will be limited to microbial inactivation and disinfection.

Rudimentary photodynamic inactivation of microorganisms was first shown in the late 1920s, when Schultz and Krueger inactivated *Staphylococcus* bacteria with a combination of visible light and methylene blue [129]. In a 1933 report, Perdrau and Todd [130], using a similar combination of methylene blue and visible light, showed suppression of several viruses—not just bacteria, including herpes virus, vaccinia virus, "fowl plague" (also known as avian flu), "louping-ill"(a virus that causes fatal encephalitis), "Borna disease"(also known as sad horse disease), canine distemper (a virus that attacks the respiratory, gastrointestinal and nervous systems of puppies and dogs) and Fujinami's tumor, an avian RNA tumor virus. Their study which revealed that oxygen was a *sine qua non* for successful photodynamic inactivation of microorganisms, is one of the earliest reports showing that visible light has viricidal potential.

Despite these early developments, it was only within the last 50 years that photodynamic inactivation of bacteria and viruses began to gain clinical recognition, as rapid acceleration of research in the field became fueled by technological innovations that gave rise to more efficient light sources. Beginning from the 1970s, improvements in technology led to several areas of clinical application of PDI, including treatment of herpes [131], laryngeal papilloma [132], hepatitis A, B and C [133-135], and blood-borne diseases [136-140], including HIV-AIDs [134,141-148], Zika virus [149], and dengue, Ross River viruses and chikungunya [150]. Further, innovations in quantitative laboratory methods have also enabled rapid precision quantitation of treatment induced changes in bacterial and viral loads, RNA and DNA concentrations, and microbial infectivity.

In 1997, van der Muelen et al. [151] used δ-aminolaevulinic acid (ALA) to induce porphyrin production in Gram-negative *Haemophilus parainfluenzae (H. parainfluenzae)*. After confirming that the ALA indeed caused the bacterium to produce intracellular porphyrins, they irradiated the cultures with 630 nm light and reported "substantial killing" of bacteria, which they had found impossible to attain without ALA induced intracellular porphyrin production. One significance of this work is that it is one of the earliest evidences that photoinactivation of a pathogen is possible with a substance that stimulates the microorganism to generate the photosensitizer itself, which in turn triggers downstream production of ROS, not just by co-culturing a microbe with a light absorbing photosensitizer that can prompt ROS production. Here, the implication is that if a microorganism can produce porphyrin either on its own or by being induced to do so—for example, with ALA—it is susceptible to photodynamic inactivation *ceteris paribus*.

To confirm this hypothesis, in a 2003 study, Ashkenazi, Malik, Harth and Nitzan of Bar-Ilan University Israel examined the potential antimicrobial effect of 407 – 420 nm blue light on *Propionibacterium acnes* [28]. First, they confirmed the rich presence of intracellular porphyrins naturally present in Gram-positive micro aerophilic *P. acnes*. Then, irradiation was carried out at a dose of 75 J cm^{-2} using a broad-spectrum metal halide lamp of 20 mW cm^{-2} irradiance. The treatment reduced the viability of the cells progressively as it was repeated; three consecutive treatments at 24 h intervals yielded significantly less culture viability (five-fold decrease) than a single irradiation. Adding ALA, an enhancer of intracellular porphyrin synthesis to the culture, potentiated bacterial inactivation, decreasing viability seven-fold, thereby confirming a strong correlation between bacterial kill and intracellular amounts of porphyrins [28].

In a similar study, Feuerstein, Persman and Weiss [105] tested the effect of visible broad spectra 400 – 500 nm light and infrared 830 nm radiation on the viability of oral bacteria, including *Porphyromonas gingivalis, Fusobacterium nucleatum, Streptococcus mutans,* and *Streptococcus faecalis*. Treatment was carried out with 260 – 1300 mW cm^{-2} irradiance for up to 3 min, using a quartz-tungsten-halogen lamp, a diode, or a plasma-arc lamp as light source. While infrared treatment did not inactivate any of the bacteria, visible light did. In further experiments, they confirmed that inactivation of these bacteria was oxygen dependent, and that hydroxyl radicals played an important role in the process [152].

These early results have been corroborated repeatedly, and it is now well established that a multitude of microorganisms possess endogenous chromophores (photosensitizers) which, when excited by light, trigger the production of hydroxyl radicals, including ROS [111-125;153]. These chromophores include porphyrins, flavins and other photo-active pigments [20, 27,153]. However, as noted in a recent study [154], mere absorption of light by a chromophore does not automatically imply ROS production, *i.e.*, not all blue light absorbing chromophores have the requisite biochemical architecture or enzymatic machinery to prompt downstream production of microbial-killing ROS. Nevertheless, this discovery of photo-active endogenous chromophores in microorganisms, and repeated successes in photo-inactivating a wide range of microorganisms, has progressively rendered the use of exogenous photosensitizers nonessential in many cases of microbial suppression [20,24,27-31], and this may be a relevant consideration in the ongoing effort to advance the antiviral effects of violet-blue light.

Microbial inactivation with violet-blue light

Since the early 2000s, a large volume of work has accumulated showing that expensive lasers are not necessary to inactivate pathogens, and that direct irradiation with commonly available blue or violet LEDs significantly inactivates pathogens without the need for an exogenous photosensitizer [20,24,27-31]. This development may not seem as momentous as it was in those days because of the widespread use of LEDs for photo-eradication of disease-causing microorganisms today. Back then it was transformative, because notwithstanding decades of efforts to emphasize the fact that dose and wavelength—not the source of light, *i.e.*, expensive laser or commonplace LED—critically determined the outcome of treatment [155], the prevailing notion was that the source must be a coherent laser or high-power broad spectra light. Further, the idea that visible light in the violet-blue range could be antimicrobial on its own without combining it with an exogenous photosensitizer was nascent and had not been firmly grasped.

Pioneers of this development which has made LEDs the light source of choice for microbial inactivation today include and the duo of J. Stephen Guffey and Jay Wilborn of Arkansas State University in the US [156,157], Chukuka S. Enwemeka and his research team, then at the New York Institute of Technology, Old Westbury, New York, USA, and currently at San Diego State University, San Diego, California, USA [17, 18,158], and the team of Michelle MacClean, Scott J. MacGregor, John G. Anderson, Gerry Woolsey and others at the University of Strathclyde, Glasgow, Scotland, UK [159]. Their studies [17,18,156-159] have been widely corroborated [19-21,24-27,29-31, 160-163], and this has prompted the bourgeoning use of violet-blue LEDs for microbial inactivation and disinfection [3, 164-170], and the ongoing effort to improve the technology [19-21].

Advantages and disadvantages of UV and violet-blue light for microbial inactivation and disinfection

Advantages and disadvantages of germicidal UV

The use of UV as a non-chemical disinfectant should be quite familiar with clinicians and researchers worldwide, since laboratory safety hoods, and clinical and non-clinical equipment used for handling pathogens in research facilities, hospitals, and industry are often equipped with germ-killing UV. It is an efficient germicidal; however, its popularity does not negate its dangers: (1) It is potentially carcinogenic, particularly UV-C which induces the most damaging effect on DNA. (2) UV-B wavelengths are known to induce sunburns and skin tan, as well as basal and squamous cell carcinomas [171-173]. (3) UV-A, which has relatively much lower photon energy, causes accelerated aging, wrinkling of the skin and melanomas over a prolonged exposure period [172].

These facts raise the question: Can UV kill microorganisms without collateral damage to the host cells? This question is timely, given COVID-19 and the resurgence of germicidal UV, and as microbial eradicating light technologies are being tested to stem the spread of viral pandemics. Proponents of UV as a safe disinfectant suggest that far UV is safe for environmental disinfection, even when humans are present. It can be argued that far UV rays, being of shorter wavelength, are less-penetrating; therefore, the rays are quickly absorbed within the outermost layer of skin and do not reach the underlying epithelium where they could be harmful [1,2,4-9]. If the shortness of these high energy far UV-C rays is the only reason that they are safe, then a counterargument could be made that it might be safer to use much shorter wavelengths below 205 nm, since they have less cutaneous penetration.

Compared to visible light, UV inactivates microorganisms at relatively low irradiation fluences; they are the most efficient wavelengths for microbial inactivation, particularly UV-C wavelengths around 260 nm. It is suggested that the benefits of UV at relatively low doses far outweigh its harmful effect [174,175], but it does not take much irradiance for UV to engender harmful effects because of its high photon energy. For example, when Mohr et al. used UV-C to decontaminate platelets, they achieved a 4 log_{10} reduction in the amount of Gram-positive *S. aureus, Bacillus cereus* and *S. epidermidis*, as well as Gram-negative *E. coli, P. aeruginosa* and *Klebsiella pneumoniae*, but the treatment altered the metabolism of the platelets [176].

Similarly, in an *in vitro* study, UV-C inactivated 99% of bacteria cocultured with keratinocytes but with a concomitant decrease in the viability of the keratinocytes [175]. This finding is corroborated by another study [99] which showed 99% inactivation of *Candida albicans* and 18.9% decrease in the viability of keratinocytes. Furthermore, *in vivo* irradiation of infected mouse skin confirmed the fungicidal effect of UV-C; however, it caused mild wrinkling of the skin, even though the skin recovered its appearance over time [100]. Moreover, the damaging effect of UV was greater with UV-B than UV-C [100]. These and other studies clearly show that treatment with UV is not entirely safe even though it is considerably effective in eradicating viruses and other pathogens [171-173].

That far UV-C is less harmful than UV-B is supported by recent studies showing that it is a safer alternative to other UV-C ranges. This development has triggered efforts to advance far UV-C as an environmental disinfectant, particularly in spaces without human presence. [1, 2,4-9]. It is noteworthy that this is a significant departure from medically available UV lamps, such as broad-spectrum UV or 254 nm UV-B

produced by xenon lamps and mercury vapor lamps respectively. Far UV-C has the advantage that: (1) It is highly effective against viruses, bacteria, and other microorganisms. (2) Its depth of penetration in humans is minimal; therefore, its potentially harmful effect is said to be limited to the epidermis, not subcutaneous tissue, and (3) compared to UV-B, UV-A and visible light, the irradiation dose needed to kill microorganisms with far UV-C is usually low—in the mJ cm^{-2} range; this further limits its potential to harm human beings exposed to the rays.

While these advantages make far UV-C attractive for reducing viruses and other microorganisms whenever it is possible to avoid human exposure, its tendency to degrade equipment and devices made of plastics and other poly-carbon cannot be ignored. UV interacts with plastics and other poly-carbons, making them brittle and giving them a discolored chalky appearance. The potential for far UV-C to degrade hydrocarbon may be greater on account of its powerful photons [13-16]. Therefore, even if it were possible to shield humans from the dangerous effects of UV, its destructive impact on devices and equipment made of hydrocarbon remains a concern. The potentially harmful effects of byproducts of the reaction between UV and assorted plastics, rubber, and similar materials remains poorly understood. In addition, there is insufficient data to understand the short-term effects of far UV-C. Less clear are its potential long-term effects on equipment and humans. Since microbial nucleic acids are damaged both by UV and violet-blue light, and considering that violet-blue light is safer and not known to damage hydrocarbons, it seems logical to pursue the violet-blue light option as a safer way to eradicate microorganisms.

Antiviral potential of blue light

Clues to the possibility of photo-eradicating viruses with blue light come from several sources. First early experiments with visible light clearly show that it is antiviral when combined with an exogenous photosensitizer [113,124,125,129]. As early as 1933, Perdrau and Todd [130], irradiated several viruses with a combination of harmless visible light and methylene blue and showed effective suppression of herpes virus, vaccinia virus, two avian viruses, canine distemper virus and others. Further, with improvements in available light technologies, a combination of various spectra of visible light and methylene blue and other photosensitizers has been used since the 1970s to inactivate viruses in blood products, including Ebola, HIV, Middle East Respiratory Syndrome coronavirus (MERS-CoV), [177], SARS, Criean-Congo haemorrhagic fever virus and Nipah virus [178], Zika virus [149], hepatitis virus [133,134,135], cytomegalovirus, human parvovirus B19, human T-cell lymphotropic virus Types I and II, and others [179-188]. These and other studies indicate that damage to viral nucleic acid, including fragmentation of the viral core are some of the mechanisms involved [189,190]. Further, enveloped viruses, such as SARS-CoV-2 which is responsible for COVID-19, have been shown to be more susceptible to photo-destruction than non-enveloped viruses [191-193]. This suggests that coronaviruses, such as SARS-CoV-2, are quite susceptible to photodynamic inactivation.

The second source of evidence, which suggests that blue light is antiviral comes from the observation of a significant reduction in the titers of baculoviruses exposed to visible light for a prolonged period. In this study, viruses stored at temperatures ranging from −85 °C to 37 °C remained stable—whether stored in polypropylene tubes or glass tubes—so long as they were not exposed to light, indicating that the reduction in virus titer was neither due to temperature nor the storage device, but exposure to light alone. [194]. A significance of this study is that virus inactivation occurred in the absence of an exogenous photosensitizer; that is, the effect was due solely to the antiviral effect of visible light. A similar finding was reported by Richardson and Porter, who found that prolonged exposure to visible light significantly reduced the infectivity of murine leukemia virus [195]. The brighter the light, the faster the reduction in viral titer. Moreover, storing the virus for a long time at the highest light intensity cleared the virus completely, as no detectable titer was found in such samples. Furthermore, by filtering out UV, they demonstrated that the effective antiviral wavelength was between 420 – 430 nm. Adding imidazole, a known quencher of singlet oxygen, did not prevent the light-induced loss of viral infectivity, indicating that the effect was due to the direct germicidal effect of 420 – 430 nm light [195]. While the defect in infectivity was associated with the viral core, no detectable defect was found on the viral envelop, again confirming that violet-blue light damages viral nucleic acids [195].

A third source of evidence lies in the simple fact that most of the germ-killing rays reaching the earth from the sun are in the blue wavelength ranges [196]. Solar UV is absorbed mostly by ozone in the upper atmosphere; this keeps humanity safe from the damaging effects of UV rays [196]. Since sunlight reaching the surface of the earth is well-known to be antimicrobial against viruses, bacteria, and other microorganisms, it follows that some of the germ-killing effects of the sun may be due to blue light. Further support for this view comes from the fact that the peak transmission of sunlight at the surface of the earth is in the blue region; when combined with violet rays from the sun, it is ten times more than the amount of UV rays reaching the surface of the earth [196]. Since it has been shown that most microorganisms are suppressed by blue light [195], at least a fraction of the sun's germ-killing power could be attributed to blue light. This is confirmed by a recent study which showed successful inactivation of aerosolized influenza virus using simulated sunlight [196,197].

High potency pulsed blue light technology

Emerging evidence suggest that the novel pulsed blue light (PBL) technology could be a viable alternative to harmful UV, given its high potency and superior germicidal efficiency compared to conventional continuous wave (CW) blue light. Recent reports show that PBL inactivates pathogens—including the deadly methicillin resistant *Staphylococcus aureus* (MRSA)—with 40 – 100 times less irradiance than CW blue light [21]. This presents a ray of hope. The underpinning science of PBL may be summarized as follows. First, the technology takes advantage of wavelengths adjacent to UV-A, in particular wavelengths that are virtually harmless because of their lower photon energy. Second, PBL technology radically modifies violet-blue rays to enhance its germicidal efficiency, bringing its germ-killing effects closer to those of UV but without the dangers posed by UV. Thus, the high potency of PBL at each of the violet-blue wavelengths makes it significantly more germicidal at lower irradiances and fluences than CW light [21]. Without this innovation, conventional continuous wave violet-blue rays are much less germicidal than UV.

Specifically, the PBL technology consists of a sequence of pulses, each with a peak irradiance and a pulse duration sufficient to optically excite photoactive molecules—such as porphyrins—into an excited singlet state. The light pulses are separated by an off time sufficient to allow the photoactive molecules to return to their ground state; this transition creates a reaction with triplet oxygen, reducing the oxygen molecule to a highly reactive singlet state, including singlet oxygen ($^1O_2$), hydroxyl radicals (OH) and superoxide (O_2^-) ions depending on which photochemical pathway is triggered, Type I or Type II. In sufficient amounts, these free radicals disrupt the cellular structure of microorganisms, thereby inactivating and photo-eradicating all or a portion of the microorganisms. The broad-spectrum nature of this mechanism of microbial suppression is evidenced by several reports which show that various wavelengths in the violet-blue region produce mildly varying but similar antimicrobial effects and can inactivate a multitude of microorganisms [19-21].

A major difference between PBL and CW light is that CW light continually excites and maintains photoactive chromophores in an excited state; fewer chromophores return to their ground state, and they do so randomly instead of in unison with light that pulsates their excitation at a certain rate. A recent fluorescence study in which irradiation was timed to coincide with replenishment of porphyrins, resulted in

orchestrated surging and ebbing of bacterial fluorescence to maximize bacterial kill [21].

Continuous wave irradiation reduces the effect of light compared to the resulting "pumping" action of PBL, which is configured to pulse light emission when chromophore fluorescence has been depleted to a preset level and there is insufficient photo-activity to maintain bacterial kill, and then restart emission when the fluorescence has returned to another preset level, at which point the light-absorbing chromophores have been replenished sufficiently by the target pathogen. The pulsing also enables timing of irradiation to coincide with the replication cycle of microorganisms to yield maximum microbial kill, as shown in recent studies [19-21,198], and as evidenced by PBL's capacity to disrupt bacterial cell replication at a sub-lethal dose due to pulsing [199].

This underlying science makes PBL a more efficient suppressor of microbial growth than CW irradiation, otherwise their fundamental antimicrobial mechanisms do not differ *per se*. In generally: (1) Both approaches take advantage of the well documented Type I and Type II photochemical reactions as previously detailed [200-203]. (2) Both PBL and CW light have been shown to disrupt biofilm formation in a wide range of microbial colonies; again because of its potency, PBL has been shown to disrupt bacterial biofilm architecture at lower fluences relative to CW light [19]. (3) Both forms of light inactivate microorganisms by perturbing their cell membranes, causing rapid membrane depolarization and lysis, and altering and disrupting membrane structure and cell replication [28, 199]. This finding may be relevant in the ongoing effort to inactivate viruses since disruption of the viral capsid and fragmentation of viral nucleic acid are two critical mechanisms for the viricidal effect of light [195]. (4) Moreover, both PBL and CW light induce A-DNA cleavage, a mechanism that has the potential to impair DNA viruses [204,205].

Thus, given the effectiveness of PBL, could it be the much-needed safe alternative to germicidal UV? The cogency of this question is heightened by a recent report which showed that cleavage of A-DNA in microbial cells is another potential mechanism for the germ-killing effect of blue light [204]. This capacity to alter A-DNA, coupled with the recent finding that violet-blue light does not collaterally impair normal human cells [204–206], raises the possibility that the nearness of blue light to UV may not be a problem, so long as irradiation dose is controlled.

Conclusion remarks and suggested guidelines for the role of far UV and PBL in photo-eradication of microorganisms

It is evident from the foregoing that in addition to vaccination strategies, there are pressing reasons to closely examine germicidal light as an additional way to reduce the threat of pandemic diseases. First, many pathogens have developed a repertoire of evasive mechanisms against some of our most potent pharmaceutical agents. Second, experience with COVID-19 and other pandemics have shown that the usual dash to develop one or more vaccines that can potentially reduce the morbidity and mortality caused by each pandemic leaves much to be desired. For decades, we have had vaccines for many coronavirus diseases, yet thousands of people continue to die each year from such diseases. Many of these diseases have been with mankind from time immemorial, intermittently, causing havocs of epic proportions. Instead of seeking ways to eradicate pandemic viruses, humanity seems to have resigned itself to living and coping with deadly viruses that can mutate into new epidemic or pandemic strains.

The limited effectiveness of vaccines can be seen from the following example. Vaccines for influenza A and B have been available for decades [206-209], but during the last three recent influenza seasons (2016–17, 2017–18, and 2018–19), the US Centers for Disease Control (CDC) recorded over 105 million infections and more than 133,000 deaths in the US alone [210,211]. The simple fact that—even with vaccinations—two of the coronaviruses responsible for as many as 30% of the common cold, HCoV 229E and HCoV OC43, have been endemic in human populations for over 50 years [212], underscores the need for a paradigm shift in the ongoing search for an enduring solution to the devastating effects of disease epidemics and pandemics.

Vaccines do not kill viruses; light does. This scenario calls for urgent research into ways of exploiting the germicidal effect of light-based technologies on microorganism. One area of application of germicidal light technology is environmental disinfection. Far UV and PBL would be highly effective in this regard. Both technologies could be used to disinfect spaces where there is no likelihood of human presence, and where the potential to damage materials made of hydrocarbons is very low. PBL is recommended for disinfecting spaces where human presence or potential presence is unavoidable. Moreover, it is also recommended in situations where there is a high chance that far UV will damage plastics and similar materials.

A major advantage of photo-disinfection is that, unlike sterilization with chemical disinfectants, light is environmentally friendly. In particular, the eco-friendliness of PBL, makes it a treatment of choice over chemical disinfectants. Further, light based technologies are more suitable for disinfecting hard to reach spaces and crevices. As such, they are better suited for disinfecting homes, offices, schools, factories, and similar spaces, as well as transportation systems, such as trains, cars, airplanes, and ambulances.

With respect to COVID-19 for example, its causative virus, SARS-CoV-2, is highly contagious. Human to human transmission occur through viral droplets and particles which can survive on various surfaces and be airborne for hours. The virus is quite resistant to environmental conditions, and this makes it readily transmissible. While the transmission of disease can be reduced by wearing of masks, social distancing, ventilation of indoor spaces, air filtration of viral particles, improved educational discharge instructions, and hand washing, adding photo-disinfection of the environment could be crucial in limiting the spread of disease. Far UV and PBL technologies can reduce the spread of COVID-19 and other viral diseases. Both technologies inactive microorganisms and can serve as effective COVID-19 disinfection tools.

Patient care is a second area of application of some of these emerging light technologies. Coronaviruses, such as SARS-CoV-2, typically invade the human body through the oral cavity, the nasal passages, and the upper airways, and remain predominantly in these biomes during the initial few days of infection [213]. Each infected person can harbor the virus in the oronasal cavity and emit thousands of contagious viral particles into the environment, including large droplets and medium or small aerosol particles which can remain in the environment until they are either ventilated, filtered, fall onto fomites, or infect another person.

Consequently, the oronasal cavity presents an ideal location for photo-eradication of the virus. It is easily accessible, and for this type of treatment, we recommend PBL since it may be unsafe to apply far UV in the oronasal cavity. Irradiating the oral cavity with PBL should not pose a concern. Blue light has been used in dentistry for decades, in the form 450 nm light used in oral surgery to cure resins.

Another advantage of treating the oral cavity with light is that saliva acts as an exogenous photosensitizer; it potentiates the antimicrobial effect of blue light [214]. In one study for example, a 5.1 $\log_{10}$ reduction in the infectivity of feline calicivirus cultured in saliva was found following irradiation with 405 nm light [214]. Therefore, in addition to the potential direct antiviral effect of PBL, the technology has the potential to decontaminate the oral cavity of coronaviruses indirectly, by causing saliva, an exogenous photosensitizer, to promote ROS production sufficient to inactivate the virus. ROS production is a major mechanism for light-induced bacterial inactivation too. Therefore, PBL irradiation of the oral cavity could help clear the mouth of many opportunistic bacteria that worsen coronavirus infections. Clearing such bacteria with light can reduce the overall debilitating effect of viral infection.

These recommendations are just one of several initiatives that could help stem pandemic diseases. Successful protection of world populations requires a multi-faceted strategy. This includes improved ventilation of

indoor spaces, improved air filtration with filters capable of trapping viral particles, effective efficient personal mask, hand hygiene, social distancing, appropriate medical management, prophylactic medication management, adequate patient educational discharge instructions to home, rapid affordable testing, transparent-honest communication, a leadership team with a focused well designed community, national and international action plan, and other strategies.

Further studies should be done by simulating complex environmental conditions in which several variables can be tested to determine the effectiveness, dosing, and possible side effects or complications related to photo-disinfection. Such studies could help refine the technology and prompt the evolution of new applications that could be used for generations to come to protect the world against future viral epidemics and pandemics, and help limit or prevent the huge socioeconomic toll, high morbidity and massive deaths associated with disease pandemics.

Declaration of Competing Interest

The authors certify that this manuscript is an original work and that besides presentation at conferences and related abstract publication, it has not been submitted or published, in whole or in part, in any other medium and is not under consideration for publication in any other journal. Furthermore, we the authors are liable for its content and for having contributed to the conception, design and implementation of the work, data analysis and data interpretation, and for having participated in writing and reviewing the text, as well as approving the final version submitted. Likewise, we accept the introduction of changes to the content, if necessary subsequent to review, and of changes to the style of the manuscript by the journal's editorial staff. We also declare that conflict of interest does not exist.

Acknowledgment

We thank Dr. Jack Greiner of Harvard University and Dr. J. Chris Castel of Carewear for their review of this paper. With gratitude, we thank Ms. Samantha Suess for preparing a clear version of Fig. 1B *pro bono*.

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