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Application of ultraviolet light sources for in vivo disinfection

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Development of antibiotic resistance is a major challenge for antibiotics as an effective treatment approach of infectious diseases and pathogenic microbes with resistance to antibiotics will become difficult to be treated. Therefore, a new therapy method, which is safe and can inactivate pathogenic microbes effectively without developing a resistance, is highly needed. Ultraviolet irradiation is well known for its ability of effective microbial inactivation and it is widely used in sterilization of inanimate objects based on conventional ultraviolet light sources. Meanwhile, applying ultraviolet irradiation in human disinfection application is an emerging and rapidly progressing field. This review focuses on recent studies in ultraviolet based disinfection methods including both animal and human studies. We will introduce different microbial inactivation mechanisms, which are associated with the ultraviolet irradiation wavelength. Relevant research work will be summarized with a focus on their microbial inactivation effect and safety issues. © 2021 The Japan Society of Applied Physics

1. Introduction

Ultraviolet (UV) radiation is part of the electromagnetic spectrum and has a shorter wavelength than visible light and a longer wavelength than X-rays. It is often classified into three bands: UVA (315–400 nm), UVB (280–315 nm), and UVC (100–280 nm), which can be utilized in various applications depending on the different biological effect. Today, UVA is commonly used in UV curing, UV lithography and UV sensing; UVB can be used in food industry (i.e. Vitamin D production), medical (i.e. skin cure, disinfection) and agriculture (i.e. plant growth lighting) applications; while UVC is often used in water purification, surface sterilization and disinfection.[1,2)]

Among all the applications, UV disinfection and sterilization has the longest history and is probably one of the most important UV applications. Back in the 19th century, scientists discovered the bactericidal effect of UV part of the Sun light, which can inhibit the growth of various kinds of bacteria.[3)] Since then, UV irradiation has been proven as a highly efficient, inexpensive and reliable disinfection and sterilization method without adding toxic chemicals, changing composition, or introducing harmful side effects. Especially UVC irradiation is capable of inactivating more that 99.99% pathogenic microbes within seconds by damaging the deoxyribonucleic acid (DNA) structures and disrupting the DNA replication process. Recent research confirms that UVC irradiation has the potential for inactivation of airborne human coronaviruses.[4,5)] Meanwhile, UVB and UVA are also capable of inactivating microbes based on different mechanisms, but are relatively less effective in direct DNA damage. It is because the DNA structure has a strong UV absorption in the UVC range with an absorption peak at around 260 nm.[6)] On the other hand, conventional UVC light source at 254 nm can also damage healthy host cells and lead to skin cancer and cataracts. Therefore, conventional UVC irradiation is a health hazard while UVA is relatively safe for humans. UVB is in an intermediate region where depending on the irradiation dose some wavelengths are harmful and others are actually beneficial since the UVB wavelengths play an important role in Vitamin D production in humans. Today, UVC irradiation is mainly used for sterilization of inanimate objects (water, air, material surface, etc).[7)]

Infectious disease is one of the major burdens of the world's healthcare system. Especially for developing countries, five types of infectious diseases are among the top ten causes of death for humans.[8)] Broad-spectrum antibiotics is an effective disinfection approach that can significantly lower the mortality rate of the infectious diseases. However, pathogens could also develop a resistance to the antibiotics and then become difficult to be treated. Over the last 60 years, the development of antibiotic resistance has accelerated due to many factors such as overuse and inappropriate use of antibiotics.[9)] Infections caused by antibiotic resistant microbes are often hard to treat due to the limited therapy options.[10)] For example, surgical site infection (SSI) is one of the most severe complications arisen from surgical treatment and it is often associated with *Staphylococcus aureus*. Methicillin-resistant *Staphylococcus aureus* (MRSA) shows resistance to multiply antibiotics and MRSA caused SSI has already become a major clinical challenge.[11)] Therefore, there is an urgent need for new approaches that can inactivate pathogens effectively without harming healthy cells and developing a resistance. UV irradiation shows a non-specific microbial inactivation effect most likely without developing resistance. It could be a promising therapy method to treat infectious disease on human if the safety concerns (mainly for UVC) can be addressed.

This review aims to give an overview of recent in vivo studies of UV irradiation based disinfection therapy methods, including both animal and clinical studies. It is well noted that the in vivo UV disinfection is still in its early research and development stage and the relevant work is much less than the in vitro UV disinfection. We will introduce different microbial inactivation mechanisms that associated with the UV irradiation wavelength and will discuss about the relevant work with a focus on the microbial inactivation effect, safety and application limitations.

2. UV induced DNA damage

UVC and part of UVB irradiation can inactivate the microbes such as bacteria, viruses and fungi in a short time by damaging their DNA structures. The UVC irradiation with high photon energy can penetrate through the cell membrane of the microbes and produce cyclobutane pyrimidine dimers (CPDs) between the pyrimidine residues in the nucleic acid

strands. The formation of the CPDs causes a deformation of the DNA molecule and therefore disrupts the multiplication of the DNA structures, which leads to the death of cells.[12] More importantly, UVC irradiation based microbial inactivation works on unspecific microbes regardless of antibiotic resistance.

As conventional UVC light source, a low-pressure mercury vapor lamp with an emission peak wavelength at 254 nm is considered hazardous to host tissues. However, some research findings suggest that its adverse effects to host tissues are relatively minor compared to its high eradication efficiency on pathogens. Dai et al. discovered that 254 nm UVC irradiation can rapidly eradicate *Candida albicans* in mice with burn infection,[13] and *Pseudomonas aeruginosa* and *S.aureus* in mice with cutaneous wound infections.[14] DNA lesions were observed after applied UV irradiation, but were quickly repaired by DNA repair enzymes in 24–48 h. A clinical study also shows that 254 nm UVC irradiation can reduce wound bacterial burden and facilitate wound healing on patients with chronic ulcer infected with MRSA.[15] Nevertheless, the chronic irradiation of 254 nm light still presents a great health risk to humans. Therefore, it is preferred to avoid employing 254 nm UVC irradiation on humans.

In the 1960s, Freeman et al. proposed that UVC irradiation in 220 nm was about 20 times less capable of inducing erythema on human skin than the UVC irradiation in 250 nm.[16] It is because, compared with conventional 254 nm UVC light, UVC irradiation in the spectral range of 200–230 nm (far-UVC) has a strong protein absorption. As shown in Fig. 1, far-UVC is too short to penetrate stratum corneum layer (dead cells) of human skin and reach the epidermis layer, where cancer stem cells are considered to reside.[17,18] Meanwhile, it is still able to penetrate the membrane and damage the microbes due to the fact that microbes (0.1–1 μm) are much smaller than human cells (10–25 μm).[6,19] This suggests that far-UVC irradiation has an effective bactericidal performance, with less damaging effect on human skin that is associated with conventional 254 nm UV irradiation. In addition, it is also considered safe for the human retina due to the protection by the cornea layer.[19,20] Therefore, far-UVC irradiation is sometimes referred to as "safe UVC irradiation" in respect to human health. The in vitro study of far-UVC irradiation based microbial inactivation on human and animal cells were well reviewed by Hessling et al.[6]

Far-UVC irradiation is an effective way to reduce the rate of SSI such as superficial surgical wound infections without harming the healthy host tissues. Research shows that 222 nm irradiation can effectively prevent the MRSA infection on superficial skin wounds of mice.[11,21] It demonstrated the same bactericidal effect as conventional 254 nm UVC irradiation but without the associated skin damage (CPD formation). Clinical human study shows that 222 nm irradiation with minimal erythema dose (MED) up to 500 mJ cm^{-2} has a significant bactericidal effect on human skin.[22]

Animal study of mice show that 222 nm UVC irradiation is safe for mouse skin and no detectable formation of mutagenic CPDs were observed by both acute irradiation (157 mJ cm^{-2}, delivered in 7 h)[23] and chronic irradiation (500 mJ cm^{-2}, 3 times a week for 10 weeks),[17] even by high dose chronic irradiation (450 mJ/cm/day on days 1, 2, 3, 4, 5, 8, 9 and 10).[24] Safety of 207 nm UVC irradiation was also verified in a similar animal study.[25] In addition, far-UVC irradiation shows no harmful effect on the mouse retina with an irradiance up to 5000 mJ cm^{-2} at 222 nm and 15000 mJ cm^{-2} at 207 nm.[26]

Although far-UVC irradiation is safe for host mammalian tissues, it is worth noting that the irradiation from current far-UVC lamps can still be harmful. Today, most commonly used far-UVC light sources are krypton–chlorine (Kr–Cl) excimer lamps with an emission peak at 222 nm and krypton–bromine (Kr–Br) excimer lamps with an emission peak at 207 nm. The full width at half maximum (FWHM) of the emission spectra of the excimer lamps is in the range of a few nanometers. However, the UV irradiation from the excimer lamps has a long wavelength component (>230 nm) in the emission spectrum which is still capable of inducing both erythema and CPD formation in human skin.[22,27] Therefore, it is important to apply a filter on the excimer lamps to block any emission with a wavelength outside the far-UVC spectral range.[21,28]

Furthermore, it is generally believed that UV irradiation will not develop a resistance of microbes. However, some researches show that microbes may develop a resistance to UVC irradiation if the exposure is repeated excessively.[29] Such resistance is a long-term effect through processes of mutation and selection and the associated UVC irradiation is

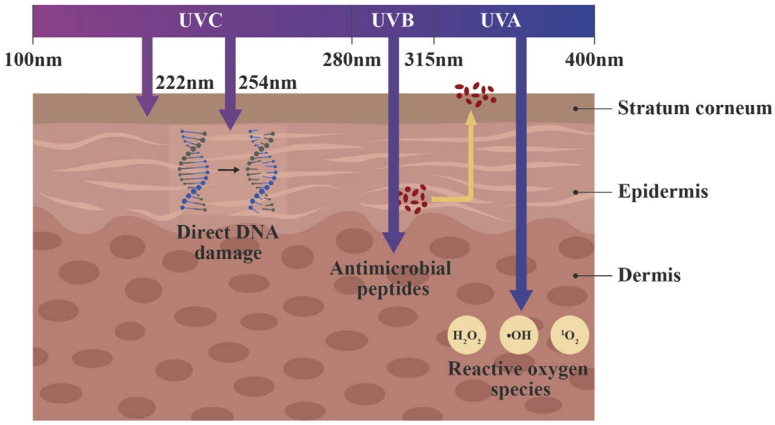

Fig. 1. (Color online) Penetration of UV irradiation into human skin. Far-UVC (200–230 nm) is completely absorbed by the stratum corneum layer, conventional UVC at 254 nm can reach the epidermis, most part of UVB is absorbed by the epidermis, and UVA can penetrate into the dermis.

much higher than the exposure limit for humans.[30] Therefore, more knowledge about the long-term effect of UVC irradiation is needed.

3. UV induced immune system modulation

Another UV irradiation based microbial inactivation mechanism is an indirect approach by introducing diverse effects on the immune system, more specifically inducing the innate immune response and suppressing the adaptive immune response.[31,32] It is known that epidermis of the human skin absorbs nearly 90% of the UVB irradiation.[33] As illustrated in Fig. 1, the UVB triggered innate response can induce certain antimicrobial peptides (AMPs) in the keratinocytes, which is the primary cellular component of epidermis and the AMPs play an essential role in the bacterial defense system of human.[34] For instance, human β-defensin (hBD)-2 is bactericidal for gram-negative bacteria, psoriasin can effectively fight against *Escherichia coli*, human cathelicidin LL-37 exhibit antimicrobial effect against skin pathogens such as *S.aureus* and *C. albicans*, and hBD-3 and ribonuclease (RNase) 7 show a broad-spectrum antimicrobial effect against *staphylococci* such as MRSA and vancomycin-resistant *Enterococcus faecium*.[34–37] Therefore, this method can be an effective and safe approach to regulate certain types of skin infectious diseases and promote wound healing.

In a clinical study, Gläser et al. demonstrated the induction of multiple AMPs in human skin after UVB irradiation.[31] Subjects with skin types II and III were irradiated by UVB light with a peak wavelength at 313 nm in different dose level (250–1500 J m^{-2}). Punch biopsies of skin in the buttocks area were taken before and 1 and 6 d after UV exposure. It is found that hBD-3, RNase 7 and psoriasin were expressed in all the samples and the expression of hBD-2 was found in only one individual. In addition, enhanced expression of AMPs were detected in samples obtained even 6 d after the UV exposure. A similar clinical study conducted by the same research group shows that hBD-3, RNase 7 and psoriasin expression have no correlation with the age of the patients while hBD-2 expression was detected more frequently in older individuals.[38]

Some clinical studies show that UVB irradiation can decreases the *S.aureus* carriage in patients with atopic dermatitis[39–41] but has no effect on *Staphylococcus epidermidis*.[39] It can also modulate the expression of hBD-1 and hBD-2 for atopic eczema,[42] and improve psoriasis[43] and atopic dermatitis via regulated expression of hBD-2 and LL-37.[44]

The UVB induced expression of mouse β-defensin (mBD)-3 and cathelin-related antimicrobial peptide (CRAMP) which are the murine homologs of hBD-2 and LL-37, respectively, were demonstrated in a mouse model.[45] The study was conducted on female hairless mice which were exposed to low doses UVB irradiation (40 mJ cm^{-2}, equivalent to 1/2 MED) daily for 1 or 3 d. Real-time reverse transcription polymerase chain reaction, western blot and immunohistochemical staining results show that the AMPs expressions were markedly upregulated by the repeated UVB irradiation and AMPs were found largely localized to the outer epidermis of murine skin. It is also found that the recovery of permeability barrier function was improved in parallel with AMPs expression. The authors suggested that the barrier recovery and AMPs expression were mediated through increased cutaneous vitamin D3 production, which is also a result of UVB irradiation that confirmed in this study.

Using vitamin D synthesized by UVB irradiation to upregulate the AMPs expression is also studied in a human model by Mallbris et al.[46] After a UVB irradiation (280–315 nm, 2.3 mW cm^{-2}) with a single MED dose, both hCAP18 (whose C-terminal peptide is LL-37) and vitamin D receptor (VDR) were found expressed significantly in the skin samples of volunteers with skin types II and III. This finding indicates that vitamin D may be a natural regulator for hCAP18 expression in the skin. However, the correlation of VDR and AMPs is still unclear and some researchers disagree with this hypothesis.[31]

4. UV based antimicrobial photodynamic inactivation (aPDI)

The mechanism of UV irradiation based aPDI is mediated by the generation of reactive oxygen species (ROS) which can make an oxidative damage to a wide range of biomolecules including lipids, proteins and DNA/RNA, as illustrated in Fig. 2. When the endogenous or exogenous photosensitizer in microbes absorb an UV photon, it can generate ROS such as hydrogen peroxide (H_2O_2) and hydroxyl radicals (·OH) in the presence of oxygen through the electron transfer mechanism (type I), or singlet oxygen ($^1O2$) through the energy transfer mechanism (type II).[47,48] The formation of ROS leads to the oxidative damage effect such as peroxidation of lipid, disruption of cell membrane, and denaturation of protein, which ultimately result in lethal damage of cells.[7,47,49] The UV based aPDI can be used to treat not only dermatological diseases but also for internal infection applications.

Recent investigation conducted by Rezaie et al. demonstrates an effective inactivation on various bacteria (*P. aeruginosa, Klebsiella pneumoniae, E. coli, Enterococcus faecalis, Clostridioides difficile, Streptococcus pyogenes, S. epidermidis, Proteus mirabilis*), yeast (*C. albicans*) and viruses (Coronavirus-229E and Coxsackievirus B) in vitro by UVA irradiation.[50] In vivo safety studies show that both single (2.0 mW cm^{-2} for 30 min) and repeated (3.0–3.5 mW cm^{-2}, 20 min daily for 2 consecutive days) intracolonic UVA exposure are safe for mice based on the endoscopic examination and full-thickness pathologic assessment results.

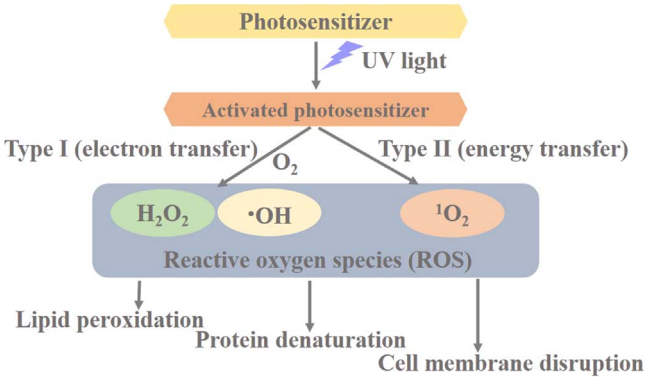

Fig. 2. (Color online) Mechanisms of reactive oxygen species generation by UV irradiation: electron transfer mechanism (type I) with the presence of oxygen and energy transfer mechanism (type II).

In addition, UVA irradiation demonstrate an effective antifungal performance on yeast infection because fungi contain porphyrins, which are endogenous photosensitizer with a strong light absorption at around 400 nm.[51)] Clinical study shows that patient with vulvovaginal candidiasis present a reduction of inflammation and disappearance of symptoms of pruritus and burning after a treatment by UVA light emitting diode (LED).[52)] In the study, a single session UV exposure (400 nm, 3 mW cm^{-2}) was applied within the vaginal canal for 30 min and then on vulva part for another 30 min. The patient was reassessed 21 d after the treatment.

Recently, endotracheal UVA based aPDI has also been investigated in the treatment of SARS-CoV-2 infection on human patients.[53)] This preliminary human study was based on five newly intubated mechanically ventilated adults with SARS-CoV-2 infection, while all subjects scored 9/10 on the World Health Organization (WHO) clinical severity scale (10 = death). Controlled UVA LED was adapted to an endotracheal tube with a size of 7.5 mm or greater. The UVA irradiation, with a peak wavelength at around 340 nm and an irradiance of 2 mW cm^{-2}, was delivered at the level of tracheal mucosa for 20 min daily for 5 d. Four out of five subjects were clinically improved and scored 2, 4, 5, and 7 on the WHO scale at day 30 after the treatment. Meanwhile, it is observed that the slope of viral load reduction during UVA treatment correlated with the slope of improvement in clinical WHO severity score over time. The results indicate that, endotracheal UVA phototherapy under specific conditions is safe and can deliver a significant reduction in respiratory SARS-CoV-2 viral load on human patients.

The UVA based aPDI can also be used to treat against SARS-CoV-2 virus on human with the assistance of Riboflavin as exogenous photosensitizer.[54)] In this clinical study, 40 patients with confirmed SARS-CoV-2 infection were in an early infection stage with mild symptoms like fever, dry cough, headache, hard breathing, fatigue etc and were divided into two groups: one experimental group received UVA based aPDI and one control group receive conventional care. Patients in the experimental group took a Riboflavin capsule first and then had dissolved Riboflavin solution sprayed on both nostrils and mouth. An UVA/blue LED device (peaks at 375 and 447 nm) was used to give a 20 min exposure treatment on nose applicator and then another 20 min on mouse applicator. The treatment was repeated daily for 5 d. Fourteen out of 20 patients had a negative quantitative polymerase chain reaction (QPCR) test after 5 d of aPDI treatment and the other 6 patients showed a significant reduced clinical symptoms and viral load. In contrast, no significant improvement in clinical symptoms and viral load assessment was observed from all 20 patients in the control group. This primary human study shows a potential of UVA based aPDI as an effective approach for treating early stage SARS-CoV-2 infection.

In addition, it is found that UVB irradiation based aPDI has an effective microbial inactivation performance on certain types of oral bacteria. UVB irradiation at 310 nm can eradicate *Porphyromonas gingivalis* without introducing a damage to human oral epithelial cells[55)] and gingival fibroblast.[56)] UVB irradiation at 296 nm shows a more efficient inactivation on *P. aeruginosa* than the antibiotics (colistin and tobramycin) and conventional UVC irradiation.[57)] These findings suggest that UVB irradiation based aPDI can be effective for oral infection treatment.

5. Summary and outlook

UV irradiation shows a significant potential of being an effective therapy method for infectious disease. UV irradiation in different wavelength band can inactivate microbes based on different mechanisms. UVC and part of UVB irradiation is capable of making a direct damage to microbes by disrupting their DNA replication process within a very short time. It shows a high inactivation efficiency on almost all kinds of pathogenic microbes even with a low dose level. UVB irradiation could trigger the innate immune response and induce the expression of certain AMPs, which can eradicate certain types of microbes. UVA and part of UVB irradiation, combined with photosensitizer, can generate ROS and lead to an oxidative damage to pathogenic microbes. Compared with the latter two mechanisms, UV based DNA damage shows an efficient microbial inactivation performance on a wider range of microbes. Some recent research findings of animal and clinical studies of UV irradiation based disinfection application are summarized in Table I.

Apart from the microbial inactivation efficiency, safety of UV irradiation is another major concern for its in vivo disinfection applications. Clinical research confirm that specific wavelengths in the UVB and UVA regions in a reasonable dose are safe for human. They can treat both dermatological diseases and internal infection in an effective and safe way. Meanwhile, unlike conventional 254 nm UVC irradiation, light in far-UVC range is also more safe for both human skin tissues and eyes. The emerging of the far-UVC light sources pave a new way for UVC irradiation based human disinfection. It should be stressed that clinical research also show that unfiltered far-UVC irradiation from excimer lamp is still harmful due to the long wavelength component from its emission spectrum.

Today, UV irradiation has already been playing an important role in the society. Since the COVID-19 pandemic outbreak at the beginning of 2020, UV irradiation has been used to inactivate airborne human coronaviruses (in vitro application, UVC) and treat the patients infected with SARS-CoV-2 virus (in vivo application, UVA). To further explore the potential of UV irradiation in human disinfection application, better UV lighting technology is desired. Compare with mercury vapor lamp and excimer lamp, UV LED and laser diode (LD) have some well-recognized advantages, which include narrow emission spectral width, flexibility of wavelength engineering, compact device size, environmentally friendly, and longer device lifetime. Novel AlGaN-based UV LED can emit UV light in a wide spectral range (210–400 nm) that covers from UVC to UVA by tuning the composition in the material growth process.[1)] The device efficiency of UV LED/LD has been continuously improved thanks to the rapid progress of III-nitride material technology.[58,59)]

It is foreseen that compact UV LED/LD device can be utilized not only in dermatological diseases but also in dental infection and internal infection treatment in the future via wireless power transmission technology. It is likely, with the development of lighting technology, UV irradiation can be a long-term effective and safe therapy method for human infectious diseases, and can be well adapted to different clinical scenarios.

Table I. Animal and clinical studies in UV irradiation based disinfection application.

Light source	Exposure conditions: irradiance/dose/time	Research target: microbe/disease/safety/AMP expression	Research finding	Setting	References
UVC: peak at 254 nm • Mercury lamp • Broadband	2.7 mW cm^{-2}: 18 min in day 0, or 40 min in day 1	• *C. albicans* burn infection in mice • Safety study	• Exposure in day 0 gives a 99.2% reduction of fungal burden, exposure in day 1 gives a 95.8% reduction of fungal burden • CPD were observed by immunofluorescence in normal mouse skin immediately after UV irradiation, and the damage was extensively repaired within 24 h	Animal	13
UVC: peak at 254 nm • Mercury lamp • Broadband	2.7 mW cm^{-2}: 16 min	• *P. aeruginosa* and *S. aureus* cutaneous wound infections in mice • Safety study	• A 10-fold reduction of the *P. aeruginosa* and *S. aureus* burden on mice skin • CPD-positive nuclei were observed in the immunofluorescence micrograph of a mouse skin, and the damage was extensively repaired within 48 h	Animal	14
UVC: peak at 254 nm • Mercury lamp • Broadband	180 s; 7 treatments over 14 d + 4 treatments over 1 month	• MRSA infected chronic ulcer on human	• UVC irradiation reduced wound bacterial burden and facilitated wound healing for all three patients • Two patients had complete wound closure following 1 week of UVC irradiation	Clinical	15
UVC: peak at 222 nm • Kr–Cl excimer lamp • FWHM: 2 nm	40 mJ cm^{-2} and 300 mJ cm^{-2}	• MRSA infected superficial skin wound of mice	• Both 222 and 254 nm irradiation show a statistically significant reduction of bacteria counts on day 2 and day 7	Animal	21
UVC: peak at 254 nm • Mercury lamp • Broadband		• Safety study	• 222 nm light showed the same bactericidal properties of 254 nm light but without the associated skin damage (CPD formation)		
UVC: peak at 222 nm • Kr–Cl excimer lamp • FWHM: 2 nm	75, 150, and 450 mJ cm^{-2}	• MRSA infected skin wound of mice	• 222 nm irradiation shows a significant bactericidal effect, which was equal to or more effective than 254 nm irradiation	Animal	11
UVC: peak at 254 nm • Mercury lamp • Broadband		• Safety study	• CPD expressing cells were found in both epidermis and dermis with 254 nm irradiation, but not with 222 nm irradiation		
UVC: peak at 222 nm • Kr–Cl excimer lamp • FWHM: 2 nm	50–500 mJ cm^{-2}	• Bactericidal effect on healthy human skin • Safety study	• The number of bacterial colonies in the skin swab culture was reduced significantly; • The CPD amount produced in the irradiated region was slightly but significantly higher than that of the non-irradiated region	Clinical	22
UVC: peak at 222 nm • Kr–Cl excimer lamp • FWHM: 2 nm	157 mJ cm^{-2}: delivered in 7 h	• MRSA (*in vitro*) • Safety study (*in vivo*)	• Both 254 and 222 nm irradiation can kill MRSA efficiently • Unlike 254 nm, 222 nm UVC irradiation is safe for mouse skin and no detectable formation of mutagenic CPDs were observed	Animal	23
UVC: Peak at 254 nm • Mercury lamp • Broadband					

Continued on next page.

Table I. Continued.

Light source	Exposure conditions: irradiance/dose/time	Research target: microbe/disease/safety/AMP expression	Research finding	Setting	References
UVB: peak at 313 nm • Fluorescent lamp • FWHM: 41 nm	250–1500 J m^{-2}	• AMP expression	• Expression of AMPs (hBD-3, RNase 7 and psoriasin) were detected on all subjects, hBD-2 expression was detected only on one subject.	Clinical	31
UVB: • Xenon arc lamp • 280–315 nm	2.3 mW cm^{-2}	• AMP expression	• hCAP18 (whose C-terminal peptide is LL-37) was found expressed significantly in the human skin	Clinical	46
UVB: peak at 313 nm • Fluorescent lamp • FWHM: 41 nm	40 mJ cm^{-2}:daily for 1 or 3 d	• AMP expression	• Expression of mBD-3, cathelin-related antimicrobial peptide (CRAMP) and LL-37 were observed • Recovery of permeability barrier function was also improved	Animal	45
UVB: peak at 311 nm • Fluorescent lamp • FWHM: 2.5 nm	Up to 1.6 J cm^{-2}	• Atopic eczema • AMP expression	• UVB irradiation can modulate the expression of hBD-1 and hBD-2 for atopic eczema	Clinical	42
UVB: peak at 311 nm • Fluorescent lamp • FWHM: 2.5 nm	0.13–8.88 J cm^{-2}	• Atopic dermatitis and psoriasis • AMP expression	• Enhanced expression of LL-37 and decreased expression of hBD-2 after UVB treatment • Significant improvement of psoriasis and atopic dermatitis	Clinical	44
UVB: peak at 306 nm • Fluorescent lamp • FWHM: 34 nm	1.68 J cm^{-2}	• Atopic dermatitis with *S. aureus* and *S. epidermidis*	• The UVB irradiation shows a good antimicrobial effect against *S. aureus*, but no effect on *S. epidermidis*.	Clinical	39
UVB • Narrow band	About 4.3 accumulated joules	• Atopic dermatitis with *S. aureus*	• UVB irradiation demonstrates a great suppression of superantigen production from *S. aureus* in patients with atopic dermatitis	Clinical	40
UVB: peak at 305 nm • Fluorescent lamp UVA: peak at 352 nm • Fluorescent lamp	UVB: 0–100 mJ cm^{-2} UVA: 0–50 mJ cm^{-2}	• Atopic dermatitis with *S. aureus*	• UVB and UVA irradiation markedly inhibited the proliferation of *S. aureus*	Clinical	41
UVA: peak at 400 nm • LED • FWHM: 12 nm	3 mW cm^{-2}: 30 + 30 min	• Vulvovaginal candidiasis	• Patient with vulvovaginal candidiasis present a reduction of inflammation and disappearance of symptoms of pruritus and burning after a treatment	Clinical	52
UVA: peak at 343 nm • LED • FWHM: 5 nm	2.0 mW cm^{-2}: 30 min, or 3.0–3.5 mW cm^{-2}: 20 min daily for 2 d	• Multiple bacteria, yeast, and viruses (in vitro) • Safety study (in vivo)	• UVA exposure demonstrates effective inactivation on various bacteria, yeast, and viruses. • Single and repeated UVA irradiation are safe for mice based on the endoscopic examination and full-thickness pathologic assessment results	Animal	50
UVA: peak at 343 nm • LED • FWHM: 5 nm	2 mW cm^{-2}: 20 min daily for 5 d	• SARS-CoV-2 infection	• Four out of five subjects were clinically improved at day 30 after the treatment. It shows that endotracheal UVA phototherapy under specific conditions was safe for human with a significant reduction in respiratory SARS-CoV-2 viral load	Clinical	53
UVA: peak at 375 nm • LED	20 + 20 min, repeated daily for 5 d	• SARS-CoV-2 infection	• 14 out of 20 patients had a negative QPCR test after 5 d of aPDI treatment and the other 6 patients showed a significant reduced clinical symptoms and viral load.	Clinical	54

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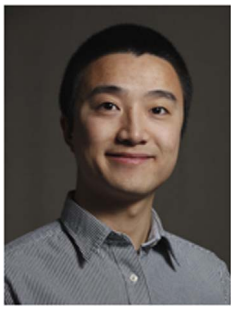

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