Phototherapy application in controlling COVID-19 and associated complications: highlighting recent findings in the literature

Shaghayegh Shahrigharahkoshan [1]
Fariba Ghalamkarpour, MD [2,3*]
Mohammadhossein Ghasempourabadi [4]
Fahimeh Abdollahimajd, MD [2,3*]

1. Faculty of Medicine, Laval University, Quebec City, Canada
2. Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Clinical Research Development Unit, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Research Scholar, Laval University, Quebec City, Canada

*Corresponding authors:
Fariba Ghalamkarpour, MD
Skin Research Center, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: fghalamkarpour@yahoo.com

Fahimeh Abdollahimajd, MD
Skin Research Center, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: fabdollahimajd@sbmu.ac.ir

Received: 08 October 2021
Accepted: 25 January 2022

The coronavirus disease 2019 (COVID-19) pandemic, the scale of its damage to all sectors, and its high rate of mortality urgently called all scientists and researchers into action to find solutions that can mitigate its multi-dimensional burden. As of October 1st, 2021, COVID-19 has claimed more than 4.5 million lives and infected more than 200 million individuals. Therefore, every small effort that can positively contribute to the alleviation of the disease and its spread can tremendously help minimize the damage. The application of light as a therapeutic agent has been effective since the beginning of civilization. During the last century, artificial light and its combination with other chemical substances to fight microorganisms have been applied substantially in many domains, such as therapeutics and immunomodulation. In this review, we present the scalable application of light as an antimicrobial and immunomodulatory agent and its potential in fighting COVID-19 and in mitigating its damages by representing the recent developments in this area.

Keywords: antimicrobial agent, artificial light, coronavirus disease 2019, ultraviolet light

Iran J Dermatol 2022; 25: 53-59

DOI: 10.22034/ijd.2022.309430.1444

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has urged scientists worldwide to prepare for the fight against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by looking for innovative methods with the potential to alleviate the disease and mitigate its spread. On March 11th, 2020, the outbreak was recognized as a pandemic by the World Health Organization (WHO) [1]. As of October 1st, 2021, over 233.5 million cases and more than 4.7 million deaths have been reported [2].

The virus can be transmitted via airborne routes

or direct contact and can remain viable in aerosols for more than three hours [3]. A wide range of clinical manifestations have been reported, such as acute respiratory distress syndrome (ARDS), pneumonia, diarrhea, sialadenitis, hepatomegaly, acute tubular injury (ATI), vesicular or maculopapular eruptions, cardiomegaly, and hemorrhagic white matter lesions [4]. The fight against COVID-19 is multi-dimensional and encompasses different healthcare domains, from prevention to treatment approaches.

Ultraviolet (UV) light radiation is a promising method that can be deployed to address various aspects of a pandemic, such as being used as a therapeutic agent. In this study, we review the potential of the electromagnetic spectrum to minimize the damages inflicted due to the current COVID-19 pandemic on the health outcome of individuals who contract the virus and manifest clinical signs and symptoms.

HELIOTHERAPY AND ITS EVOLUTION TO MODERN PHOTOTHERAPY

The earliest records of sun therapy, known as heliotherapy, date back to ancient Egypt, 5000 BC, where it was used to treat chronic ulcers. Ever since, other civilizations worldwide, such as Greeks and Romans, used sunlight as a healing and empowering agent. Far back in 1400 BC, Hindus innovated a type of phototherapy using the combination of sunlight and a photosensitizing herb to treat vitiligo, creating the essence of modern photodynamic therapy [5]. During the second half of the 19th century, evidence supporting the bactericidal effects of light, either visible or ultraviolet (UV) light, started to build up. The germicidal effect of sunlight was initially demonstrated by Downes and Blunt in 1877, who showed that light effectively kills *Bacillus anthracis* [6]. Since then, sunlight has been widely used to treat different pathologies, including rickettsia, peritoneal tuberculosis, syphilis, and lupus vulgaris [5-8], mainly due to its bactericidal activity. Up until the late 19th century, the sun was the only source of light. The beginning of the 20th century was marked by the invention of artificial light sources to treat dermatological disorders. The documented scientific approach to clinical phototherapy, using artificial UV light, was not presented until 1901 by Neil Finsen, who used sealed quartz mercury vapor lamps as the main source of artificial light to treat tubercular infections of the skin [9]. It was only after the invention of new antibiotics that the application of light as an antimicrobial treatment was diminished [5] and re-oriented to be used for certain skin disorders.

The electromagnetic spectrum of light is composed of several parts; those commonly used for their antimicrobial properties start from ultraviolet (UV) light with the smallest wavelengths (10-400 nm). Visible light comes after that, encompassing the violet, blue, and red spectra, among other colors (380-750 nm). Near-infrared (750-1,200 nm) and mid/far-infrared (1,200-10,000 nm) occupy the far end extreme of the electromagnetic spectrum. The UV light spectrum is subdivided into four other subtypes starting with vacuum UV, which occupies the shortest wavelength between 10-200 nm; this part of the light is blocked away by the ozone layer. The next three subtypes are well-known, including UVC (200-280 nm), UVB (280-315 nm), and UVA (315-380 nm), with the 250-270 nm UVC band being the most germicidal [10,11]. Figure 1 graphically illustrates the various spectra of light.

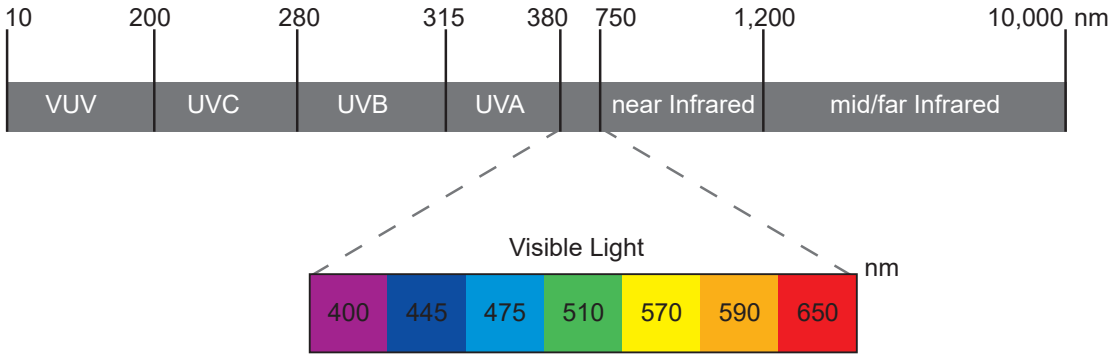

Figure 1. Different spectra of electromagnetic light that are commonly served for therapeutic purposes or decontamination.

LIGHT AS A THERAPEUTIC AGENT

Phototherapy has a long-standing reputation as a therapeutic agent for various types of skin disorders. UVB, either broadband (BB-UVB) or narrowband (NB-UVB), is mostly used in phototherapy centers. The UVA spectrum is usually applied in combination with an oral photosensitizing agent (PS), psoralen; this treatment method is abbreviated as PUVA. Both NB-UVB and PUVA are the cornerstones of phototherapy treatment [12]. PS agents are chemicals that only get activated after irradiating a specific type of light on them. Light irradiation in the presence of a PS agent and oxygen is called photodynamic therapy (PDT), where the formation of reactive oxygen species (ROS) can damage target cells (e.g., malignant cells in cancer) [13] and induce apoptosis or destroy microorganisms by altering their membrane integrity [14].

It is now well-known that various light spectra are efficient in inactivating microorganisms, with each spectrum being served to inactivate a specific type of microorganism [14]. UVC is the most germicidal, with the potential to inactivate all types of pathogens. However, it hardly reaches the lower tissue layers and can damage the host cells [14]. Regarding its germicidal mechanism, the viral RNA or bacterial or host cell DNA absorbs the UV radiation and forms pyrimidine dimers, rendering viral or cellular replication non-functional [15]. Several experiments were designed to examine the effect of UVC on superficial infected ulcers; all yielded promising results, showing reduced loads of topical microorganisms [16,17]. However, skin exposure to UVC induces DNA lesions and mutations, leading to an increased risk of skin cancer [14]. UVB also induces structural changes in the DNA of cells in the epidermal-dermal junctions of the skin, causing apoptosis. UVA penetrates deeper in the skin and reaches the dermis, where it induces apoptosis of dermal blood vessels, dendritic cells, fibroblasts, endothelial cells, and mast cells [18].

Studies suggest that violet/blue light (400-470 nm) is the most bactericidal type of light, particularly in the 390-420 nm wavelengths [14,19]. It has antimicrobial effects against various bacteria, such as *Propionibacterium acnes* [20], methicillin-resistant *Staphylococcus aureus* [21], *Pseudomonas aeruginosa* [22-25], *Candida albicans* [26], and *Acinetobacter baumannii* [27,28]. One study showed that blue light inactivates multiple virulence factors of *P. aeruginosa* and increases its susceptibility to antibiotics [22]. Experimental studies show that blue light can destroy SARS CoV-2 via photo-excitation of its acquired porphyrins, on which it depends to survive [29].

Blue light has a better penetration ability than UVC, does not damage host cells, and requires no PS agent to exert its effect [30]. Red light, on the other hand, can penetrate profoundly but has no activity unless combined with a PS agent [14]. Thus, depending on the purpose of the therapy, a particular spectrum might be applied to treat the underlying cause of the disease.

Fighting COVID-19 co/superinfections

Bacterial or fungal co/superinfection is a common complication of viral respiratory disorders, broadly studied for the influenza virus [31-35]. Studies show that the course of illness of around 5.8-8.1% of hospitalized COVID-19 patients was complicated by bacterial co/superinfection. Severely infected patients or those in intensive care units receiving mechanical ventilation are at more important risk of bacterial or fungal complications [36,37]. The main reason for co/superinfection is the administration of immunosuppressive drugs, which hampers the immune response or dysregulates the immune system following the viral attack. Co/superinfection following COVID-19, compared to other viral infections, is less reported and affects patients to a lesser extent [36,38]. The most common organisms involved in the pathogenesis of bacterial co/superinfection of COVID-19 patients reported are *Mycoplasma* species, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* [36]. Light-induced germ eradication might not be as effective as antibiotics but has several advantages over antibiotics and can be used as adjuvant therapy. Studies demonstrate that shining light increases the susceptibility of the bacteria to the antibiotics; in addition, no significant bacterial resistance develops after multiple cycles of light exposure [39,40].

Photodynamic therapy effectively eradicates skin infections by inducing microorganism destruction after shining light to the infected site where PS has been topically introduced beforehand [14]. This might be particularly compelling in treating skin-related adverse effects of COVID-19 patients

due to the fairly high prevalence of its cutaneous manifestations, which are partly virus-related and partly treatment-induced [4,41]. That may result in a significant reduction of antibiotic prescription, which is excessive in about 70% of COVID-19 patients.

In addition, the respiratory tract is a site of predilection for microbial colonization, and the pulmonary system is by far the most common organ system affected by COVID-19 [42,43]. PDT has shown promising results so far in reducing the microbial load at these sites and treating various respiratory diseases [44,45]. One case series applying PDT to treat pharyngotonsillitis showed complete alleviation of the symptoms 24 hours following treatment [46]. They made the patients gargle a PS (curcumin) and then illuminated the oropharynx with a light-emitting diode. Local application of PDT not only reduced the microbial load but also hindered them from penetrating the mucosal barrier by aiding phagocytes [44]. In another attempt, scientists showed that the inhalation of indocyanine green while illuminating infrared light helped the eradication of *Streptococcus pneumoniae* in murine models [47]. Soares *et al.* proposed the application of PDT as prophylaxis against bacterial biofilm formation in the respiratory tract [48]. Recent studies investigated the application of PDT in disinfecting the nasopharynx cavity of patients affected by COVID-19 at its early stages, which sounded promising had considerable limitations given the systemic manifestations of COVID-19 and the local application of PDT [49].

Since pneumonia and acute respiratory distress syndrome (ARDS) in COVID-19 patients are the most prevalent and deleterious complications and no effective antiviral drug against SARS-CoV-2 has been developed to date [42], PDT might be of help in destructing microorganisms colonized in the respiratory tract. Of note, PDT is not a method to fight the microorganisms systematically; nevertheless, it reduces the microbial load of the respiratory tract, decontaminates liquids and surfaces, and activates the antimicrobial effect of certain materials such as fullerenes, carbon nanotubes, and graphene [29,44].

Mitigating COVID-19 complications

Pulmonary involvement is one of the most reported complications of COVID-19 [43]. Due to the occurrence of ARDS and pneumonia following the SARS-CoV-2 attack, severe damage might be inflicted on the lungs, which in the long term may result in irreversible fibrotic interstitial lung disease [42,50]. The underlying pathophysiology of pulmonary damage following ARDS is poorly understood, though studies suggest that the systemic release of cytokines and collagen deposition in the lung parenchyma are involved, triggered by the virus, lung inflammation, epithelial cells, and fibroblasts [50,51].

Apart from antifibrotic drugs, which are proven to be partly effective [52], experiments show red and near-infrared light application called photobiomodulation (PBM) may ameliorate the pulmonary consequences of COVID-19. In a recent experiment on murine models, Brochetti *et al.* [51] irradiated light to the respiratory tract of mice with induced lung fibrosis. The results supported the protective role of light against alveolar inflammatory cells, collagen production, interstitial thickening, and static and dynamic elasticity of the lungs. In another attempt, de Brito *et al.* [53] evaluated the effect of laser therapy on pulmonary fibrosis progression. The results were promising and indicative of attenuated lung inflammation in the group with lung fibrosis due to reduced secretion of pro-inflammatory cytokines (TNF, IL-1β, IL-6, IFN-γ, and TGFβ) and fibrogenic factors, as well as the upregulation of protective anti-inflammatory IL-10 in the lung. Besides, the immunomodulatory effect of PBM has shown to be an effective therapeutic approach in diseases such as chronic obstructive pulmonary disease (COPD) [54]. Despite the preliminary nature of these investigations, the low incidence of adverse effects following light therapy, as well as the paucity of efficacious drugs against SARS-CoV-2 and its fatal complications such as lung fibrosis, warrant the conduction of more experiments to explore the potential of this new therapeutic approach.

Vitamin D activation

It is now widely known that ultraviolet radiation (UVR), specifically UVB, is a triggering factor for the production of vitamin D. Epidermal 7-dehydrocholesterol (7-DHC) absorbs UVB and, through several reactions, transforms it into vitamin

D and subsequently to 25-hydroxyvitamin D [55]. Vitamin D helps maintain the integrity of various cell-cell junctions, which are compromised during viral attacks, leading to an infection [56]. Vitamin D also plays an active role against various infections by inducing antimicrobial peptides, cathelicidin [57], and defensins [58], which modulate cellular innate immunity. Other than the antimicrobial activity of these two peptides, they both possess the potential to regulate repair and inflammation [59]. Vitamin D slows down viral replication and reduces the pro/anti-inflammatory cytokine cascades triggered by the innate immune system after exposure to bacteria or viruses like SARS-CoV-2. Therefore, it declines the harmful effect of the cytokine storm syndrome and prevents multi-organ failure due to inflammation. In addition, studies show that vitamin D down-regulates angiotensin-converting enzyme 2 (ACE2) expression on the surface of kidney and lung cells, which is the entry point of SARS-CoV-2 [60]. In addition, vitamin D plays a role against endothelial cell dysfunction and vascular thrombosis secondary to massive inflammatory response after SARS-CoV-2 contraction. It has been reported that individuals with vitamin D deficiency are more prone to develop thromboembolic complications following SARS-CoV-2 infection [61].

Given the potential of phototherapy centers in irradiating both narrow and broadband UVB on the skin and the role of UVB to activate epidermal 7-DHC and increase serum 25-hydroxyvitamin D [62], phototherapy sessions not only prevent the deterioration of the underlying skin condition but also strengthen the immune system of the patient against SARS-CoV-2 infection [63]. Thus, it is recommended that phototherapy centers continue to operate during the current pandemic while respecting the public health recommendations such as limiting the number of patients in a closed space, keeping social distancing, and so on [64]. Therefore, to benefit from the immunomodulatory effect of light during the COVID-19 era, we propose a maximum of 30 minutes of daily sunbathing to help the immune system of the body eradicate the virus.

CONCLUSION

In an effort to mobilize every single tool to advance the fight against SARS-CoV-2, we conclude that the application of various spectra of light is a promising method in treating COVID-19 and its complications. Although preliminary, many studies were innovative and offered compelling results, warranting more thorough investigations. In addition, we know that light application is not limited to therapeutic purposes and can be deployed in other domains such as blood supply chains, environmental decontamination, equipment disinfection, and immunomodulation. Thus, many avenues exist to explore the potential of light to fight COVID-19. More reviews are encouraged to cover other applications of light during the pandemic.

Taken together, given the potential of light in defeating the virus, we propose to factor light therapy in the ongoing strategic plans for curbing COVID-19. This report does not undermine the efficacy and importance of vaccination against SARS-CoV-2, and we acknowledge the necessity of vaccination to combat this virus. However, we believe that supplementary measures remain necessary for the proper control of SARS-CoV-2, especially in regions with limited access to vaccines.

Conflict of Interest: None declared.

REFERENCES

1. Timeline of WHO's response to COVID-19. 2020; https://www.who.int/news-room/detail/29-06-2020-covidtimeline. Accessed 16 August 2020, 2020.
2. WHO Coronavirus (COVID-19) Dashboard. 2021; https://covid19.who.int/?adgroupsurvey = {adgroupsurvey}&gclid = EAIaIQobChMIn_Xb5-CX8QIVhRoGAB1jjgToEAAYASABEgLaevD_BwE. Accessed 2021/10, 2021.
3. Buonanno M, Welch D, Shuryak I, et al. Far-UVC light (222 nm) efficiently and safely inactivates airborne human coronaviruses. Sci Rep. 2020;10:10285.
4. Tabary M, Khanmohammadi S, Araghi F, et al. Pathologic features of COVID-19: a concise review. Pathol Res Pract. 2020;216:153097.
5. Enwemeka CS, Bumah VV, Masson-Meyers DS. Light as a potential treatment for pandemic coronavirus infections: a perspective. J Photochem Photobiol B. 2020;207:111891.
6. Roelandts R. The history of phototherapy: something new under the sun? J Am Acad Dermatol. 2002;46:926-30.
7. Chesney RW. Theobald palm and his remarkable observation: how the sunshine vitamin came to be recognized. Nutrients. 2012;4:42-51.
8. Lloyd JJ. Sun Treatment of Tuberculosis. Am J Nurs. 1925;25:743-6.
9. McDonagh AF. Phototherapy: from ancient Egypt to the

new millennium. J Perinatol. 2001;21:S7-S12.

10. Tursen U, Tursen B, Lotti T. Ultraviolet and COVID-19 pandemic. J Cosmet Dermatol. 2020;19:2162-4.
11. Hessling M, Hones K, Vatter P, et al. Ultraviolet irradiation doses for coronavirus inactivation-review and analysis of coronavirus photoinactivation studies. GMS Hyg Infect Control. 2020;15:Doc08.
12. Hönigsmann H. History of phototherapy in dermatology. Photochem Photobiol Sci. 2013;12:16-21.
13. Hamblin MR. Antimicrobial photodynamic inactivation: a bright new technique to kill resistant microbes. Curr Opin Microbiol. 2016;33:67-73.
14. Hamblin MR, Abrahamse H. Can light-based approaches overcome antimicrobial resistance? Drug Dev Res. 2019;80:48-67.
15. Budowsky EI, Bresler SE, Friedman EA, et al. Principles of selective inactivation of viral genome. I. UV-induced inactivation of influenza virus. Arch Virol. 1981;68:239-47.
16. Dai T, Garcia B, Murray CK, et al. UVC light prophylaxis for cutaneous wound infections in mice. Antimicrob Agents Chemother. 2012;56:3841-8.
17. Dai T, Kharkwal GB, Zhao J, et al. Ultraviolet-C light for treatment of Candida albicans burn infection in mice. Photochem Photobiol. 2011;87:342-9.
18. Fisher S, Ziv M. COVID-19 effect on phototherapy treatment utilization in dermatology. J Dermatolog Treat. 2022;33:789-91.
19. Dai T. The antimicrobial effect of blue light: what are behind? Virulence. 2017;8:649-52.
20. Masson-Meyers DS, Bumah VV, Castel C, et al. Pulsed 450 nm blue light significantly inactivates Propionibacterium acnes more than continuous wave blue light. J Photochem Photobiol B. 2020;202:111719.
21. Enwemeka CS, Williams D, Enwemeka SK, et al. Blue 470-nm light kills methicillin-resistant Staphylococcus aureus (MRSA) in vitro. Photomed Laser Surg. 2009;27:221-6.
22. Fila G, Kawiak A, Grinholc MS. Blue light treatment of Pseudomonas aeruginosa: strong bactericidal activity, synergism with antibiotics and inactivation of virulence factors. Virulence. 2017;8:938-58.
23. Amin RM, Bhayana B, Hamblin MR, et al. Antimicrobial blue light inactivation of Pseudomonas aeruginosa by photo-excitation of endogenous porphyrins: in vitro and in vivo studies. Lasers Surg Med. 2016;48:562-8.
24. Yang P, Wang N, Wang C, et al. 460nm visible light irradiation eradicates MRSA via inducing prophage activation. J Photochem Photobiol B. 2017;166:311-22.
25. Dai T, Gupta A, Huang YY, et al. Blue light rescues mice from potentially fatal Pseudomonas aeruginosa burn infection: efficacy, safety, and mechanism of action. Antimicrob Agents Chemother. 2013;57:1238-45.
26. Zhang Y, Zhu Y, Chen J, et al. Antimicrobial blue light inactivation of Candida albicans: In vitro and in vivo studies. Virulence. 2016;7:536-45.
27. Zhang Y, Zhu Y, Gupta A, et al. Antimicrobial blue light therapy for multidrug-resistant Acinetobacter baumannii infection in a mouse burn model: implications for prophylaxis and treatment of combat-related wound infections. J Infect Dis. 2014;209:1963-71.
28. Wang Y, Wu X, Chen J, et al. Antimicrobial Blue Light Inactivation of Gram-Negative Pathogens in Biofilms: in Vitro and In Vivo Studies. J Infect Dis. 2016;213:1380-7.
29. Sabino CP, Ball AR, Baptista MS, et al. Light-based technologies for management of COVID-19 pandemic crisis. J Photochem Photobiol B. 2020;212:111999.
30. Wang Y, Wang Y, Wang Y, et al. Antimicrobial blue light inactivation of pathogenic microbes: state of the art. Drug Resist Updat. 2017;33-35:1-22.
31. Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Viruses. 2016;10:394-403.
32. Salehi M, Ahmadikia K, Badali H, et al. Opportunistic fungal infections in the epidemic area of COVID-19: a clinical and diagnostic perspective from Iran. Mycopathologia. 2020; 185:607-11.
33. Gangneux JP, Bougnoux ME, Dannaoui E, et al. Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med. 2020;30:100971.
34. Rice TW, Rubinson L, Uyeki TM, et al. Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. Crit Care Med. 2012;40:1487-98.
35. Shah NS, Greenberg JA, McNulty MC, et al. Bacterial and viral co-infections complicating severe influenza: incidence and impact among 507 U.S. patients, 2013-14. J Clin Virol. 2016;80:12-9.
36. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26:1622-9.
37. Lansbury L, Lim B, Baskaran V, et al. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81:266-75.
38. Huttner BD, Catho G, Pano-Pardo JR, et al. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020;26:808-10.
39. Giuliani F, Martinelli M, Cocchi A, et al. In vitro resistance selection studies of RLP068/Cl, a new Zn(II) phthalocyanine suitable for antimicrobial photodynamic therapy. Antimicrob Agents Chemother. 2010;54:637-42.
40. Maisch T. Resistance in antimicrobial photodynamic inactivation of bacteria. Photochem Photobiol Sci. 2015;14:1518-26.
41. Seirafianpour F, Sodagar S, Pour Mohammad A, et al. Cutaneous manifestations and considerations in COVID-19 pandemic: A systematic review. Dermatol Ther. 2020:e13986.
42. Johnson KD, Harris C, Cain JK, et al. Pulmonary and extra-pulmonary clinical manifestations of COVID-19. Front Med (Lausanne). 2020;7:526.
43. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017-32.
44. Dias LD, Blanco KC, Bagnato VS. COVID-19: beyond the virus. The use of photodynamic therapy for the treatment of infections in the respiratory tract. Photodiagnosis Photodyn Ther. 2020:101804.

45. Kurman JS, Pastis NJ, Murgu SD. Photodynamic therapy and its use in lung disease. Current Pulmonology Reports. 2019;8:215-21.

46. Blanco KC, Inada NM, Carbinatto FM, et al. Treatment of recurrent pharyngotonsillitis by photodynamic therapy. Photodiagnosis Photodyn Ther. 2017;18:138-9.

47. Geralde MC, Leite IS, Inada NM, et al. Pneumonia treatment by photodynamic therapy with extracorporeal illumination - an experimental model. Physiol Rep. 2017;5:e13190.

48. Soares RB, Costa DH, Miyakawa W, et al. Photodynamic activity on biofilm in endotracheal tubes of patients admitted to an intensive care unit. Photochem Photobiol. 2020;96:618-24.

49. Schikora D, Hepburn J, Plavin SR. Reduction of the viral load by non-invasive photodynamic therapy in early stages of COVID-19 infection. Am J Virol Dis. 2020;2:01-05.

50. Spagnolo P, Balestro E, Aliberti S, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med. 2020;8:750-2.

51. Brochetti RA, Leal MP, Rodrigues R, et al. Photobiomodulation therapy improves both inflammatory and fibrotic parameters in experimental model of lung fibrosis in mice. Lasers Med Sci. 2017;32:1825-34.

52. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020;8:807-15.

53. de Brito AA, da Silveira EC, Rigonato-Oliveira NC, et al. Low-level laser therapy attenuates lung inflammation and airway remodeling in a murine model of idiopathic pulmonary fibrosis: Relevance to cytokines secretion from lung structural cells. J Photochem Photobiol B. 2020;203:111731.

54. da Cunha Moraes G, Vitoretti LB, de Brito AA, et al. Low-level laser therapy reduces lung inflammation in an experimental model of chronic obstructive pulmonary disease involving P2X7 receptor. Oxid Med Cell Longev. 2018;2018:6798238.

55. Kechichian E, Ezzedine K. Vitamin D and the skin: an update for dermatologists. Am J Clin Dermatol. 2018;19:223-35.

56. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020;12(4):988.

57. Adams JS, Ren S, Liu PT, et al. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. J Immunol. 2009;182:4289-95.

58. Laaksi I. Vitamin D and respiratory infection in adults. Proc Nutr Soc. 2012;71:90-7.

59. Herr C, Shaykhiev R, Bals R. The role of cathelicidin and defensins in pulmonary inflammatory diseases. Expert Opin Biol Ther. 2007;7:1449-61.

60. Charoenngam N, Shirvani A, Holick MF. Vitamin D and its potential benefit for the COVID-19 pandemic. Endocr Pract. 2021;27:484-93.

61. Cereda E, Bogliolo L, de Stefano L, et al. A brief discussion of the benefit and mechanism of vitamin D supplementation on coronavirus disease 2019. Curr Opin Clin Nutr Metab Care. 2021;24:102-7.

62. Osmancevic A, Landin-Wilhelmsen K, Larko O, et al. Vitamin D production in psoriasis patients increases less with narrowband than with broadband ultraviolet B phototherapy. Photodermatol Photoimmunol Photomed. 2009;25:119-23.

63. Megna M, Fabbrocini G, Villani A. Phototherapy and vitamin D: the importance in COVID-19 era. J Dermatolog Treat. 2022;33:1165.

64. Coronavirus Disease 2019 (COVID-19). 2020; https://www.cdc.gov/coronavirus/2019-ncov/php/public-health-recommendations.html. Accessed August 15th, 2020.