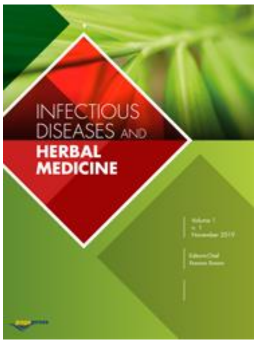
Perspectives, opinions and comments



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Is photodynamic therapy with curcumin suitable for combating monkeypox?

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Background

Monkeypox (MPX) is a zoonotic viral infection caused by the Monkeypox Virus (MPXV), which may spread person-to-person directly. It is currently being treated with previously intended drugs for smallpox or other diseases caused by the orthopoxvirus, such as tecovirimat, cidofovir, and brincidofovir. The smallpox vaccination is also the treatment for MPX, consisting of Immune Globulin (IG) combined with human plasma. However, this type of vaccine may cause several neurological adverse events such as headache, pain, vertigo, dizziness, and non-serious limb paresthesia. Up to the present, there are no available treatments, Antimicrobial Photodynamic Therapy (aPDT) may be a good choice for specifically targeting the MPXV because it is a non-invasive approach without side effects. The strategy is according to the principle of Photodynamic Therapy (PDT) and its photodynamic action of curcumin for the research process on MPX. Why do we apply PDT with "curcumin" as a Photosensitizer (PS) against MPX, and is this a possible choice?

Principle and photodynamic action

PDT has been used in clinical studies for a long time ago since it is a minimally invasive therapeutic modality that avoids systemic treatment, and limits damage to healthy cells. This occurs only when the light delivery and PS build up in abnormal cells.[1-5] The principle of PDT is a dynamic interaction between the PS and light with a specific wavelength to generate Reactive Oxygen Species (ROS), such as singlet oxygen ($^1O_2$), superoxide radical ($O_2^{-\bullet}$), hydroxyl radical ($HO^\bullet$), and hydrogen peroxide (H_2O_2) to produce oxidative damage for promoting the selective destruction of the target or biological lesion.[6]

Curcumin (*Figure 1*) is traditional Chinese medicine with non-toxic and acts as a PS for the application of PDT.[7] Because it possesses a wide range of pharmacological functions, *e.g.*, anti-bacterial,[8] anti-viral,[9] anti-inflammatory,[10] antioxidant,[11] and anti-infection[12] properties. It is activated within a range of blue wavelengths between 300 and 500 nm in the application of PDT for producing ROS to destroy bacterial, virus, or abnormal tissues.[13]

Research process

MPX is an orthopoxvirus (a double-stranded DNA virus) in the same genus as the variola virus (the causative agent of smallpox).[14] Growing evidence has shown that curcumin has anti-bacterial and anti-viral functions in the application of PDT. Although the wavelength of curcumin is blue, it is safe owing to its vast biological target and with practically no aftereffects. The wavelengths emitted from 430-490 nm fall in the visible region, which can penetrate the skin well and are already known.[15-16]

Anti-bacterial property

At the beginning of 2011, Dovigo *et al*. reported that 40 μM of curcumin was highly effective for inactivating Candida isolates during associated with light excitation at 18 Jcm^{-2} at 400-500 nm in PDT, which decreased the biofilm biomass of all species evaluated.[17] Later, he also identified the exposures to curcumin with LED light at 37.5 Jcm^{-2} caused a significant reduction in *C. albicans* viability with PDT. The most effective concentration of curcumin is 80 μM, which induced the highest log10 reduction in colony counts (4 logs).[18] Paschoal *et al*. indicated the application of PDT using different concentrations of curcumin (2000, 4000, and 8000 μM) with 24, 48, and 72 Jcm^{-2} that was able to reduce the number of *Streptococcus* *mutans* in a planktonic culture.[19] In 2017, Lee *et al*. indicated the viability of *Streptococcus mutans* in the presence of curcumin, or *Curcuma xanthorrhiza* extract, and a mixture of these two components with the concentrations of 10, 10^2, 10^3, and 10^4 ng/ml was substantially reduced during irradiation with 405nm light at 25.3 Jcm^{-2}.[20] Ferrisse *et al*. recently developed the efficacy of curcumin-mediated anti-bacterial PDT for oral antisepsis, which decreased bacterial load (0.31-0.49 log_{10} UFC/ I^2=0%).[21]

Anti-viral property

In early 2014, Leite *et al*. reported the blue light of PDT at 600 mW/cm^2 of intensity with 200 J/cm^2 of fluence using 30 mg/L of curcumin may be used for reduction of salivary microorganisms, leading to overall disinfection of the mouth.[22] Randazzo *et al*. also identified curcumin-mediated photodynamic inactivation of norovirus surrogates. The different concentrations of curcumin (13.5-1358 µM) were individually mixed with feline calicivirus at titers of california 6-7 log $TCID_{50}$/mL and photoactivated by LED blue light with a light dose of 3 J/cm^2, which reduced feline calicivirus titers by almost 5 logs.[23] Zupin *et al.* discovered that the laser light of PDT at 0.25 W/cm^2 of intensity with 15 J/cm^2 of fluence using 10 µM of curcumin inhibited SARS-CoV-2 replication (reduction >99%) in Vero E6 cells.[24] Currently, Pourhajibagher *et al.* used a computational strategy to investigate the potential of aPDT at a wavelength in the region between 250 and 400 nm using propolis-benzofuran A against the MPXV that collapsed the structure of the viral cells through the generation of ROS and prevented the attachment of viruses to the host cell surface. However, it required to re-define the therapeutic protocols in a docking model for patients with MPX.[25]

At the same time, curcumin did not need the docking model because this is a well-known PS and ligand for the application of PDT.

Limitation and future aspect

Several potential clinical applications of curcumin in PDT are its poor solubility, stability, and photostability in aqueous solutions, as well as its rapid metabolism and systemic elimination.[26] Meanwhile, curcumin has a low absorbance profile with no absorption above 600nm, and tissue transparency to light falls off below 600nm. The most effective agents that show substantial absorbance are infrared and near IR. There are two methods to extend the curcumin absorption wavelength for overcoming this issue including: i) design and synthesis of some curcumin analogs (derivatives), or ii) develop a nano-system for getting a better PDT efficacy.

Liu *et al.* reported that the curcumin derivative displayed large Stokes shifts by introducing a difluoroboron ring onto the ß-diketone structure of the curcumin molecule, and N,N-diethylamine,[27] but the application of PDT is still requiring to be an investigation. These procedures are designed for the development of curcumin as a PS because red light is part of the visible light spectrum that can deeply penetrate the skin to about 6 mm, and directly affect the fibroblast of the skin dermis. Blue light is UV-free irradiation, which is fit for treating chronic inflammatory diseases. Niu *et al*. reported the combination of curcumin with LED blue light united red-light irradiation can attain a higher efficiency in regulating proliferation and apoptosis in skin keratinocytes.[28] Besides, develop nanotechnology of PS that can have a high ROS yield, easy modification, and good stability, and overcome PDT resistance.[29]

Pourhajibagher *et al.* reported the *antibacterial property* of Nano-Curcumin (nCur) reinforced with aPDT using a Light Emitting Diode (LED) at 435±20 nm wavelength for 5 min. A 5% concentration of nCur could serve as an excellent ActivaBioActive Base/Liner (ABBL) additive in aPDT producer against *S. mutans* biofilms up to 60 days of aging period.[30] Bonfim CMD also identified the antiviral property of 80 μM curcumin-nanoemulsion associated with PDT using a blue laser at 480nm wavelength that presented 90% of cell death in HPV-16.[31] Recently, Liu *et al.* designed dual-layer silica-coated upconversion nanoparticles combined with PDT using curcumin, which displayed high antibacterial activity against *E. coli* and *S. aureus* under near-infrared irradiation at 808 nm.[32] Moreover, the monkeypox viruses cause systemic infections, which are not readily treated even with conventional PDT. According to the previous clinical study, the patient was continuously treated empirically with linezolid and piperacillin-tazobactam IV as antibacterial agents for systemic infection while requiring light photodynamic therapy just for the most important part of infection.[33]

Conclusions

The above information demonstrates that PDT with curcumin is a possible candidate for combating MPX, which is safe and non-toxic. However, curcumin has some limitations, such as low solubility and absorption, as well as much more work needs to be done, including human clinical trials of these Curcumin-aPDT for MPX.

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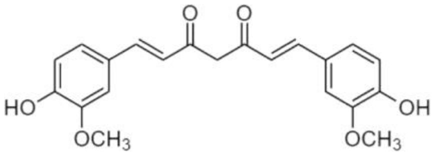

Figure 1. Chemical structure of curcumin.