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Could nanotechnology assist traditional Chinese medicine (TCM) in photodynamic therapy (PDT) against SARS-CoV-2?

Dear editor,

Could nanotechnology assist traditional Chinese medicine (TCM) in photodynamic therapy (PDT)? PDT is a minimally invasive approach to treat various diseases through a light-activated photosensitizer (PS). The natural and non-toxic PS from TCM could produce reactive oxygen species (ROS) to induce strong anti-infectious action [1]. Nanotechnology is a molecular scale system and applying in Chinese medicine for the development of nanoparticle drug-delivery vehicles. These nano-carriers are less than 100 nm in size with an ability to carry and deliver therapeutics to infection sites [2]. It is well-known that most of the active compounds from TCM are poor solubility and low bioavailability with limited applications in clinical settings. Nanotechnology is being employed to produce a nanoscale TCM, its physical specifications, chemical properties, and biological characteristics endow TCM to have a great bioavailability, solubility, transport, and effectiveness [3]. The nanotechnology also facilitates the accumulation of PS and the active compounds from TCM in an illness lesion through the enhanced permeability and retention (EPR) effect or active targeting strategies [4].

One of the famous TCM, curcumin is a polyphenol extracted from turmeric. It has anti-inflammatory, antimicrobial, and antiviral activities. This is safe and non-toxic, but it has a rather broad absorption peak (range 300–500 nm), with a maximum absorption band at wavelength 430 nm [5]. However, curcumin is poor bioavailability. Nanotechnology helps improve its solubility and therapeutic efficacy [6-8]. The photo-activation of a nano-curcumin system reduced a significant decrease in cell viability for all of the cancer cells when applied in PDT. This damage was limited to the illuminated area without long-term, and systemic side effects because of the precise light irradiation on anatomical sites [9]. Dagrada G et al. reported the self-assembled nano-micelles as curcumin drug delivery vehicles enhanced the effectiveness of PDT. The nanocarrier system efficiently delivered curcumin to solitary fibrous tumour cells. When light irradiation was applied, nanocurcumin significantly enhanced the killing activity on cancer cells and prevented cancer cell invasiveness [10].

Besides, Hosseinzadeh R et al. designed a PDT experiment using a nano-curcumin system with blue LED (465 nm; power density: 34 $mWcm^{-2}$) for the photo-activation to produce singlet oxygen. The effect of PS concentration is about 0–75 $\mu g.mL^{-1}$ used on MDA-MB-231 cancer cells [11]. Jiang S et al. also developed the solid lipid nanoparticles with curcumin used in blue LED (430 nm; power density: 50 m Wcm^{-2}) for PDT. The concentration of it curcumin nanoparticles is only required 15 μM to induce the A549 cell death more than 80% [12].

Nanotechnology improves the characteristics of curcumin and endows it to have the ability to target an infection area. Yang XX et al. reported curcumin modified silver nanoparticles (cAgNPs) with a highly efficient inhibition effect against respiratory syncytial virus (RSV) infection that prevented RSV from infecting the host cells by inactivating the virus directly [13]. Lee WH et al. discovered that curcumin nanoparticles (cur-NPs) were more effective in suppressing the expression of the inflammatory marker, Interleukin-8 (IL8) [14].

Up to the present, COVID-19 is a virus that leads to severe acute respiratory syndrome (SARS). The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is attached to an angiotensin-converting enzyme 2 (ACE2) receptor of spike glycoprotein for its viral replications. The transmembrane protease serine 2 (TMPRSS2) interacted with a disintegrin metallopeptidase domain 17 (ADAM17) to give a high level of ACE2 expression causing lung inflammation and pulmonary oedema [15].

There are some strategies of curcumin loaded with nanoparticles in the past PDT investigations. Preis E et al. identified the spray-dried curcumin-loaded nanoparticles for aPDT which possessed a good dispersibility and attached on the bacterial cell wall, low dark toxicity, minimal adverse effects, as well as high photo-inactivation when combined with aPDT. An efficient antibacterial photo-activity causing 99.99992% (6.1 $\log_{10}$) and 97.75% (1.6 $\log_{10}$) reduction in the viability of *Staphylococcus saprophyticus subsp. bovis* and *Escherichia coli* DH5 alpha respectively. The antibacterial photo-activity was only around 80% (6.1 $\log_{10}$) compared to the control (curcumin alone) for aPDT. Since nanoparticles exhibited mechanisms leading to higher permeability by directly interacting with the bacterial cell wall and disrupting its three-dimensional organization, thereby increasing the uptake of photosensitizer (curcumin), and enhancing the aPDT efficacy [16]. Pourhajibagher M et al. indicated the antibacterial properties of nano-curcumin (nCur) reinforced with aPDT. 5% of nCur serves as an excellent Activa BioActive Base/Liner (ABBL) additive in aPDT producer against *S. mutans* biofilms up to 60 days of the ageing period [17]. Trigo Gutierrez JK et al. reported curcumin in polymeric nanoparticles (NP) has a higher antimicrobial photodynamic effect for planktonic cultures than biofilms [18].

Curcumin acts as a PS and an antiviral agent against SARS-CoV-2. It inhibited the 3C-like protease ($3CL^{pro}$), and inhibition of ACE II receptor for its virus self-replication. The nanotechnology approach enhances the solubility of curcumin [19]. This is expected that nano-curcumin is more effective to target SARS-CoV-2 when PDT is applied.

All of the information demonstrates that nanotechnology with traditional Chinese medicine (TCM) is suitable for photodynamic therapy (PDT)

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against SARS-CoV-2. Does it depend on which photosensitizers (PS) do you use? Curcumin is the best choice in TCM because it is natural and non-toxic. Nanotechnology improves the physical features of curcumin and enhances its therapeutic efficacy. However, much more work needs to be done, such as the dosage and safety assessment of the nano-curcumin for PDT in humans.

Author contributions

All authors contributed to the concept, acquisition, and analysis of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content which was approved as a final version for publication.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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