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REVIEW ARTICLE

Light-related activities of metal-based nanoparticles and their implications on dermatological treatment

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Abstract

Metal-based nanoparticles (MNPs) represent an emerging class of materials that have attracted enormous attention in many fields. By comparison with other biomaterials, MNPs own unique optical properties which make them a potential alternative to conventional therapeutic agents in medical applications. Especially, owing to the easy access to the skin, the use of MNPs based on their optical properties has gained importance for the treatment of a variety of skin diseases. This review provides an insight into the different optical properties of MNPs, including photoprotection, photocatalysis, and photothermal, and highlights their implications in treating skin disorders, with a special emphasis on their use in infection control. Finally, a perspective on the safety concern of MNPs for dermatological use is discussed and analyzed. The information gathered and presented in this review will help the readers have a comprehensive understanding of utilizing the photo-triggered activity of MNPs for the treatment of skin diseases.

Keywords Metal-based nanoparticle · Skin disease · Photoprotection · Photodynamic · Photothermal

Introduction

With the rapid development of nanotechnology, metal-based nanoparticles (MNPs) have emerged as an important kind of nano-materials showing a broad range of biomedical applications, including drug delivery, bio-imaging, tissue engineering, and many more. Generally, they can be fabricated in the form of pure metal nanoparticles, metal oxide nanoparticles, metal-organic frameworks (MOFs), and metal nanocomposites, as shown in Fig. 1. By comparison with other types of nano-materials, these MNPs possess unique physicochemical properties that can be easily tuned via altering their size, shape, surface chemistry, or a combination of these terms. Also, they have the advantages of narrow particle size, great surface area, and relatively long period of stability [1]. Hence, MNPs offer versatile opportunities for various medicinal purposes, and currently, they are extensively being investigated as functional delivery systems for drug targeting, release modulation, and toxicity attenuation, and also as the theranostic system for simultaneous diagnostics and therapy.

Recently, the light-related properties of MNPs have aroused the extensive interest of scientists and technologists owing to their potential use in the light-assisted diagnostics and therapy of diseases [2, 3]. As an external stimulus, light is more controllable in terms of its wavelength, intensity, as well as illumination area. According to the wavelength, the typical illuminants can be classified into the ultraviolet (UV) light (200~400 nm), visible (VIS) light (400~700 nm), and near-infrared (NIR) light (700~1000 nm), wherein the UV light can be further divided into UVA (320~400 nm), UVB (290~320 nm), and UVC (200~290 nm) [4, 5]. The MNPs can interact with the full-spectrum light. Particularly, when the particle is smaller than the incident wavelength, the collective oscillation of free electrons around the metallic nanoparticles at the resonant frequency, which is termed the localized surface plasmon resonances (LSPR), is likely to occur. This oscillation decays via both radiative and nonradiative ways, of which the former results in the light

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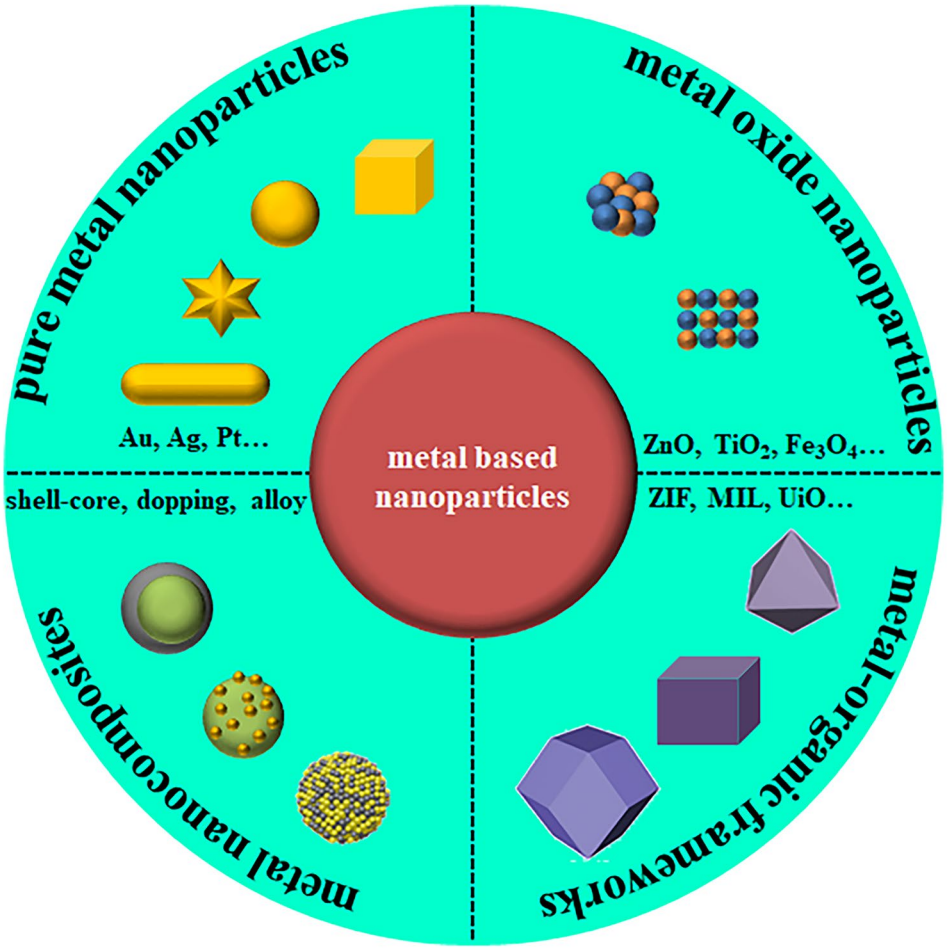

Fig. 1 Four types of common metal-based nanoparticles, including pure metal nanoparticles, metal oxide nanoparticles, metal–organic frameworks, and metal nanocomposites

scattering, and the latter contributes to the conversion of light to heat [6, 7].

Owing to the easy access to the skin, light is an especially appealing tool for use in dermatological treatment. For example, photothermal therapy (PTT) and photodynamic therapy (PDT) are two kinds of emerging methodologies that can be applied locally for the treatment of skin diseases [8, 9]. Due to the different penetration depths within the skin, the light with wavelengths from 300 to 700 nm (UV to VIS light) is often used to treat superficial tissue disorders, while the light with longer wavelengths from 750 to 1100 nm (NIR light) penetrates further and thus is more often used to treatment of deeper-seated tissue diseases [10, 11]. Noted that the UV light has much energy but is also more harmful to the skin, and the NIR light has lower phototoxicity but also less energy [12]. In practice, the therapeutic light wavelength can be adjusted according to actual demand [13]. Most importantly, the advancement of nano-optics and myriads of nanomaterials allow for better exploitation of light-assisted therapy.

Above all, significant progress has been made on designing and using metallic nanomaterials for drug delivery and imaging. However, their intrinsic activity triggered by light should not be ignored. In view of its implication on the pharmacological action of delivery systems, this paper summarized the inherent effects of MNPs commonly involved in light-assisted therapy and discussed their utilization for dermatologic treatment.

Light-related activities of MNPs

Photoprotection activity

Excessive exposure to sunlight, particularly UV radiation, may induce a series of degenerative skin changes, such as sunburn, skin aging, wrinkle formation, and even development of skin cancers, as a result of which the need for photoprotection is of particular significance [14]. Several methods have been recommended to reduce the possible cutaneous

photodamage, and an effective counterpart is the use of sunscreens. Based on the mechanism of action, sunscreens have been divided into two categories, i.e., organic absorbers and inorganic blockers (as shown in Fig. 2). After UV radiation, the organic absorbers produce a reversible transition of energy state, with the release of excess energy, which would cause damage to the skin [15]. By comparison, inorganic blockers offer quite a few advantages, including their chemical inertness, broad-spectrum protection, limited skin penetration, lack of skin sensitization, and little environmental impact [16, 17]. The most common examples of this type are titanium dioxide (TiO_2) and zinc oxide (ZnO), which are both approved by FDA as GRASE (generally recognized as safe and effective) [18]. However, a major drawback of these metal oxide sunscreens lies in their chalky texture and unfavorable appearance on the skin, due to the reflection of visual light. The current era of nanotechnology has led to the development of nano-scaled inorganic sunscreens (< 100 nm) with superior properties which are particularly desirable, such as smooth touch and transparency to VIS. The primary action responsible for their photoprotection has been found to be attributed to the absorption of UV radiation [19, 20].

However, these nanoparticulated metal oxides would become more reactive with the decrease of their particle size due to their photocatalytic activity, which might lead to the generation of free radicals and thus cause concerns about their safety [21]. To bypass this self-derived hazard, two general strategies can be adapted, either by creating defects in their nanostructures to boost the inactivation of excited electrons or by coating these nanoparticles with a chemically stable shell to avoid their direct contact with the skin [22].

In the former case, different metal elements, including aluminum (Al), ferrum (Fe), copper (Cu), cobalt (Co), manganese (Mn), and so on, can all be introduced as dopants to obtain the structural defects that are known as the recombination sites for the production of photoexcited electron–hole pairs. Dao et al. compared the effect of different metal dopants (Al, Fe, Cu) on the photocatalytic activity of the ZnO nanoparticles. The result showed that all the dopped samples could suppress the photocatalytic activity at the atomic concentration of 1%, in which the Al doping represented a promising candidate due to its VIS transparency, whereas the Fe and Cu doping could strongly increase the VIS absorption [23]. In the following study, it was revealed that the photocatalytic activity of the Al-doped ZnO nanoparticles was greatly decreased with the Al contents, and almost disappeared when the concertation was raised to 3% [24].

In the latter case, a biologically inert thin layer is usually introduced to modify the surface of metal oxide nanoparticles to minimize their skin contact for deactivating the photocatalytic activity. It can be prepared from inorganic materials, such as silica and alumina, or organic polymers like poly (methyl acrylic acid) (PMAA). It was suggested

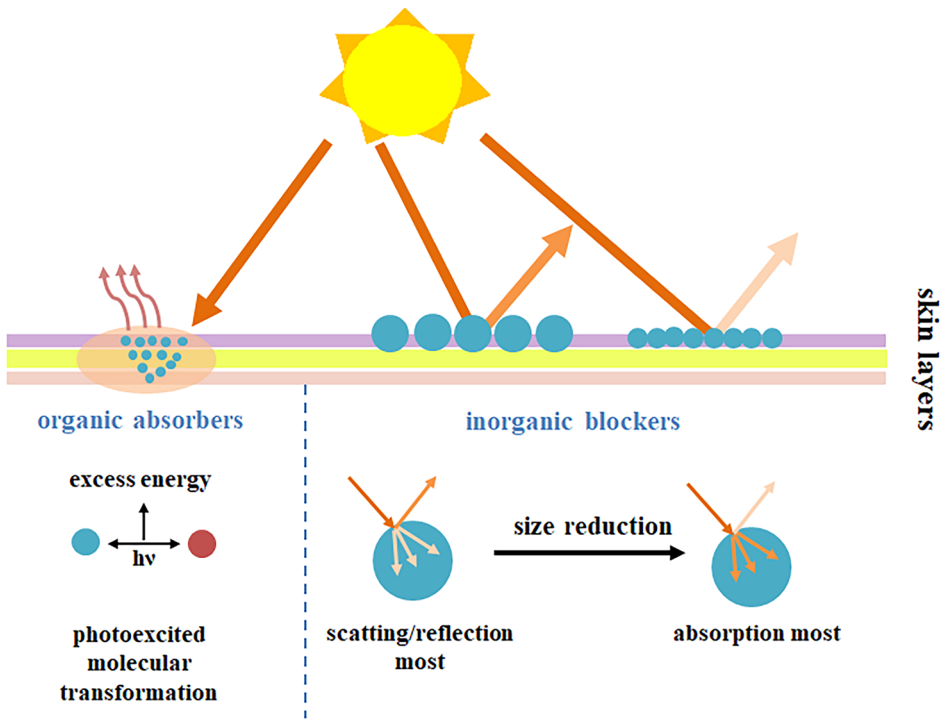

Fig. 2 Mechanisms of organic absorbers and inorganic blockers. For organic absorbers, they could produce a reversible transition of energy state with the release of excess energy which would cause damage to the skin. For inorganic blockers, the larger ones could protect skin against light radiation mainly via light reflection or scattering, while the smaller ones (e.g., < 100 nm) could play their role mainly through light absorption

that the PMAA-coated ZnO nanoparticles owned superior biocompatibility towards human lymphoblastoid cells than those coated with SiO_2 [25]. Barbosa et al. employed an ultrafast sonochemistry method to modify the surface of TiO_2 particles with different coating agents, including silica, alumina, zirconia, as well as sodium polyacrylate. All these coated particles exhibited lower photocatalytic activity than the original TiO_2 particles without a change of UV-shielding ability [26].

In addition to ZnO and TiO_2, other metals or their oxides have been also exploited for their potential use in photoprotection. It was demonstrated that silver (Ag) nanoparticles could not only provide an intermediate effect against UVB irradiation that was calculated based on sun protection factor but also effectively protect human immortalized keratinocytes from DNA damage, whereas the ZnO and TiO_2 nanoparticles promote this process instead [27]. Besides, cerium oxide (CeO_2) nanoparticles have been also proposed as advanced inorganic UV filters [28]. Due to the redox switch of Ce^{3+} and Ce^{4+} in the oxide, CeO_2 nanoparticles acted as biological antioxidants that could protect cells from the damage associated with the photocatalytic effect [29].

Photodynamic activity

PDT is a kind of light-based modality, in which the administrated photosensitizer is activated by light at a specific wavelength to generate reactive oxygen species (ROS) that can destroy pathogenic tissues, cells, or microbes in the presence of oxygen [30]. During this process, the photosensitizer would first go from its ground state (PS) to a short-lived singlet excited state (^{1}PS), and then subsequently turn to a more stable excited triplet state (^{3}PS) through an intersystem crossing. This excited triplet state of the photosensitizer allows it to react in two ways to produce different ROS, i.e., type I and type II reactions, as shown in Fig. 3. In type I reaction, the photosensitizer interacts with adjacent biomolecules via transferring electrons or protons, and forms an intermediate radical anion ($^3PS^{\bullet-}$) which can further react with the ground state oxygen ($^3O_2$) to produce superoxide anion ($O_2^{\bullet-}$). After dismutation by superoxide dismutase or one-electron reduction, the $O_2^{\bullet-}$ can be transformed into hydrogen peroxide (H_2O_2). The obtained H_2O_2 can react with $O_2^{\bullet-}$ and metal ions (e.g., iron) respectively via the Haber–Weiss reaction and Fenton reaction to form the hydroxyl radical (OH•). In type II reaction, the activated photosensitizer can react directly with the ground state oxygen to form singlet oxygen ($^1O_2$). After the reaction, the photosensitizer would return to its ground singlet state for the next series of photochemical reactions [31–33]. In most cases, the type II reaction, namely generation of $^1O_2$, was believed to play a predominant role in PDT [30, 34, 35].

Traditionally, photosensitizers are a group of organic molecules, mainly including porphyrin and its derivatives [36, 37]. However, they might suffer from a few limitations for application, including weak absorption of light, poor photostability, low selectivity towards target tissues, and high toxicity. In this regard, a variety of nanosystems have been introduced to enhance or maintain their activity. Since the phenomenon known as metal-enhanced $^1O_2$ generation (MEO) has been well documented by many studies [38, 39], metallic nanostructures show great potential for use as delivery carriers and as enhancers for photosensitizers [40, 41]. For example, Zhang et al. incorporated the photosensitizer 5-aminolevulinic acid into ethosome vesicles containing gold (Au) nanoparticles for photodynamic therapy of hypertrophic scars via transdermal administration. It was suggested that the Au nanoparticles might penetrate the hypertrophic scar tissue together with 5-aminolevulinic acid, and enhance the ROS production via a localized surface plasmon resonance under a 632 nm laser irradiation [42]. Wang et al. developed a hybrid photosensitizer using the photosensitizing agent hematoporphyrin IX and the Ag nanoparticle which could be encapsulated by a mesoporous silica shell for loading the photosensitizer and facilitating

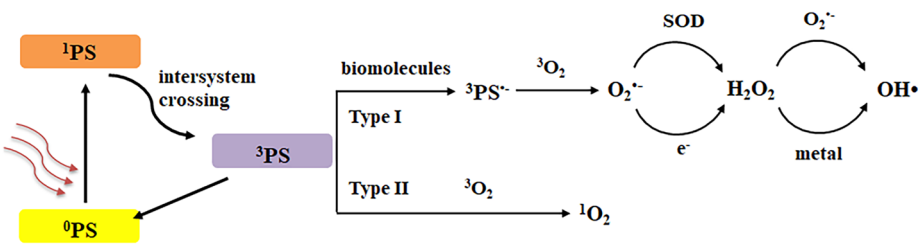

Fig. 3 The possible mechanism of PDT. Once upon light absorption, the photosensitizer at its ground state (PS) first reaches a short-lived singlet excited state (^{1}PS) and then transfers into a relatively stable excited triplet state (^{3}PS). In the presence of oxygen, either type I or type II would take place to produce different types of ROS

its interaction with the Ag. The as-prepared photosensitizing system revealed great improvement in the generation of the singlet oxygen with a portable low-power LED as the light source and displayed an effective effect for treatment on both *Staph epidermidis* and *Propionibacterium acnes* [43].

More recently, the development of novel photosensitizers based on the photoactivated biological activity of MNPs has attracted increasing attention. MOFs formed by metal ions and organic ligand via coordination bonds represent such a kind of novel nanophotosensitizers [44]. Their great surface areas and porosity facilitate the $^1O_2$ generation and the subsequent transportation. As a type of photosensitizer frequently used in PDT, porphyrins were initially used as the organic ligands for exploring the nanophotosensitizers based on MOFs [45]. To improve the penetration of light within the material, ultrathin 2D MOF nanosheets were developed, which showed a potent effect on $^1O_2$ generation under VIS irritation due to the reduction of material thickness [46]. In addition, chlorins or bacteriochlorins, derivatives of porphyrin with hydrogenation of one or two pyrrole rings, can be introduced into the structures of MOFs to achieve the absorption of red light [45]. Furthermore, doping other metals into MOFs can be also employed to improve their photocatalytic performance. For example, Han et al. introduced a moderate amount of Cu^{2+} into the porphyrin ring of porphyrinic zirconium (Zr) MOF, PCN 224 which showed good biocompatibility and chemical stability. Due to the trap of generated electrons and the consequent suppression of the electron–hole recombination, the photocatalytic property of the Cu^{2+}-MOFs was enhanced unless over dopped, and it exhibited efficient bactericidal ability and accelerated wound healing effect [47].

Nobel metal nanoparticles, such as Au [48], Ag [49], and rhodium (Rh) [50], have been also explored for their utilization as photosensitizers, owing to their unique optoelectronic properties, such as the long lifetime of the electronically excited state, and the photothermal effect on $^1O_2$ production. Among these metals, the Ag nanoparticles are relatively more frequently used in composition with organic photosensitizers to enhance their $^1O_2$ generation efficiency via the plasmon-molecular resonance interaction. For example, it was demonstrated that the Ag nanoparticles could enhance the ROS generation of the photosensitizer, and simultaneously it could be activated to promote the release of Ag ions, both of which resulted in remarkable antimicrobial efficacy and wound healing effect [51]. By contrast, the naked Au nanoparticles were shown to produce ROS especially $^1O_2$ under light irradiation with a wavelength of 532 nm [48]. Such enhancement effect on $^1O_2$ generation was observed with the Au nanoclusters under visual or NIR irradiation [52]. For switching the in vivo behavior of the Au nanoparticles and preventing possible agglomeration, they can be modified with capping albumin or ligands [53, 54]. To further enhance the activity for PDT application, bimetallic nanoparticles, such as Au-platinum (Pt) [55] and Rh-Pt [56], can be developed with high photosensitive efficacy. For example, a kind of 2-photo photosensitizer was developed based on multiple ruthenium (Ru)(II) complexes and Pt(II) building blocks, which revealed enhanced ROS generation, selective transportation, and NIR luminescence [56, 57].

As mentioned previously, ZnO and TiO_2 own photocatalytic activity, and this property makes them also promising candidates for use as nano-photosensitizers. However, they usually display a phototoxic effect with UV light activation [58], which brings to the unavoidable detriment to healthy tissues. To make them effective under the light in the NIR region which is preferable in practical use and offers deeper penetration into tissues, novel metal nanoparticles with absorption in these ranges are usually used in combination with them to develop useful nano-photosensitizers [59]. For example, Au nanoclusters were introduced into the TiO_2 nanoparticles as a small band-gap semiconductor to improve the light absorption in the VIS/NIR region. To boost the separation of electron–hole pairs, the nanocomposite could be further combined with graphene, and this heterogeneous nanocomposite showed effective use of simulated sunlight, as well as the photodynamic effect on melanoma skin cancer in vitro at the cellular level and in mice [60].

Photothermal activity

PTT is a photo-based treatment modality that utililizes localized hyperthermia generated from photothermal transduction agents under optical radiation to cause the death of diseased cells or tissues [61]. Because of its little invasiveness, remote controllability, high efficacy, and minimal drug resistance, PTT has attracted intensive attention, especially in the treatment of dermatological disorders. In PTT, NIR light with a wavelength ranging between 650 and 980 nm is preferred to be used due to its tissue permeability. Effective photothermal agents should be designed to have good optical absorption capacity, high specificity towards the site of interest, good photo-stability, easy processability, and low cost [62, 63]. So far, there have been a great variety of materials proposed for this use, among which MNPs represent one kind of popular and competitive alternative because of their excellent and tunable photothermal conversion ability [64, 65]. The LSPR effect, as shown in Fig. 4, is the main cause of the photothermal effect of MNPs. Through

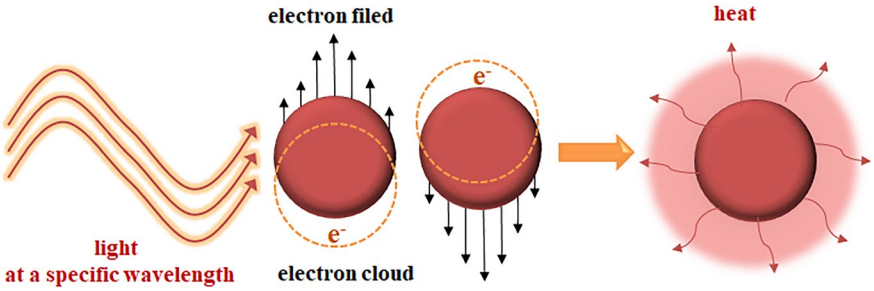

Fig. 4 LSPR of MNPs and its effect on photothermal effect. When the light at a specific wavelength was absorbed by MNPs, the collective oscillation of the electron cloud at the surface can convert light energy into heat for PTT

the electron-magnetic interaction between the metal and incident light at a specific wavelength, the collective oscillation of surface electrons occurs, which converts light energy into heat in picoseconds [66, 67]. Novel metals, especially Au nanoparticles, have been widely explored for the much enhanced LSPR response and their application in photothermal therapy [68, 69].

The photothermal conversion efficiency of Au nanoparticles is closely dependent on their particle properties, including shape, size, and surface property [70]. According to the classical theory of diffusive heat transport (Fourier's law), the temperature elevation induced by Au nanoparticles is proportional to their surface area [71]. In general, the Au nanospheres displayed relatively poor photothermal conversion ability, while elongated or sharp Au nanoparticles such as nanorods, nanostars, and nanoflowers, showed better photothermal efficiency [72–74]. For a given kind of Au nanoparticles with the same shape, larger ones would produce more heat than smaller ones [71, 75], but a further increase in particle size might result in the decrease in photothermal ability [76]. In addition, the LSPR position regarding the excitation wavelength of Au nanoparticles can be also changed with different geometry [73, 74]. Therefore, the photothermal effect of Au nanoparticles can be easily tuned by altering their structures to satisfy the clinical treatment. Commonly, a minimum of 4 °C of temperature elevation is required for local tumor tissues to cause oxidative damage [71]. Meanwhile, these particle factors might also affect cellular uptake and drug delivery behaviors, which would not be ignored in the optimization of the photothermal properties [72, 73]. The photothermal stability of Au nanoparticles should be also taken into consideration during their application in PTT, because the generated heat may destroy their nanostructure, which can affect the photothermal effect in turn [77–79]. To address this issue, the surface of Au nanoparticles can be modified with a series of polymeric materials, such as polydopamine [77] and hyaluronic acid [78], for improvement of their colloidal stability, as well as delivery performance.

In addition, bimetallic nanoparticles have been also developed to optimize the photothermal properties of MNPs, including photothermal conversion efficiency [80], tunable LSPR [81], as well as photothermal stability [82]. As the two most commonly investigated plasmonic materials, Au and Ag are being widely used for the construction of bimetallic nanostructures, which can provide photothermal properties tailored to specific applications. Generally, Ag nanoparticles may produce a stronger LSPR than their Au counterparts, although Au nanoparticles are preferred to be used in PTT [82, 83]. For Ag nanoparticles, their LSPR wavelengths are shorter, and plasmonic absorption bands are narrower and more symmetric [84]. In addition, the stability of Ag nanoparticles is relatively low [82, 85]. For achieving intermediary optical features, Au nanoparticles and Ag nanoparticles can be used in combination in two ways, i.e., alloy and core–shell. It was found that for spherical alloy nanoparticles, the LSPR bands produced a proportional shift in response to the change of composition, which was not observed with core–shell nanoparticles. For anisotropic nanoparticles (e.g., nanorods and nanotriangles), the addition of Au shell to the Ag nanorods and nanotriangles only resulted in the shift of the plasmon band, without much affecting the LSPR absorption. When the Au was added in the form of alloy, the LSPR absorption was remarkably reduced instead, and the band shift was not proportionate to the change of alloy composition [84]. In addition to Au–Ag nanoparticles, other bimetallic nanocomposites have been also exploited for satisfying different requirements of PTT, such as Au-Pt [86], Au-bismuth (Bi) [87], palladium (Pd)-Pt [88], Fe-Pd [89], MOF-Au [90], and so on.

Implication on dermatological treatment

Infection control

There have been several types of metal and metal oxide nanoparticles demonstrated for their antimicrobial efficiency, such as those developed based on Ag, Cu, ZnO, TiO_2, CuO, and so on [91, 92]. Specifically, Ag nanoparticles have been considered one of the most widely used agents to treat a series of infectious diseases, due to their

potential antimicrobial capacity against over 650 microorganisms, including bacteria, fungi, and viruses [92, 93]. Compared with traditional antibiotics, they can reduce the bacterial resistance associated with the misuse or the overuse of drugs and antibiotics [94]. Their antibacterial effects could be attributed to two aspects: (1) the toxicity brought by the free metal arising from the dissolution of the metals and (2) oxidative stress and damage by the generated ROS generation from the surface of MNPs [95, 96].

A combined effect of photogenerated ROS has been frequently reported for enhancement of the antimicrobial action of MNPs, although they might exhibit the antibacterial effect as well even without light activation [93, 97], As for different types of metal oxides, it was revealed that under UV irradiation TiO_2 nanoparticles and ZnO nanoparticles could gmyParaenerate three types of ROS ($^{\bullet}OH$, $^1O_2$, and $O_2^{\bullet-}$), while other metal oxides (CeO_2, Al_2O_3, CuO, Fe_2O_3) nanoparticles generated at most two types of ROS [98]. In the case of different single-element MNPs, the Ag nanoparticles, nickel (Ni) nanoparticles, and Au nanoparticles were shown to generate all the three types of ROS, and their antibacterial effect was ranked in the order of the Ag nanoparticles > Ni nanoparticles > Au nanoparticles [99]. The upregulation of ROS would lead to bacteria death via inducing membrane damage and intracellular oxidation [100]. However, the use of UV light is usually limited by its damage to the healthy tissue even at minimal irradiation. Recently, there have been several reports showing the possibility of using VIS light to enhance the antimicrobial effect of MNPs [101–103]. Doping with other metals can modify the photo properties of metal oxide. It was suggested that the Cu and Fe doped ZnO could achieve the VIS light-assisted antimicrobial effect via narrowing the energy bandgap. To address the thermal instability that might be caused by transition metal doping, nitrogen could be co-doped into the metal oxides and thus achieving an enhancement of the antimicrobial effect [102]. Moreover, the heterostructured nanocomposites based on TiO_2-FeS_2 were confirmed to harvest a broad range of light from UV to NIR to generate ROS, which resulted in a superior antibacterial activity [104].

This photo-activity of MNPs for suppression of bacterial infection can play a crucial role in the PDT for chronic wounds. Zhang et al. developed a kind of silver-infused porphyrinic MOF, in which the hyaluronic acid was coated on the surface of Ag ions to provide the controlled release of Ag ions. Under VIS light irradiation, a synergistic antibacterial effect was observed for wound disinfection owing to the released Ag ions and the photo-generated ROS [105]. Especially, the photoactive MOFs have been intensively explored for this use. In a recent study, a rod-like Zn-based porphyrinic MOF was developed as the theranostic nanosystem for chronic wounds. This system could make alterations in fluorescence according to the change of local elevated pH, and thus facilitate the photodynamic inactivation of bacteria in response to the infection status [106]. For expanding the practical use of MOFs, they can be attached to the supporting substrates like electrospun nanofibers to avoid their inconvenient application at the wound site in bulk and powder forms [107, 108].

Currently, a combination of PDT and PTT at different wavelengths is usually proposed to achieve a better efficacy towards bacterial infection in wounds (as shown in Fig. 5). For example, Luo et al. fabricated a core-shell dual MOF using the Prussian blue as a core and a porphyrin-dopped UIO-66-TCPP as a shell, which exerted a photocatalytic effect under a 660-nm NIR, as well as a photothermal effect under 808 nm NIR. Under the dual light illumination for 10 min, this MOF could separately kill about 99% of *Staphylococcus aureus* and *Escherichia coli* [109]. In addition, the copper ion was reported to be incorporated into the porphyrin ring of PCN 224 to improve the photocatalytic property and stimulate angiogenesis during wound healing [110, 111]. Moreover, an appropriate doping quantity of copper ions strengthened the photothermal effect. Under irradiation at one wavelength of 660 nm, the dopped MOFs with 10% copper ion achieved over 99% antibacterial efficacy as opposed to *Staphylococcus aureus* within 20 min [111].

Apart from the antimicrobial effect in the wounds, such photo-excited nanoparticles might also find application in bacterial control for the treatment of other skin diseases, such as acne and skin tumors.

Skin regeneration

Skin regeneration is a critical phase during wound healing for restoring skin functions. Inherently, metallic nanoparticles have the potential to facilitate skin repair and regeneration by promoting stem cell differentiation and cell adhesion, modulating the mechanical properties of dressing materials,

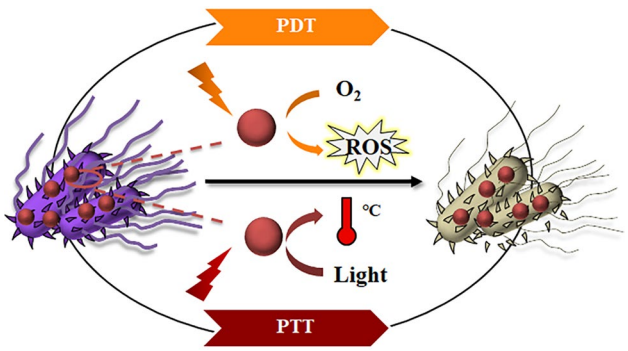

Fig. 5 Combination of PDT and PTT for treatment of bacterial infection. In general, light sources with different wavelengths (e.g., 660 nm and 808 nm) are required for achieving a combined or synergistic efficacy

as well as inhibiting bacterial infection [112]. In addition, their optical properties can be also utilized to produce a synergistic effect on the regeneration process, relying on their photothermal or photodynamic activity.

A temperature-controlled PTT is a potential strategy for accelerating skin regeneration. For example, Xiao et al. developed an ultrasmall CuS@BSA nanoparticle, of which the photothermal effect and the released copper ions could both induce the differentiation of mesenchymal stem cells to fibroblasts and promote the generation of collagen at the wound site, thus synergistically improving the skin regeneration. Note that the temperature should be strictly controlled because over-heating would impede the closure of the wound instead [113]. As a potential photothermal agent, Cu_2S nanoflowers encapsulated in electrospun membranes also displayed a positive activity on tumor-induced skin defects via the bifunction of PTT and skin regeneration effect of copper ions [114]. Also, the CuS nanoparticles incorporated in an injectable hydrogel of the hyaluronic acid were shown to enhance the collagen deposition and the expression of vascular endothelial growth factor, as well as to enhance the angiogenesis for accelerating wound healing in rats under the PTT treatment [115].

Some nanomaterials have been shown to enhance the light-therapy effect on the skin wound, not dependently on the photothermal property. As potential photosensitizers, they can increase the bacterial effect on wound healing [116]. For example, the incorporation of novel metal nanoparticles, e.g., Au nanoparticles, can make MOFs generate more ROS under VIS light irritation for eradicating the bacteria at the wound site [117]. Except for that, the ferrihydrite nanoparticles could also improve the wound healing effect of the blue light therapy both via inhibiting the inflammatory response and promoting angiogenesis, thus enhancing the proliferation of fibroblasts [118].

Anti-tumor effect

The application of PTT and PDT using various types of MNPs is receiving more and more attention for the treatment of skin cancers. In PTT, the heat local heating effect of MNPs could irreversibly damage the membranes and proteins of the cancer cells because of their relatively high susceptibility to heat in comparison with normal cells [119]. For example, the BSA-coated Ag nanoparticles were shown with good photothermal activity and stability in the form of suspensions or formulation into hydrogel films. After topical application, the BSA/Ag nanoparticles loaded with hydrogel films raised the temperature of the tumor region to over 45 ℃ for effective ablation of the tumor [120].

The photo-triggered toxicity of MNPs in PDT makes them also feasible for killing cancer cells. Considering the insufficient skin penetration of the light, inner light luminol was integrated into the photodynamic MOF which was composed of Pd-porphyrin and metal cobalt. Taking advantage of the abundant H_2O_2 in the cancer cells, the inner chemiluminescence resonance energy transfer between the MOF and luminol-H_2O_2 facilitated the production of ROS without the need for external light, which provided much promise for the treatment of deep-seated tumors in the skin [121]. In addition, considering the positive effect of Fe^{2+} on the iron-catalyzed Fenton reaction to generate the intracellular ROS, ferrihydrite nanoparticles could be used as a natural source of Fe^{2+}, which could release the Fe^{2+} under the blue light and enhance the ROS-mediated cancer therapy [122].

More recently, the combination of PDT and PTT for cancer treatment has been increasingly reported. For overcoming the challenge of their respective photo agents and excitation wavelength of the light, Liu et al. developed gold nanoclusters ($Au_{25}(Capt)_{18}$) for the concurrent treatment of cutaneous squamous cell carcinoma using PTT and PDT. Under 808-nm light irradiation, the $^1O_2$ and heat were both generated, which contributed 28.86% and 71.14% of the killing effect on the cancer cells [123].

Dermoprotective activity

Due to the excellent photoprotection effect, MNPs have seen an upsurge in cosmetics use [124]. Generally, they can help the skin from the damage caused by UV. By comparison with the conventional TiO_2 or ZnO, their nanoformulations were shown to significantly improve the sun protection ability [125]. Recently, gold nanoparticles prepared via a green process using plant extracts as reducing agents are receiving attention for dermo protective use. They displayed no toxicity towards human dermal fibroblasts and protected skin cells against the damage from UVA radiation due to their roles as the antioxidant and the free radical scavenger [126].

Challenges of MNPs for dermatological treatment

Although MNPs are increasingly explored for treatments of skin diseases, they are still facing great challenges that limit their translational application. MNPs may have no significant toxicity at therapeutic doses, but their long-term safety remains to be fully explored. Their tiny size, large surface area, and functionalized moieties make them potentially interact with the biological system [127, 128]. In addition, the compromised skin barrier in the diseased state increases opportunities for systemic exposure [129]. Therefore, toxicity may develop from dermal use of MNPs, such as skin sensitization and carcinogenesis, although there is debate as to whether MNPs can penetrate across the intact skin [130]. An over-production of free radicals and ROS, which can cause carbonylation of protein, peroxidation of lipid, damage of DNA, and so on, is accepted as a predominant

mechanism responsible for their toxicity [131, 132]. So far, the toxicity investigations mainly focus on Ag, Au, ZnO, and TiO_2 nanoparticles, while research on other kinds of MNPs is still in the initial stage [133]. Because the toxicity of MNPs may vary with the type of metals, as well as particle size and shape, a complete understanding of the relationship between the toxicity and their structures can be quite beneficial for the associated formulation design and application, which also remains to be especially explored [134, 135]. Since some MNPs are prepared via reduction of their salt precursors, the chemical reducing agents (e.g., $NaBH_4$, hydrazine, and formaldehyde) have also been implicated in their toxicity. Accordingly, green synthesis of MNPs has been proposed to solve this problem, which uses biomolecules such as plant extracts, enzymes, and microorganisms as the alternative reducing agent [136]. As an eco-friendly and cost-effective process, this method can not only reduce the toxicity of MNPs but also impart biological effects, including antimicrobial activity, antioxidant activity, and anticancer activity, as well as wound healing activity [137].

Physical injection represents a commonly used approach for direct administration of MNPs into the skin for dermatological use. While demonstrating the unique delivering efficiency, it can increase toxicity risk, and cause pain and inconvenience for patients. The transdermal route seems to be an appealing alternative to avoid the aforementioned limitations [138, 139]. However, the natural barrier function of the skin undermines the passive delivery of MNPs. To address this issue, physical enhancement devices can be employed as a robust tool to increase the penetration of MNPs to the site of interest within the skin [140, 141]. For example, microneedles and iontophoresis are often used in combination with Au nanoparticles to enhance their local accumulation and treatment effect on skin diseases [142, 143].

During light-assisted treatment, different properties of MNPs may be triggered simultaneously. In some cases, they may induce oppositional functions or adverse effects, while they can be also used in combination for improving disease treatment. Recently, PDT and PTT are attracting increasing interest in the construction of combination therapy platforms, due to their different action mechanisms and synergistic treatment effects [144]. However, it always involves the use of two distinct lasers at different wavelengths [145, 146], which causes treatment compliance and cost. Also, it has been indicated their synergistic effects may be affected by their sequence in application [147]. Therefore, a new challenge in this field is the identification of novel nanomaterials that can respond to the same safe laser to trigger the dual effect of PDT and PTT. To date, there has been an emergence of MNPs for use under a single irradiation laser for the synergistic effect of PDT and PTT [148, 149]. Yet, further efforts are needed to identify more such nanomaterials, as well as to enlarge their application.

In addition, there are other problems remaining to be solved for MNPs, including their biological fate in vivo, structure–activity relationship, controllable design, large-scale production, and so on [150, 151]. They have not achieved their full potential in this field, and more efforts should be made to promote their applications in the clinic.

Conclusion and perspective

In connection with the above, metal-based nano-technology and products provide a promising avenue for light-assisted therapy in dermatology. They can be employed as delivery systems for drugs and diagnostic reagents, and also as therapeutic agents for the management of dermatologic diseases. Their diverse and tailorable structures have proven to be beneficial for achieving customizable treatment options. Yet, their light-related property can be a "double-edged sword," not only offering therapeutic effects but also causing negative impacts for application. It is particularly important to obtain sufficient information about the toxicity of the nanoparticles possibly brought to the skin. Also, the relationship between the structures of metallic nanoparticles and their light-triggered activity waits to be successfully established. The degradation and the elimination of nano-materials from skin also remain to be elucidated. In any case, an integrated approach for light-based therapy and delivery has been provided by the development of MNPs. Boosted by the ongoing progress in nanomaterials and nano-optics, this exciting field may have more implications on the health promotion of dermatosis patients.

Abbreviations MNPs: Metal-based nanoparticles; MOFs: Metal-organic frameworks; UV: Ultraviolet; VIS: Visible; NIR: Near-infrared; LSPR: Localized surface plasmon resonance; PTT: Photothermal therapy; PDT: Photodynamic therapy; GRASE: Generally recognized as safe and effective; PMAA: Poly (methyl acrylic acid); ROS: Reactive oxygen species; MEO: Metal-enhanced $^1O_2$ generation; BSA: Bovine serum albumin; PMAA: Poly (methyl acrylic acid)

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