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ZnO based 0-3D diverse nano-architectures, films and coatings for biomedical applications

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Abstract

Thin-film nano-architecting is a promising approach that controls the properties of nanoscale surfaces to increase their interdisciplinary applications in a variety of fields. In this context, zinc oxide (ZnO)-based various nano-architectures (0–3D) such as quantum dots, nanorods/nanotubes, nanothin films, tetrapods, nanoflowers, hollow structures, etc. have been extensively researched by the scientific community in the past decade. Owing to their unique surface, charge transport, optoelectronic properties, and reported biomedical applications, ZnO has been considered one of the most important futuristic bio-nanomaterials. This review is focused on the design/synthesis and engineering of 0–3D nano-architecture ZnO-based thin films and coatings with tunable characteristics for multifunctional biomedical applications. Although ZnO has been extensively researched, ZnO thin films composed of 0–3D nanoarchitectures with promising thin film device bio-nanotechnology applications have rarely been reviewed. The current review focuses on important details about the technologies used to make ZnO-based thin films, as well as the customization of properties related to bioactivities, characterization, and device fabrication for modern biomedical uses that are relevant. It features biosensing, tissue engineering/wound healing, antibacterial, antiviral, and anticancer activity, as well as biomedical diagnosis and therapy with an emphasis on a better understanding of the mechanisms of action. Eventually, key issues, experimental parameters and factors, open challenges, etc. in thin film device fabrications and applications, and future prospects will be discussed, followed by a summary and conclusion.

Keywords: Thin film technology; Nano-architecting; 0-3D ZnO nanostructures; Nano-biotechnology; biomedical applications.

1. Introduction

In recent years, there has been a significant amount of study dedicated to exploring several types of nanomaterials, such as polymeric materials, metals, and metal oxides, across various research domains including energy, environment, and biomedical applications[1-5]. Nanostructured materials, specifically metal oxides, have demonstrated significant promise in the realm of biomedical applications[6, 7]. This is primarily attributed to their inherent capability for facile nano-patterning/structuring and modification, resulting in alterations to their structural, optical, electrical, magnetic, and morphological properties [8-10]. Among various metal oxide nanostructure materials, an extensive study has been carried out on fabrication and modification of ZnO nanostructures (ZNSs). These ZNSs have been tailored [11-13] in view of their multifunctional applications including solar cells, light emitting diodes, field emission, gas sensors, biosensors, thin protecting films, drug delivery, photodegradation etc.[14-18]. Moreover, due to promising intrinsic properties i.e., viability, bio-acceptability, high isoelectric point, tunable morphology, etc. ZNSs are found suitable for various biomedical applications such as antimicrobial, biosensing, bioimaging, drug delivery, anticancer, diagnosis, wound healing treatment etc.[8, 19-21]. More specifically, ZNSs have been extensively investigated in biomedical applications due to their biocompatibility and ease of tailoring their optical, electrical, structural, and morphological properties[22-24].

Interestingly, various dimensions of ZNSs such as zero dimension (0D), one dimension (1D), two dimension (2D) and three dimension (3D), have been investigated due to their unique surface properties as well as morphological dissimilarity. Furthermore, ZNSs display intriguing electrical properties because of their typical n-type conductivity, which results from a variety of defects, and primarily oxygen vacancies [25]. Additionally, the direct bandgap of 3.37 eV allows ZnO to effectively absorb UV light which extend upto the visible regions through surface modifications and engineering nano-architectures [26-28]. An electronic device can effectively be employed for a variety of sensing purposes due to both features, n-type conductivity, and UV-sensitive bandgap, if it can be constructed utilizing suitable nano- and microstructures. For example, 1D ZNSs show piezoelectric characteristics because of their non-centrosymmetric crystal structure. Consequently, a device based on 1D ZNSs could be used for a variety of purposes [29, 30]. Such nanostructured materials in form of thin films or coatings are also promising for the development of various

technology. For example, ZNSs have been used to develop biosensors for the detection of a wide range of analytes, including glucose, cholesterol, urea, and cancer markers[31]. The high surface area and unique electronic properties of ZnO nano-architectures make them ideal for detecting and quantifying low concentrations of analytes. For example, a recent study developed a ZnO nanowires (NWs)-based biosensor for the detection of glucose. The biosensor was fabricated by growing ZnO NWs on a microelectrode and then functionalizing them with glucose oxidase. The biosensor was able to detect glucose concentrations as low as 1 μM , and it showed excellent selectivity for glucose over other interferents[32]. Another recent study developed a ZnO nanorods (NRs)-based biosensor for the detection of cancer cells. The biosensor was fabricated by coating ZnO NRs with a layer of antibodies that are specific to cancer cells. The biosensor was able to detect cancer cells with high sensitivity and specificity[33]. ZNSs have also been used to develop scaffolds for tissue engineering applications. The high surface area and biocompatibility of ZnO nano-architectures make them ideal for promoting cell adhesion and proliferation. For example, a recent study developed a ZnO nanofiber (NFs)-based scaffold for bone tissue engineering. The scaffold was fabricated by electrospinning ZnO NFs onto a substrate. The scaffold was able to promote the adhesion and proliferation of osteoblast cells, and it showed good biocompatibility[34]. Another recent study developed a ZnO nanoparticles (NPs)-based scaffold for cartilage tissue engineering. The scaffold was fabricated by mixing ZnO NPs with a hydrogel. It also promoted the adhesion and proliferation of cells showing good biocompatibility. ZnO-based nano-architectures have also been used to develop drug delivery systems [35]. For example, a recent study developed a ZnO NPs-based drug delivery system for the delivery of cancer drugs. The drug delivery system was fabricated by encapsulating cancer drugs in ZnO NPs. The drug delivery system was able to deliver the drugs to cancer cells with high efficiency, and it showed good cytotoxicity against cancer cells. Another recent study developed a ZnO NWs-based drug delivery system for the delivery of genes. The drug delivery system was fabricated by coating ZnO NWs with a layer of DNA. The drug delivery system was able to deliver the genes to cells with high efficiency, and it showed good transfection efficiency[36, 37]. Above discussion shows that ZnO is promising material for multifunctional biomedical application as it provides a better platform with high surface area, biocompatibility, adhesion and unique optoelectronic properties which facilitate the interaction of bio/-molecules leading to the better sensitivity and selectivity in a particular application.

Similarly, in recent past, ZNSs thin films with diverse nano-architectures (0-3D) have gained great attention due to their superior structural stability, optoelectronic properties, and ease of device fabrications. Although ZnO has been researched extensively, however, thin films composed of 0-3D nano-architectures with promising thin film device bio-nanotechnology applications, have rarely been reviewed. For example, several recent published reviews are focused on green synthesis of ZnO materials and biomedical applications [38-44] with major emphasis on eco-friendly approach of green synthesis route. Several reviews are focused on some particular biomedical applications such as antibacterial[45-48], wound healing [49], cancer therapy[40, 48], drug delivery [50], bioimaging [47, 51]etc. Some reviews are focused on ZnO/polymer nanocomposites and their biomedical applications [52, 53]. Weng et al.[54] reported on stimuli-responsive ZnO-based nanomaterials in biomedical applications, whereas, Sun et al. [55] reviewed ZnO based photocatalyst for biomedical applications. This review is intended to comprehensively report on recent advances on the synthesis and engineering technologies involved in ZNSs based 0-3D diverse nano-architectures, thin films growth, coatings, tailoring of their properties, characterization, and device fabrication in addition to the multifunctional biomedical applications. Additionally, recent advancements in the field of biosensing, tissue engineering/wound healing, antimicrobial, antiviral, anticancer activities, biomedical diagnosis, therapy etc. using such ZNSs and thin film device applications with an emphasis on better understanding of the mechanism of actions have been discussed. Finally, various key issues in 0-3D ZNSs based thin film device fabrications and their real practical applications have been discussed followed by prospects and summary.

2. Design and engineering of ZnO thin films with diverse nano-architectures for biotechnology applications

2.1 ZnO thin films

ZnO-based thin films serve a significant role as chemical sensitizers, which have the ability to intelligently react to the relevant changes in the external environment when subjected to external stimuli, hence exerting specialized roles in biomedical application research [30, 56, 57]. Several methods have been reported to produce ZNSs based nano-architectures and thin films/coatings including chemical and physical routes. However, fabricating a thin film with nano-dimension,

high quality and desirable optoelectronic/physiochemical properties still remained a great challenge [57, 58]. It is reported that excellent ZnO thin films with better crystallinity can be prepared by varying the precursor nature[59] and annealing time[60] during the spray pyrolysis deposition method. Similarly, it is reported that ZnO thin films with excellent optoelectronic properties [61] could be fabricated for various applications. For example, Domínguez et al.[30] deposited thin ZnO films on corning glass substrates by ultrasonic spray pyrolysis and used these films as platforms for enteropathogenic E. coli antibody immobilization and detection. During the deposition process, various surface and chemical modifications took place which were studied by atomic force microscopy (AFM) and Fourier transform infrared (FTIR) spectroscopy respectively (Figure 1 a-c). With the help of FTIR spectra after functionalization, changes in amino group (NH_2) derived from silane (3-aminopropyltrimethoxysilane) were studied which provided the signals corresponding to the $\text{C}=\text{O}$ stretching vibrations and $\text{N}-\text{H}$ scissor vibration mode. These signals could be correlated with the presence of antibody immobilized on the ZnO film. The change in the morphology of the ZnO film was monitored at every stage that provided the information of the antibody distribution on the immobilized surface (**Figure 1 d**). Similarly, an ultrasensitive troponin-T biosensor was fabricated by leveraging the zinc termination-based surface chemistry on ZnO thin film for selective protein immobilization. It was shown that ZnO thin film-based biosensor could be tailored for enhanced sensitivity by tuning the fabrication parameters during the synthesis of ZnO film[62]. Cao et al.[57] demonstrated the preparation of highly ordered and uniform nano-crystalline ZnO thin films based sensor surfaces on polyethylene terephthalate (PET) using colloidal dispersion technique as shown in **Figure 1 e-f**. These ZnO thin films were characterized by means of impedance spectroscopy which confirmed high reproducibility of the films for C-reactive protein detection.

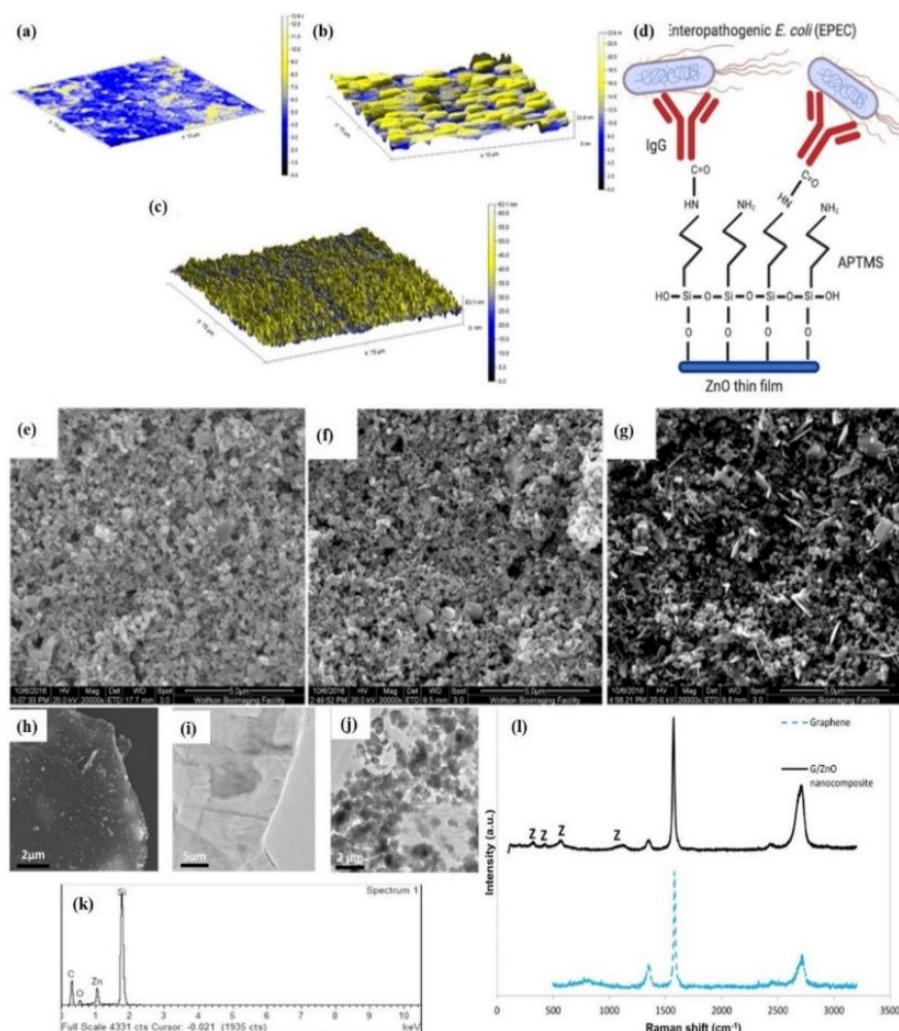


Figure 1: AFM images of the (a) ZnO thin film, (b) after functionalization, and (c) after the immobilization process (d) schematic of the same. Adopted from Ref. [30]. SEM images for ZnO nano-surfaces on PET via suspensions at different amounts of ZnO nano-crystals: (e) 5% ZnO; (f) 1% ZnO; (g) 0.5% ZnO. Adopted from Ref. [57]. ZnO-graphene nanocomposite (h) SEM and TEM images of (i) graphene, (j) ZnO-graphene nanocomposite, (k) EDAX analysis (l) Raman spectra. Reproduced from Ref. [63] with permission from [Elsevier], copyright [2015].

A ZnO thin film transistor based biosensor was developed by Chakraborty et al.[56] by depositing ZnO on SiO₂ using sol-gel technique. It was used for biomolecule detection in complex analytes like serum. In a similar work, it was found that thickness of active layer plays a major role in the electrical performance [64]. 2D graphene based NSs have been recently paid much attention to enhance the various optical, electrical properties of semiconductors for advanced energy, environmental and biomedical applications [65-69]. Particularly, nanocomposites with graphene nanostructures have extensively been studied [70, 71]. For example, ZnO-graphene nanocomposite films were grown on screen-printed carbon electrode (SPCE) for DNA sensing for

the detection of Avian Influenza H5 gene[63]. The morphology of the nanocomposites was investigated by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) as shown in **Figure 1 (h-k)**. It was observed that ZnO NPs of around 200 nm were attached and uniformly distributed onto the surface of the graphene sheet which was also confirmed by EDAX analysis. TEM exhibited the transparent nature of the graphene sheet indicating the exfoliation of graphite into the thin sheets along with the attached ZnO NPs on the graphene sheets. Similarly, Raman spectra also exhibited the growth of ZnO NPs on the graphene sheet as shown by z in the **Figure 1 (l)** which is evidenced by the presence of the peak at $\sim 432\text{ cm}^{-1}$ correspond to the E_2 mode of ZnO wurtzite structure and shift in the D/G/2D bands of graphene structures at $\sim 1349\text{ cm}^{-1}/\sim 1574\text{ cm}^{-1}/\sim 2717\text{ cm}^{-1}$ respectively. The ZnO based nanocomposite film on SPCE showed excellent electrocatalytic activity due to better electrical conductivity of graphene and good electroactive property of ZnO resulting in the enhanced electrochemical DNA biosensor.

Above discussion suggests that ZnO based thin films could be synthesized with tunable optoelectronic and physiochemical properties for biomedical applications in different fields. Along with this, it is suggested that ZnO thin films could be fabricated following several deposition techniques with excellent surface properties compatible with low-cost electronics.

2.2 1D ZnO nanostructured thin films

1D NSs have been extensively studied due to their unique physical, structural, and optoelectronic properties and their applications in fabricating nanoscale devices. It includes generally large aspect ratio (AR i.e. length to width), NRs, NWs, NFs, nanobelts (NB), nanotubes (NTs) etc. Such 1D NSs exhibit large surface-to-volume ratio and quantum confinement with excellent electronic, magnetic, and optical properties useful for various applications in energy, environment and biomedical fields[72]. Particularly, 1D ZNSs have attracted the scientific community because of their various 1D morphologies and greater surface area, and confinement in the radial direction which make 1D ZNSs more valuable than other morphologies [73, 74].

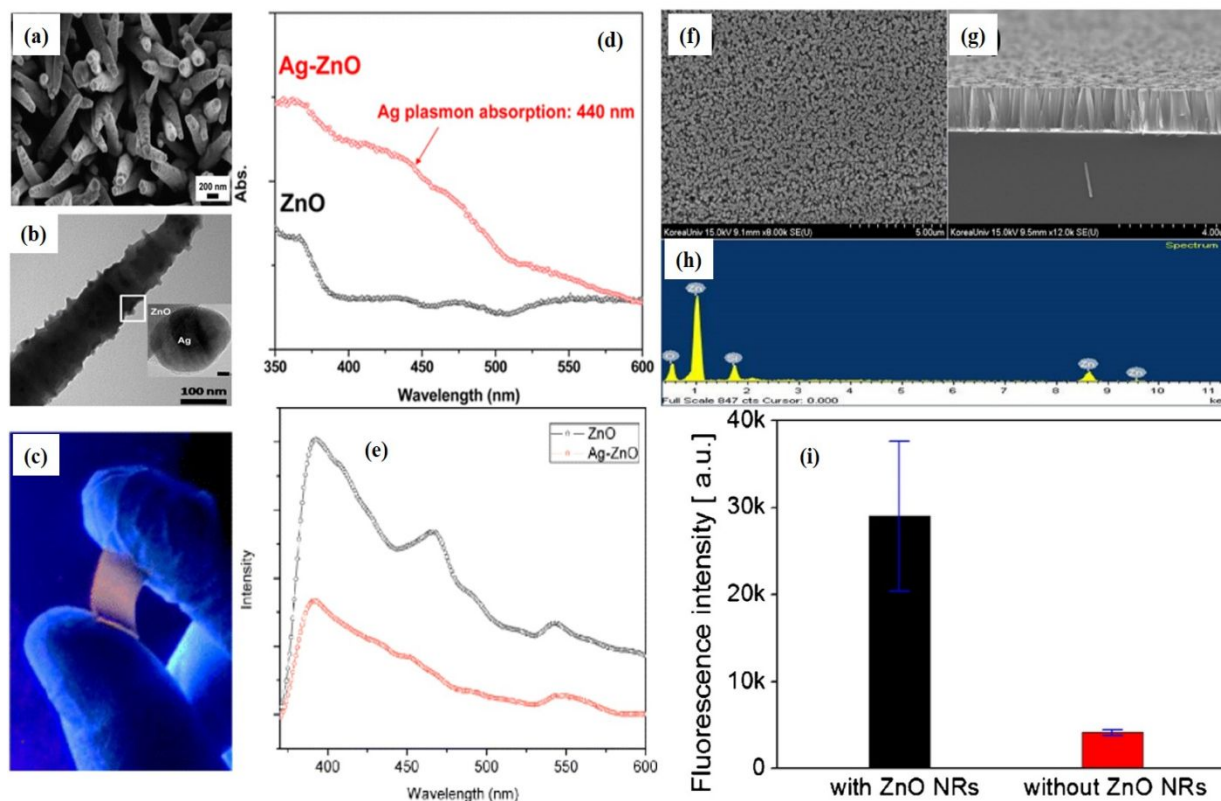


Figure 2: (a) Field emission (FE)-SEM image of Ag-ZnO NRs array on PDMS, (b) TEM image of Ag-ZnO NRs, inset small image is the HRTEM micrograph of Ag-ZnO interface with 5 nm scan bar (c) A photo of the flexible Ag-ZnO NRs array on PDMS taken under a UV lamp (120 V/60 Hz Fisher). (d) UV-visible spectra of ZnO and Ag-ZnO NRs arrays on PDMS. (e) PL spectra of ZnO and Ag-ZnO heterostructured NRs arrays on PDMS. Adopted from Ref. [75]. SEM images and EDX result of the ZnO NRs grown on the PDMS sensor region by hydrothermal method. (f) Top view, (g) cross section view, (h) EDX result, and (i) comparison of the fluorescence intensity due to the presence of ZnO NRs on the PDMS surface. Reproduced from Ref. [76] with permission from [Elsevier], copyright [2015].

ZnO Nanorods

NRs are 1D rod like nanostructures with AR of 1-10 and diameter of around 1-100 nm.[77] Several strategies have been reported to enhance the optical, electrical, morphological and transport properties of 1D ZNSs in NRs forms for multifunctional applications. Recently, Sun et al.[78] demonstrated the fabrication of Bi doped ZnO NRs array and studied their optoelectronic and photoelectric properties. It was found that with 5% Bi doping, the fluorescence intensity was the lowest as compared to undoped ZnO and other Bi doped ZnO, illustrating that the carrier recombination rate was the lowest in 5% Bi doped ZnO with enhanced photoelectric catalytic effect. Like doping[79, 80], noble metals have shown promising role in enhancing the various optical and transport properties of functional NSs due to their unique plasmonic properties [81-

86]. Various ZnO based plasmonic ZNSs have been studied for their potential applications in the variety of fields because of their recyclability [87, 88]. Embedding or coupling of such ZNSs with polymeric materials provide additional characteristics for potential practical applications [89-91]. Chen et al.[75] demonstrated the fabrication of 1D Ag-ZnO NRs array vertically grown on flexible polydimethylsiloxane (PDMS) through a hydrothermal method followed by an in situ deposition of Ag NPs via a photoreduction process as shown in **Figure 2 (a-c)**. These 1D Ag-ZnO heterostructured NRs were found to be of 160 nm diameter and of length around 2 μm along with deposited Ag NPs of size around 22 nm. It was found that these heterostructured Ag-ZnO NRs exhibited better UV-visible absorption properties as compared to the ZnO NRs with an emission in the visible region at wavelength of 542 nm as shown in **Figure 2 (d-e)**. The photoluminescence (PL) spectra of ZnO and Ag-ZnO NR array on flexible PDMS showed near UV emission around 390 nm corresponding to the near band edge (NBE) emission of ZnO, a blue emission around 466 nm along with a broad green emission peak around 542 nm attributed to the oxygen/zinc vacancies and interstitials. Decrease in PL intensity of ZnO was observed after Ag NPs deposition. It was attributed to the inhibition of electron hole recombination due to the presence of Ag NPs acting as electron sink. These hybrid 1D ZNSs showed excellent antimicrobial efficiency as compared to the bare ZnO NRs array. Han et al. [76] reported a multi-detectable and nano-flow immunosensor based on ZnO NRs thin film fabrication on PDMS surface using hydrothermal method. **Figure 2 (f-h)** shows SEM micrograph and cross section image of the produced ZnO NRs along with EDX. It indicates the uniform deposition of ZnO NRs of diameter 100–130 nm and length 1.5 μm on PDMS sensor region. It was reported that ZnO NRs with high surface area and bonding site were capable of capturing antibodies contributing to signal amplification. It was studied by investigating fluorescence spectra of the ZnO NRs after coating with FITC-IgG and its effect on signal amplification as shown in **Figure 2 (i)**. It was found that fluorescence intensity of the PDMS with ZnO NRs coated with antibodies increased by 6 times higher as compared to that of the PDMS without ZnO NRs attributed to the capability of ZnO of immobilized capture antibodies. The results indicate that ZnO NRs thin film grown on PDMS surface improves the sensitivity of the immunosensor attributed to the enhanced PL properties. The immunosensor was used for the sensing of H1N1, H5N1, and H7N9 influenza viruses simultaneously using electrochemical method[76]. Similarly, an immunosensor made by depositing patterned ZnO NRs networks was reported for detection of H1N1 swine influenza virus[92].

ZnO Nanowires

NWs are similar to NRs in diameters of a few to tens of nanometers, however, their lengths are not limited i.e. may vary from nm to μm and aspect ratio is high as compared to NRs[77]. Wu et al.[93] fabricated ZnO NWs decorated with ZnO quantum dots (QDs) exhibiting highly antibacterial activities under visible-light irradiation and dark conditions. ZnO QDs (3–5 nm) deposited on ZnO NWs (length around 2–3 μm) were synthesized by varying the chemical reaction time using oil-bath (silicon oil) chemical reaction process. It was found that ZnO NWs/QDs synthesized at greater time (30 min) exhibited smoother surface because of agglomeration of QDs forming irregular surfaces. The PL study revealed that the ZnO NWs/QDs synthesized at lowest reaction time (5 min) showed lower recombination rate due to the production of defect-related trapping centers on their surface which was also confirmed by X-ray photoelectron spectroscopy (XPS) study resulting in highest antibacterial activities. Similarly, a heterojunction of $\text{Ag}_x\text{Zn}_{1-x}\text{O}$ –ZnO NWs was developed using an UV decomposition process with an excellent antibacterial activity under visible light and dark conditions[94]. It was proposed that these NWs embedded in a flexible and transparent PDMS film could be useful for antibacterial touch screen applications.

Singh et al.[95] demonstrated that coating of ZnO NWs on various substrate such as glass, silicon, quartz, PDMS polymers, could develop hydrophobic surfaces useful for various biomedical applications. The modification of these substrates by a biocompatible durable and water-resistant ZnO material was studied by contact angle (CA) measurement using blood droplet of ethylenediaminetetraacetic acid (EDTA) anticoagulated whole blood (EDTA-WB) as shown in **Figure 3 (a-b)**. A great variation was found on CA on different surfaces. SEM image of ZnO NWs coated on Si surface is shown in **Figure 3 (c)**. Finally, the change in CA of EDTA-WB on these substrates before and after ZnO NWs coating was investigated as shown in **Figure 3 (d)**. Interestingly, ZnO NWs coating turned hydrophilic surfaces into hydrophobic for EDTA-WB. It was concluded that developing such ZnO based biomaterials surfaces for EDTA-WB could be very useful for various applications in medical sciences, like in the field of biosensors, transducers, corrosion resistance, liquid transportation, micro-fluidic systems, and bioengineering.

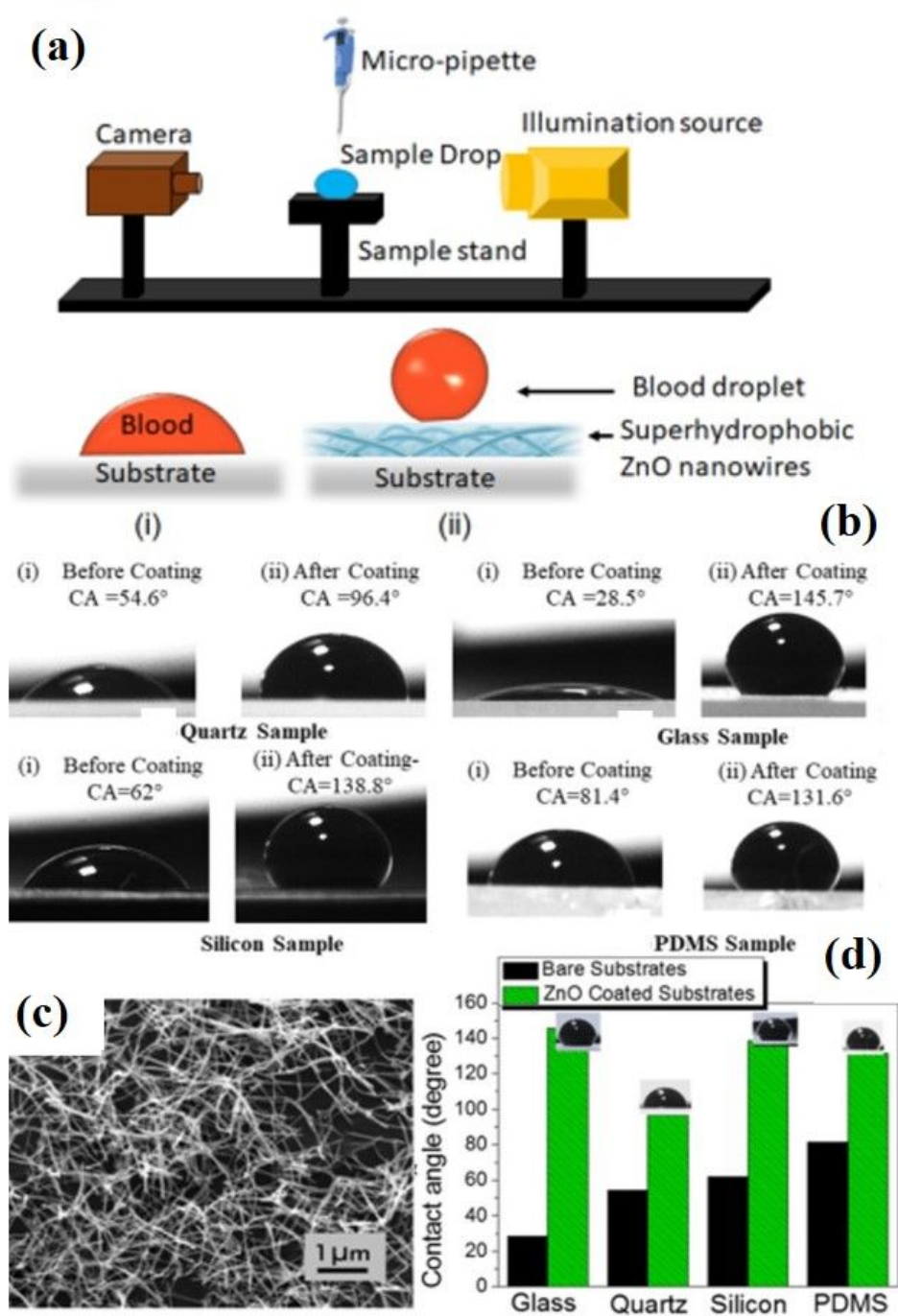


Figure 3: (a) Schematic diagram of the CA measurement setup with a schematic representation of the variation in CA on the outer surface of the substrate (i) before ZnO nanowires coating and (ii) after ZnO nanowires coating for decreased blood wettability. (b) CA on various substrates before and after ZnO NWs coating: quartz, glass, silicon, PDMS substrates. (c) SEM image of ZnO NWs-coated on Si substrate (d) CA of EDTA-WB on various substrates before and after ZnO nanowires coating. Reproduced from Ref. [95] with permission from [Springer Nature], copyright [2018].

In preparation of ZnO NWs based biosensors, the bonding between the ZnO surface and biomolecules is very important[96]. Ciofani et al.[97] demonstrated the adhesion, proliferation and differentiation of mammalian cell lines on ZnO NWs arrays which significantly exhibited the interaction of biomolecules with ZnO NWs. It was found that geometry and size of ZnO NWs could readily be designed in such a way that it could be accessible to the interiors of living cells facilitating the operations of stimulation and sensing.

ZnO NWs were directly synthesized on paper working electrodes through hydrothermal synthesis method to develop electrochemical impedance biosensors for accurate, rapid, and low-cost diagnostics of infectious diseases. It was found that the morphological and electrochemical surface areas of ZnO NWs significantly affect the sensitivity and detection range of developed biosensors[98]. In a study, radially grown ZnO NWs on poly-L-lactic acid (PLLA) microfibers with unique 3D ZNSs has been applied as therapeutic cancer vaccines and that significantly inhibit tumor growth[99]. Similarly, several other ZNSs such as NFs [34, 100] have also been studied for biomedical applications.

As discussed above, various 1D ZNSs have been developed with excellent optical and surface properties for variety of biomedical applications. Looking at their potential for tailoring their surface and optical properties, such ZNSs can be of a great futuristic materials for advanced biomedical applications.

2.3 Tetrapod ZnO nanostructures based thin films

Tetrapods 3D NSs have received great attention in last decade due to their unique morphology, i.e. four arms connected to one centre [101, 102]. A tetrapod is formed by four 1D NRs including the physio-chemical and optoelectronic properties of NRs providing unique 3D spatial tetrapod geometry, surface structure and hence properties[103]. Such tetrapod networks exhibit excellent electronic properties due to the semiconducting nature of ZnO semiconductor, which is useful in electron extraction and transportation[101]. It has been reported that such tetrapod ZNSs are probably the most important structure from the application point of view in the various fields including biomedical applications. For example, Deip et al. [104] fabricated a flexible and transparent ZnO tetrapods-based polymer nanocomposite thin film using an inverse soft lithography stamping method as shown in **Figure 4 (a-d)**. It was found that the PL properties were not affected even by embedding in a polymer substrate. Interestingly, it was also demonstrated that

when the films were subject to the flexural bending, its optical response was found to be constant over more than 100 cycles exhibiting excellent behavior towards its potential application as a flexible UV-responsive material. It was proposed that such nanocomposite films could be more potentially used in many different applications where mechanical strain may occur. Similarly, Chen et al.[14] fabricated film like tetrapod ZnO NSs i.e. rod–wire junction, dumbbell-like and cone-like as shown in **Figure 4 (e-f)** with excellent PL properties using a vapor oxidation method. These tetrapods ZnO NSs were found to have single crystal hexagonal wurtzite structure. They studied the PL properties of these tetrapod ZnO NSs. The PL study exhibited a strong UV emission (about 380 nm) and three broad green emission peaks, (about 505, 526 and 545 nm) showing good potential for photoluminescent applications as shown in **Figure 4 (g)**. The small blue shift was observed for the nanocone and dumbbell NSs as compared to rod–wire junction NSs was due to the reduced size of those ZnO NSs. These NSs were found to be with larger aspect ratios with defects exhibiting intense UV emissions. They proposed that intense UV emissions of the tetrapod ZnO NSs could be applicable potentially in optoelectronic devices.

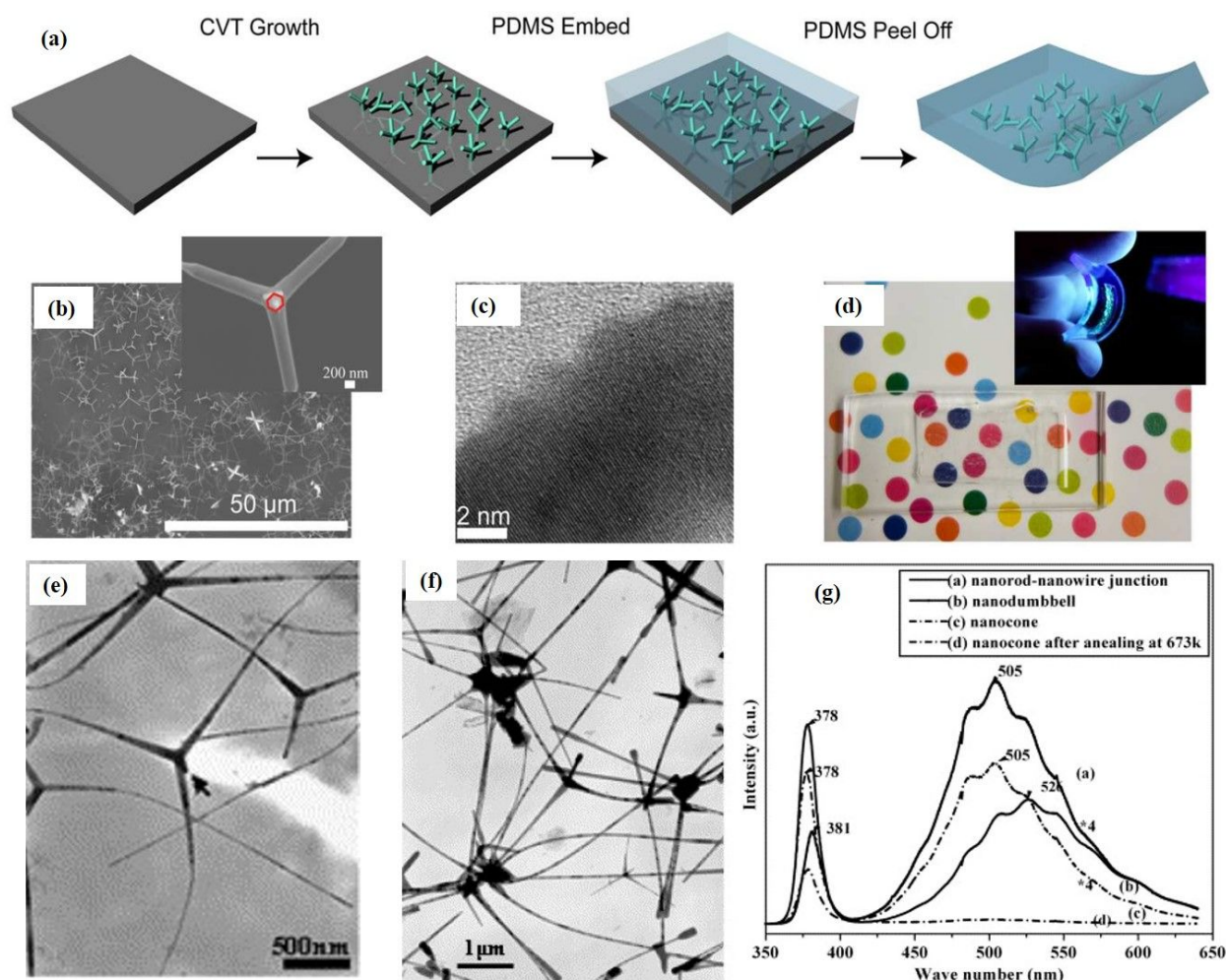


Figure 4: (a) Schematic of the process for fabricating the ZnO NTP-PDMS composite material. (b) Scanning electron microscope image of as-grown ZnO NTP structures on the silicon growth substrate, with hexagonal basal plane of the tetrapod legs visible (inset). (c) Transmission electron microscope image of a nanotetrapod leg shows lattice fringes with spacing 2.6 Å. (d) Photograph of composite material exhibiting transparency and fluorescence under UV light (inset). Reproduced from Ref. [104] with permission from [American Chemical Society], copyright [2016]. TEM images of various tetrapod ZnO nanostructures (e) rod-wire junction, (f) dumbbell-like and (g) their PL spectra. Reproduced from Ref. [14] with permission from [Elsevier], copyright [2006].

Tetrapodal ZnO nanocrystals have also been used for mechanical interlocking of non-adhesive polymers such as PTFE and cross-linked PDMS [105]. It was found that this approach provided was easily applicable leading to the higher peel strength without any chemical modification of the polymeric surfaces attributed to the tetrapod 3D shape of the ZnO nanocrystals (**Figure 5 a**). In a study, a self-reporting tetrapod ZnO embedded silicone elastomer was fabricated, and the stress-induced PL response was investigated to study the applied tensile stress. It was found that applied

tensile stress could be followed in composites with low and high ZnO filler fractions by measuring PL response of ZnO tetrapod nanostructures. It was concluded that the deformation of interlocked ZnO network was important factor for the self-reporting mechanism which could be useful for many applications in variety of research fields (**Figure 5 b**)[106]. Tiginyanu et al. [107] fabricated tetrapods ZNSs film deposited on the surface of aerographite material as shown schematically in **Figure 5 (c-e)** forming a carbon-metal oxide hybrid hierarchical network using magnetron sputtering technique. Such hybrid hierarchical system showed promising PL properties attributed to the carbon impurities and inherent host defects in ZNSs along with broad light absorption from UV to visible extending up to IR region. Such a novel hybrid material with broadband photoabsorption and strong visible light scattering behavior were proposed to be very promising candidates for optoelectronic technologies. Zhao et al.[108] reported a tetrapod ZnO-graphene based nanocomposite foam as a self-powered sensor. Such tetrapod ZnO based foam sensor was able to simultaneously detect light and temperature attributed to the conjuncted photothermoelectric effect. It was found that the output current under light, heating, and cooling of the device with the best ZnO/graphene ratio (8:1) for the foam could reach 1.75 μA , 1.02 μA and 0.70 μA , respectively, which are approximately three-fold higher than them of devices with other ZnO/graphene compositions. It was also reported that such tetrapod ZnO-graphene nanocomposite foam-based devices exhibited excellent thermoelectric and photoelectric performances which show their potentials towards fabrication of low cost and one-circuit-based multifunction sensors and systems (**Figure 5 f-i**). Similarly, Low et al.[63] reported a ZnO-graphene nanocomposite based electrochemical sensor for the detection of H_2O_2 with a sensitivity 3.2580 $\mu\text{A}\text{mM}^{-1}$ with a limit of detection of 7.4357 μM . The nanocomposite sensing device was also used for the detection of Avian Influenza *H5* gene as a DNA biosensor.

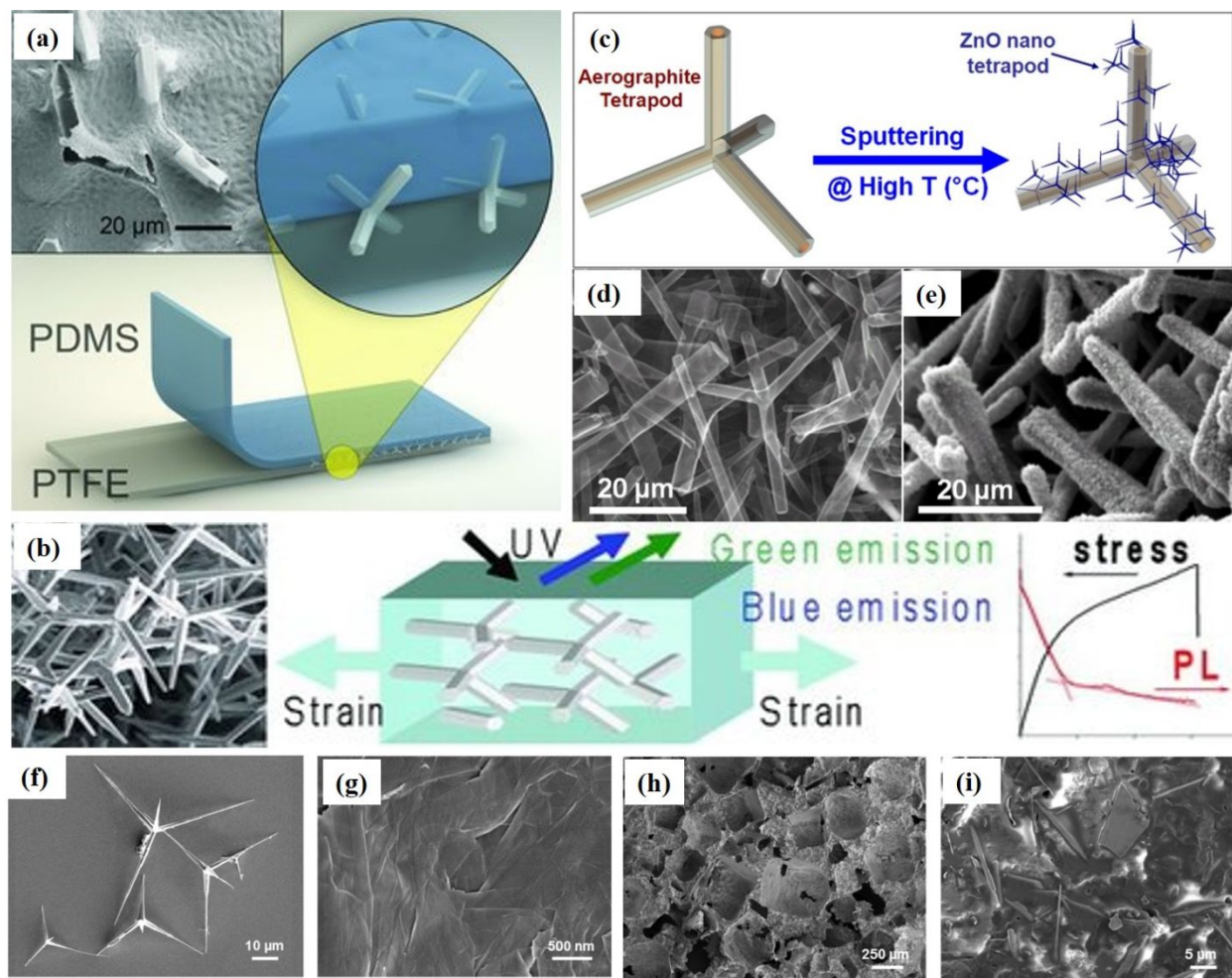


Figure 5: (a) A schematic of study of adhesion between polymer surface using tetrapod ZnO nanocrystals. Reproduced from Ref. [105] with permission from [John Wiley and Sons], copyright [2012]. (b) Representation of stress applied through PL investigation in a self-reporting materials composed of ZnO tetrapod filled elastomers. Reproduced from Ref. [106] with permission from [John Wiley and Sons], copyright [2012]. (c) Schematic of fabrication process for depositing ZnO tetrapod on aerographite material using sputtering process. By changing the deposition time, the morphology of loaded nanostructures can be tailored. (d–e) SEM micrographs of aerographite backbone before and after depositing with ZnO nanostructures respectively. Adopted from Ref. [107]. SEM micrograph of (f) tetrapod-like ZnO (g) graphene (h) optimized foam (8:1) at low magnification (i) optimized foam (8:1) at high magnification. Adopted from Ref. [108].

2.4 Spherical 3D ZnO nanostructures based thin films

3D NSs with hollow and spherical geometries provide a large surface area with a advantage of higher adsorption properties of the analytes on their surfaces [103]. Such NSs show low specific weight, and high mechanical strength beneficial for several applications including biomedical fields. For example, Liu et al.[109] synthesized ZnO hollow nanospheres (**Figure 6 a-b**) with porous shells using a simple hard-template method followed by calcination. The synthesized ZnO

hollow nanospheres were then encapsulated with mildew-proof agent and modified by polydopamine. Cumulative releasing of mildew-proof agent from these hollow ZnO nanospheres and dopamine-modified hollow ZnO nanospheres are shown in **Figure 6 (c)**. The dopamine-modified hollow ZnO nanospheres showed higher release content. Thereafter, antimicrobial casein-based coatings were prepared through mixing drug-loaded ZnO and casein latex. Antimicrobial testing results revealed casein-based hollow ZnO/mildew-proof agent nanocomposite films showed better antibacterial activities. Interestingly, similar observation was made even after 1 year on those ZnO hollow nanospheres. Similarly, antibacterial casein-based ZnO nanocomposite coating with improved water resistance was fabricated via double in situ polymerization as shown in **Figure 6 (d)**[110]. The morphological investigations showed that the average size of casein based ZnO nanocomposite spheres was approximately 259 nm. It was found that at 3% ZnO precursor concentration, the water resistance of the composite film was highest and antibacterial inhibition zone was expanded from 0 mm to 9.0 mm. It was suggested that such nanocomposites could be a potential candidate for functional coatings in relative fields for biomedical or healthcare applications. Ma et al.[110] fabricated uniform mulberry-like ZnO nanosphere particles using microwave assisted hydrothermal method and studied its antibacterial property. It was found that such ZnO nanospheres showed stronger antibacterial effects on *Candida albicans* than other 2D sheet-like or 3D flower-like ZNSs.

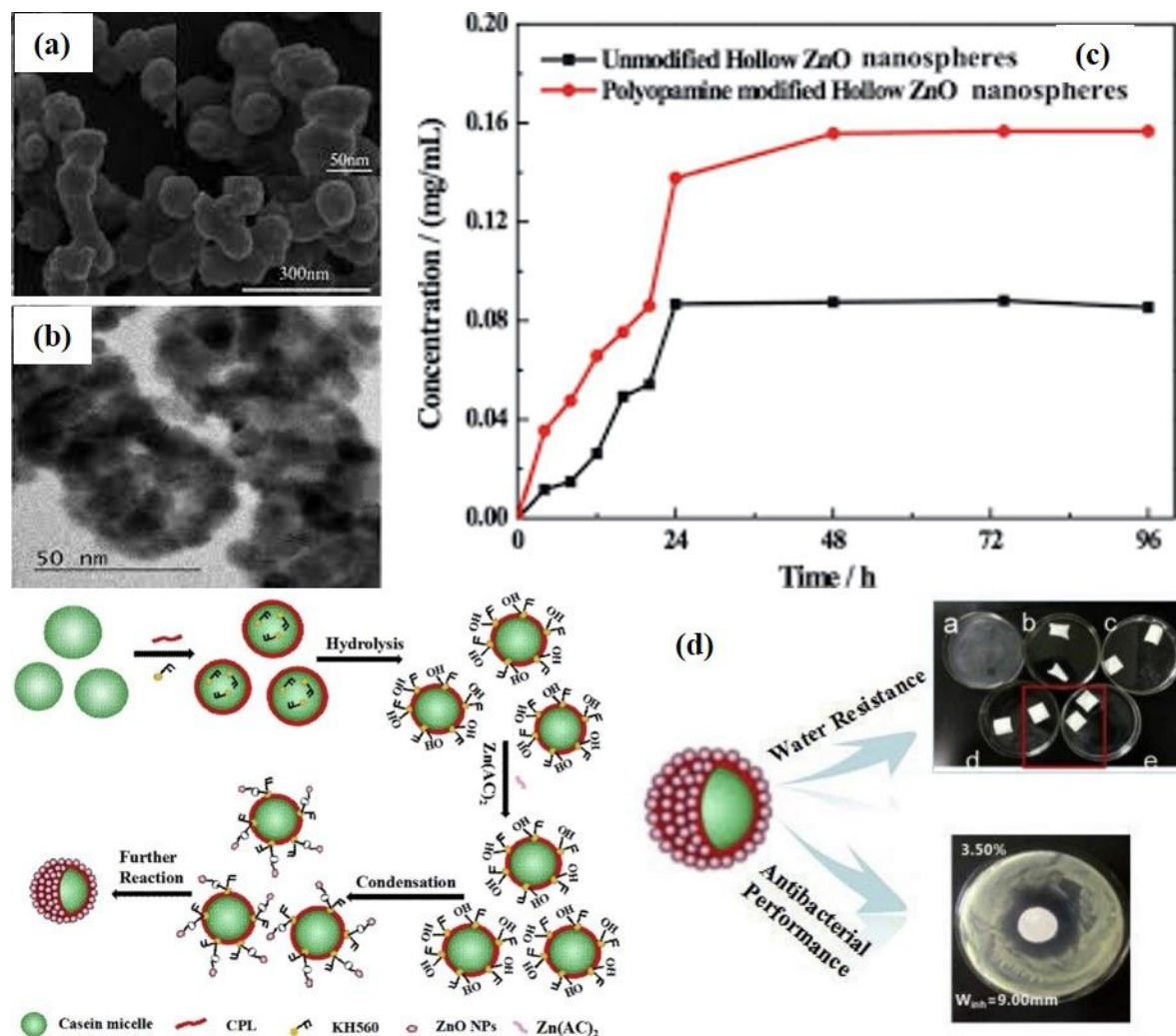


Figure 6: (a) SEM image of ZnO hollow nanospheres (b) HRTEM image of ZnO hollow nanospheres (c) Cumulative releasing of mildew-proof agent from different samples. Reproduced from Ref.[109] with permission from [John Wiley and Sons], copyright [2016] (d) Schematic representation of the formation of casein-based ZnO composite latex via double in situ route and its applications as water resistance and antibacterial surfaces. Reproduced from Ref. [110] with permission from [Elsevier], copyright [2019].

2.5. Nanoflowers based ZnO nanostructures thin films

3D Nanoflower structures are like plant flowers in a nanoscale range of 100–500 nm [103, 111]. Such 3D morphologies show unique properties in terms of their surface and physicochemical properties which can potentially be tuned in order to enhance the functionalities and device performances in many research fields including biomedical applications[111]. For example, Wang et al. [112] fabricated an antibacterial casein based ZnO nanocomposite i.e., caprolactam-casein/ZnO nanocomposite (CCZ) for flexible coating with flowerlike ZnO aggregation as shown

in **Figure 7 (a)**. TEM image also showed the formation of core-shell casein-based ZnO nanocomposite as shown in **Figure 7 (b)**. The nanocomposite films showed excellent mechanical and antibacterial properties displaying polymer-based nanocomposite antibacterial coating which could be applied in several fields, such as textile, leather, packaging, paper making and indoor wall coating. Chen et al. [113] fabricated ZnO nanoflowers and also metal decorated nanoflowers which showed excellent sensing applications. Tang et al. [114] produced ZnO NRs, nanowalls and nanoflowers developing a hydrothermal route. The nanoflower structures were fabricated with high densities and high degree of uniformity on Al-coated SiO₂ substrates. It was observed that the morphology of the ZnO nanoflower structures could be controlled by changing the growth rate of ZnO NRs through the grooves created on the substrate as shown in **Figure 7 (c-e)**. The role of concentration of the solution and reaction time was optimized and emphasized for the production of such 3D ZnO nanoflower structures.

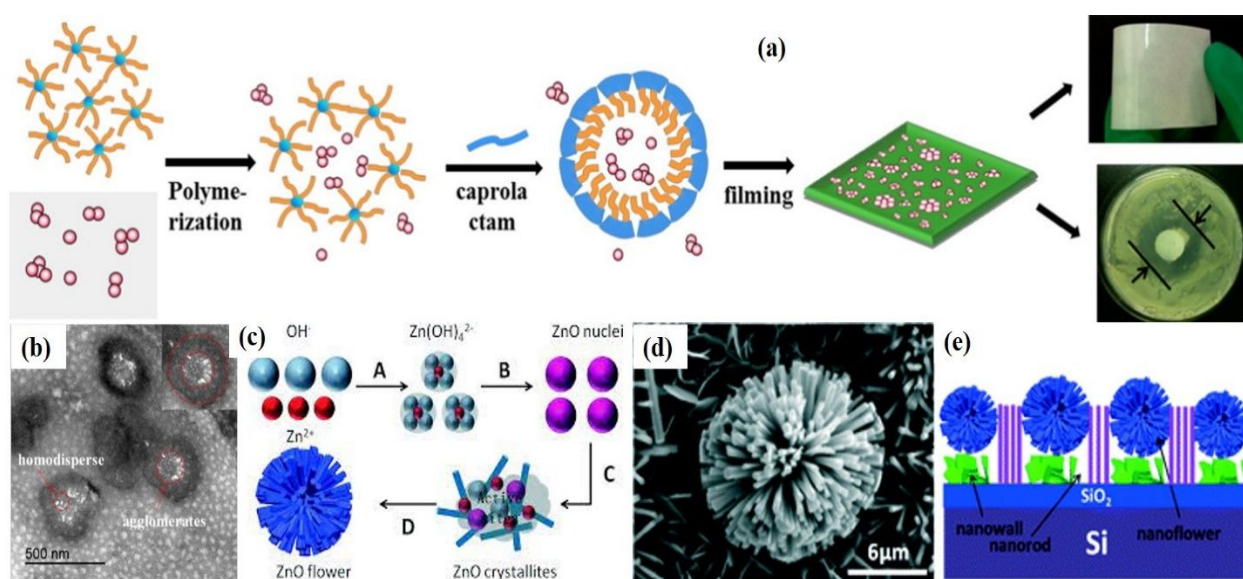


Figure 7: (a) Schematically representation of synthesis of flexible hybrid CCZ coating by in-situ polymerization method (b) TEM image of CCZ4 composite, exhibiting the core-shell structure of latex. Reproduced from Ref. [112] with permission from [Elsevier], copyright [2016]. (c-e) Schematic representation of growth mechanism of the ZnO nanoflowers and SEM image. Reproduced from Ref. [114] with permission from [Royal Society of Chemistry], copyright [2015].

Above details on the various morphology of ZNSs show promising optical and other surface properties with possible potential applications in the field of biomedical applications. It has also been emphasized that the such properties could possibly be tuned by varying the various experimental parameter, concentrations of starting materials and other operating conditions for

maximum enhancement in their properties. Thin films or coating of such diverse nanostructures could be more efficient for practical applications on the surfaces, making solid state devices and optoelectronic devices for biomedical applications. Such multifunctional biomedical applications of ZnO nanostructured thin films with diverse nano-architectures will be discussed in the next section.

3. Mechanisms and various biomedical applications of ZnO thin films with diverse nano-architectures

3.1 Applications in antibacterial activity

Antimicrobials should not be used carelessly since this has resulted in the emergence of bacterial strains that are resistant to antibiotics [115]. Because of this, a significant number of studies have concentrated on the search for novel antimicrobial drugs. Because of the non-specific action of inorganic antimicrobial agents, there has been a significant rise in interest in the application of ZNSs for the purpose of optimizing efforts to combat microbial resistance. ZnO NPs antibacterial activity can be improved thanks to their low particle size and high surface area, both of which cause an increase in surface reactivity [116]. Since the surface features of ZnO NSs (as shown in **Figure 8(a)**) influence their interactions with cells, surface modifiers covering ZnO NPs can also play a role (**Figure 8 (b)**) in mediating antimicrobial activity; however, this may interfere with the antibacterial impact of ZnO NPs [117].

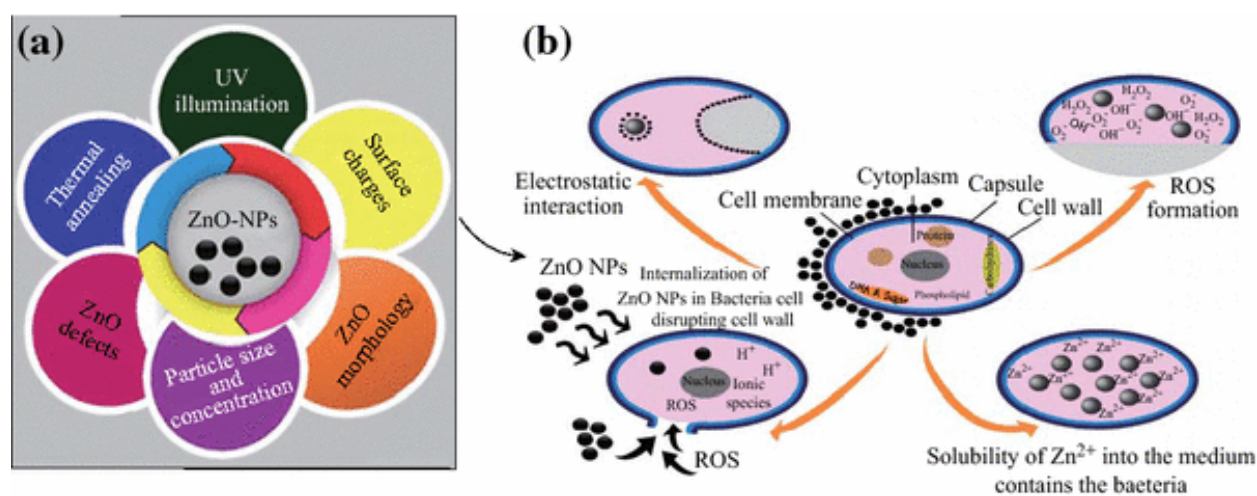


Figure 8: (a) The key factors of ZNSs on the antibacterial response and b) potential mechanisms of ZnO-NPs antibacterial activity by ROS generation. Adopted from Ref. [118]

ZnO NPs are highly effective in preventing the development of biofilms [119] and have excellent antibacterial activity against a variety of both gram-positive and gram-negative bacteria [120-122]. ZnO is being studied as an antibacterial agent in formulations at the nano- and microscale levels. When ZnO particles are reduced to the nanometer range in size, they exhibit strong antimicrobial properties. Once within the bacterial cell, they interact with the surface and/or the core of the bacteria and exhibit specific bactericidal activities [123]. ZnO has numerous antimicrobial effects, including (i) cell membrane rupture through Zn ions and (ii) release of ROS, [118, 124]. Sublethal ROS concentrations have been demonstrated to induce the emergence of defense mechanisms. This is known as hormesis [125]. Hormesis activates defense mechanisms on two fronts. The first is enzymatic (short-term reaction). Antioxidant enzymes are triggered at this level. Long-term adaptability is the second stage. Long-term adaptability is divided into two levels: transcriptional and genomic. ROS induces adaptation at the transcriptional level within a few hours or days due to the activation of antioxidant mechanisms [126]. ROS can induce damage to the DNA structure at the genomic level, which activates the systems for repairing DNA damage [127-129]. Homologous recombination and excisional repair are two of these strategies. Two of the DNA polymerases responsible for DNA synthesis in these mechanisms have low validation activity and may contain aberrant bases in DNA strands, resulting in a high frequency of spontaneous mutations and genome plasticity under bad conditions [130]. Such genomic plasticity may result in the development of resistance to metals and metal oxide nanoparticles. Although the specific processes governing ZnO's bactericidal activity are still up for debate, it is believed that there is a relationship among various systems that permits the concurrent delivery of many antibacterial actions.

Various ZnO NSs and hybrid 0-3D nano-architectures have been synthesized and applied in form of thin film/coating for antibacterial applications. For example, Wu et al. [93] produced ZnO NWs decorated with ZnO QDs (3-5 nm) and investigated antibacterial properties against *S. aureus* and *E. coli* while under visible-light irradiation and dark circumstances. It was found that these NWs decorated with QDs exhibited very high antibacterial activity under visible-light irradiation resulting from generation of ROS disinfection mechanism. These NWs coated with QDs of ZnO were deposited on the PDMS based screen window as an antibacterial coating. It was concluded that the photocatalytic activities were attributed to the active sites available on the surface of NWs/QDs. The O-H bonds and Zn²⁺ ions, which acted as the active sites in ZnO QDs, accelerated the migration of photogenerated carriers produced under the influence of visible light from the

QDs to the NWs. The active sites were formed as a result of surface defects which directly excited electrons from the ground state of the defect sites to the CB of the ZnO QDs and then transferred to the CB band of ZnO NWs under visible light irradiation. It offered an electronic coupling between the adsorbate orbitals (i.e. oxygen vacancies) and the 2p orbitals in Zn core-level. As a result, the electrons reacted with the dissolved oxygen to form oxygen ions and produced ROS to enhance photocatalytic activity. In case of antibacterial activity in dark conditions, the release of Zn^{2+} ions was found to be responsible for inhibition of growth of the bacteria.

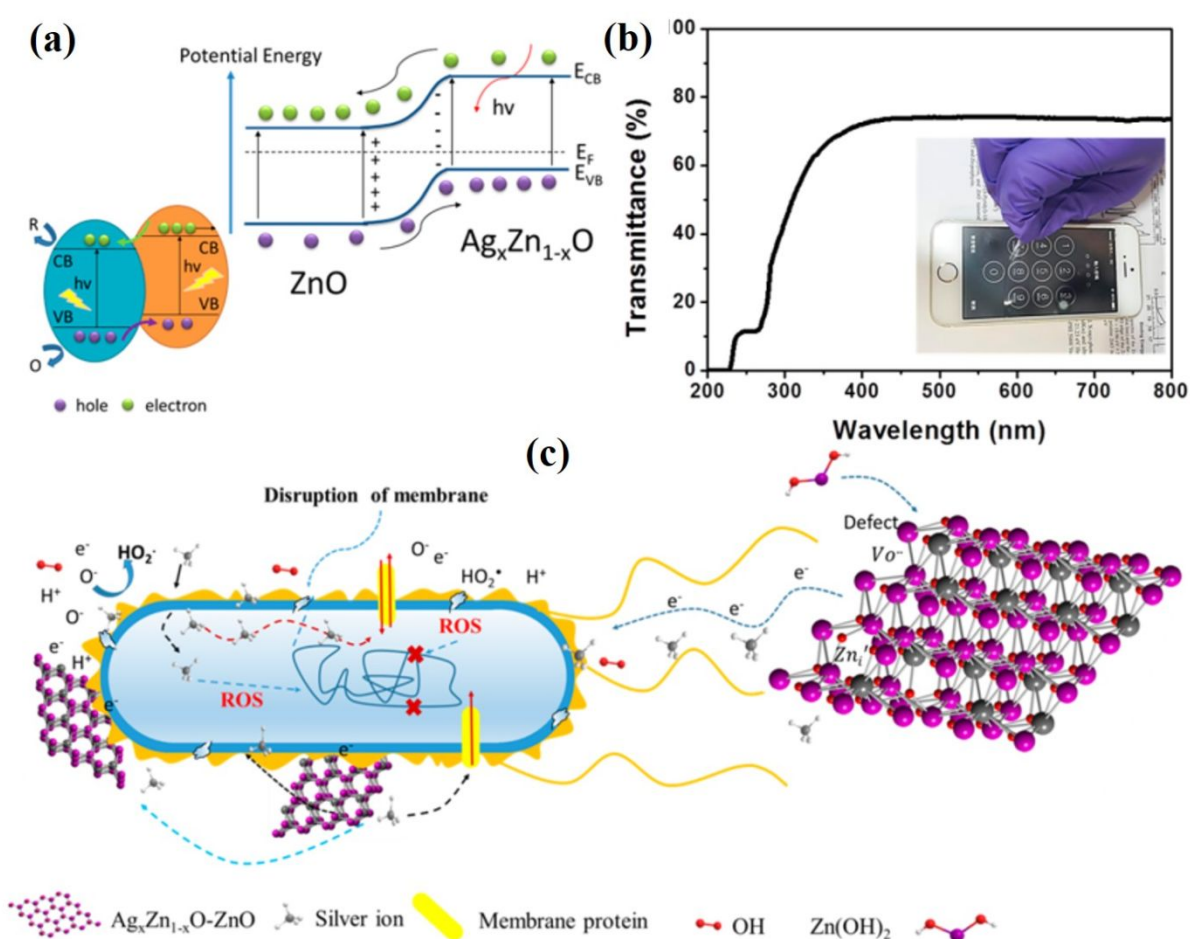


Figure 9: (a-b) Photocatalytic mechanism of the Ag-ZnO NWs along with the transmittance spectrum and digital picture of the NWs implanted on the surface of a thin PDMS substrate, (c) antibacterial mechanism of Ag-ZnO NWs in dark conditions. Reproduced from Ref. [94] with permission from [American Chemical Society], copyright [2015].

Similarly, Wu and group [94] fabricated Ag NPs deposited ZnO NWs and studied the antibacterial activity. Finally, they implanted these 1D Ag-ZnO NWs PDMS substrate for fabricating

antibacterial touch-screen surface for promising practical applications (**Figure 9 a-b**). These substrates embedded with 1D Ag-ZnO NWs exhibited stronger antibacterial activities under visible light as well as dark (as shown in **Figure 9 c**) attributed to the ROS generation and damaging of bacterial membrane. This kind of hybrid ZnO based materials and their coatings are useful in sunlight as well as in dark conditions with could be potential candidates to apply in home or hospitals for long term and continuous day or night bacterial protection.

Chen et al. [131] demonstrated the growth of arrays of heteronanostructured ZnO NRs vertically on PDMS surface by hydrothermal synthesis method followed by Ag NPs deposition via in-situ photoreduction on the NRs. Antibacterial efficacy investigation of Ag-ZnO heterostructured NRs array exhibited markedly superior effect as compared to that of ZnO NRs without Ag NPs against murine fibroblast cell lines. In addition, Zhang et al [132] have produced flower-shaped, prism-shaped, snowflake-like, and rod-like morphologies of ZnO by heating the material to a high temperature of 180° C for 13 h. The ZNSs were also reported to be produced in the form of prisms and prickly spheres [133] with different activities due to their unique shapes and also with different mode of actions. These different ZNSs could be promising for antibacterial activities. It is well recognized that various common bacteria can infect hospital implants, which can result in life-threatening infections [134]. A number of researches have been reported developing various ZNSs embedded in polymer matrix for antibacterial coating making it promising for novel biomedical device coatings [135]. The biomedical applications of these findings are advantageous. Such ZNSs coating could help in reducing bacterial infections associated with devices and hospital places [135]. ZNSs based antibacterial coatings have been applied for skin protection such as mixed in skin lotions as a health care product[118]. Stankovic et al. [136], demonstrated the use of polymer for better stability of such ZNSs as they found that the inclusion of PVA, polyvinylpyrrolidone (PVP), and poly(α , γ , L-glutamic acid) PGA as stabilized and improved ZnO shape and antibacterial activity. Li et al. [137] fabricated ZnO based hybrid NPs coated on Ti surface and proposed that the antibacterial results of this coated surface would be promising for clinical applications. The hybrid NPs were prepared by coating N-halamine and ZnO NPs on the templates polystyrene-acrylic acid (PSA) as shown in **Figure 10 (a)**. The antibacterial activity of hybrid coating on Ti surface was studied against *P. aeruginosa*, and *E. coli* and it was found that N-helamine on ZnO surface enhanced the antibacterial effect as compared to the ZnO NPs without such coating.

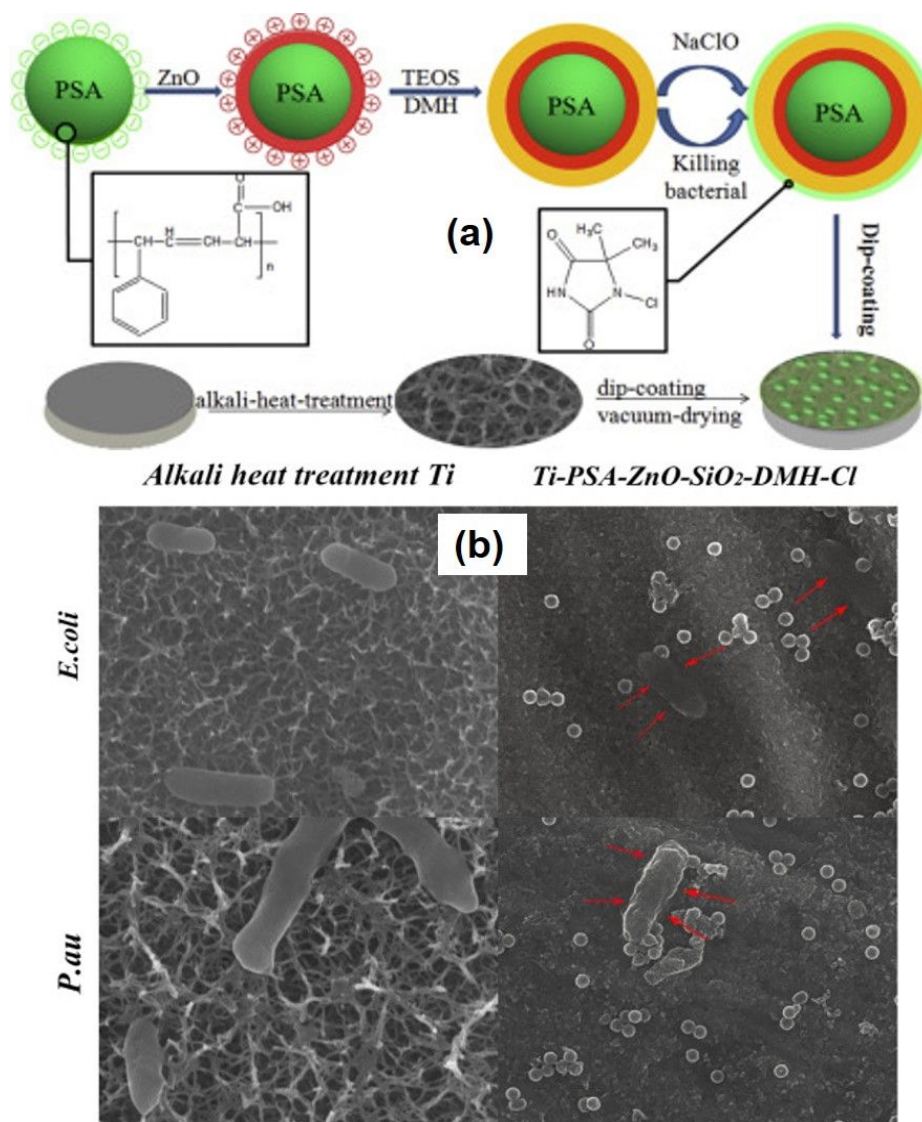


Figure 10: (a) Schematic preparation of Ti surface coating with ZnO hybrid nanomaterials (b) SEM patterns of *P. aeruginosa*, and *E. coli* cells on the samples. (The scale bar is 1 μ m). Reproduced from Ref. [137] with permission from [Elsevier], copyright [2017].

Above discussion show that ZNSs are promising antibacterial agents and in these NSs exhibit different antibacterial activities when applied in different shape/size. Thin film or coating on the surfaces provides better practical applications in indoor or outdoor locations as they show promising antibacterial effect in sunlight and dark conditions. Particularly, such NSs coatings could be applied on biomedical devices or indoor walls/floors in hospitals where bacterial infections spread faster. Embedded ZNSs in some nanothin matrix like polymers would be more

promising as a coating material on the most frequently surfaces to inhibit the bacterial infection. However, this research needs more thorough investigations for practical realization.

3.2 Applications in drug delivery and antiviral activity

Infections caused by viruses are a worldwide public health concern that have had a negative impact on activities on a global scale in recent years [138]. In many cases, there is no medication that can specifically treat the viral infection; instead, treatment focuses on relieving the symptoms. In recent years, nanoscience and nanotechnology research have shown significant progress in the field [139-142]. The nanomaterials have demonstrated promising antibacterial and antiviral properties; among those, several photocatalyst nanomaterials with variable morphologies have been investigated [143, 144] and exhibited promising antiviral activities [2, 102, 116, 141]. In 2019, a new coronavirus i.e. severe acute respiratory syndrome coronavirus (SARS-CoV-2) caused COVID-19 which resulted in a pandemic. The whole world is still dealing with this today even after the invention of a number of vaccines. In addition, since then, a wide variety of approaches to the prevention and control of COVID-19 have been the subject of research and have been practicing [139, 142]. Finding suitable inorganic/organic agents that work to neutralize the virus infectivity, destabilize, and possibly dismantle the virus particles, is therefore crucial and need of the hour in nanomedicine research [141, 142, 145]. Recent advances in nanotechnology enable re-exploration of the biochemical activity of known antimicrobial compounds by manipulating their sizes [2].

ZNSs are fascinating alternatives to overcome the challenges caused by viral infections in medical applications due to their size, the exceptional properties they possess, and the practical applications they have in a wide variety of fields. The question is, what makes nanoparticles such a desirable candidate for use in antiviral tools? as illustrated in **Figure 11**, how NPs can exert their antiviral properties and advantages associated in design [146]. Typically, nanocarriers with an average size between 200 and 300 nm have a better chance of avoiding early renal extraction and, as a result, have a longer plasma half-life. Furthermore, nanocarriers with a mean size between 50 and 250 nm are hospitable to blood-brain barrier penetration.

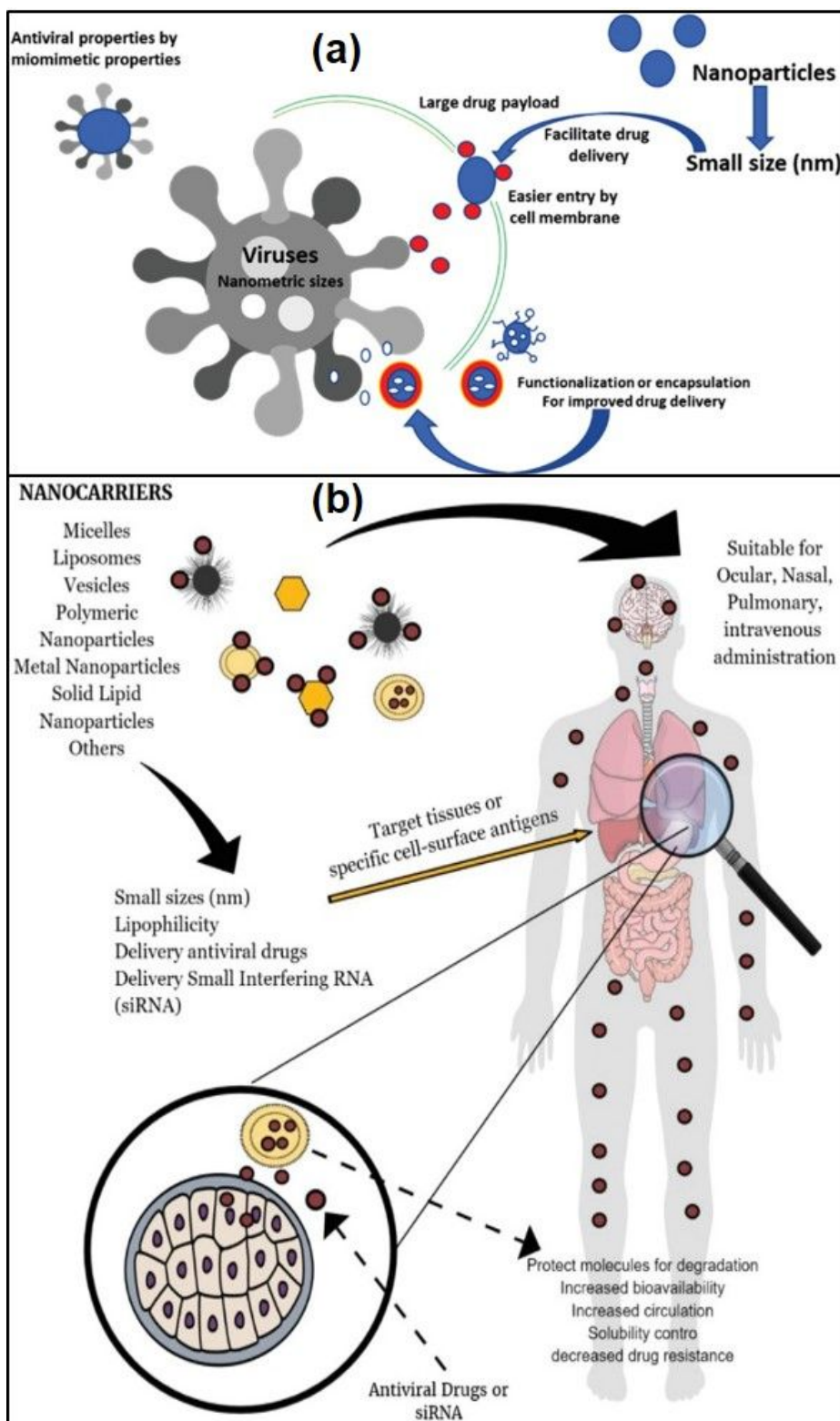


Figure 11. Mechanisms through which (a) NPs exert antiviral properties and (b) advantages of NPs as antiviral drug carriers. Adopted from Ref. [146].

A recent study by Ghaffari et al. reported the inactivation of the H1N1 influenza virus by ZnO NPs[141]. The research was focused on how ZnO NPs and ZnO-PEG-NPs affect the reproduction of H1N1 influenza virus, one of the most difficult viruses that threatens human health. According to the findings of the study, PEGylated ZnO NPs have the potential to be an innovative, effective, and promising antiviral agent against H1N1 influenza virus infection. Future studies might be planned to investigate the precise antiviral mechanism of such ZnO NPs.

ZnO is well-known for its antibacterial, antifungal and antiviral properties [147, 148]. During the COVID-19 period, it was realized that along with the medications, an antiviral surface with promising antiviral properties is also required which must be effective in outdoor as well as indoor conditions [2, 116]. Additionally, the cleaning and disinfection of the various surfaces, mainly where there is more possibility of spreading of viruses i.e. hospitals and clinical laboratories, schools, transport, and public places, are important [139]. Nanomaterials coating has been found to be very promising for this purpose along with various other important issues[149-151]. ZNSs based thin film coatings have been investigated in deactivating various kinds of viruses[152]. For example, Ghaffari et al. [141] reported the inhibition of H1N1 influenza virus using ZnO thin film coating. Similarly, ZnO NPs based thin film coating was found to be very promising for the reduction of infectivity of SARS-CoV-2 (>99.9% in 1 h) [153]. Even ZnO based antiviral nanospray coating has been developed [150]. It has also been found effective antiviral in packaging of materials [154]. Kumar et al. [155] developed nanostructured ZnO coated antiviral silk fabric using electrospinning followed by atomic layer deposition (ALD) technique for personal protective equipment (PPE) applications. The developed ZnO based nanocomposite fabric exhibited 85% better antibacterial activity as compared to the control silk fabric and also showed substantial superoxide dismutase–mimetic activity. It was tested for antiviral activities against two different respiratory tract viruses: coronavirus (OC43: enveloped) and rhinovirus (RV14: non-enveloped) and the results are shown in Figures 12 (A-D). Figure 12 (A) shows the A TEM image of deactivated OC43 coronavirus. Figures 12 (B-D) show the coronavirus OC43 (B) and rhinovirus (C and D) applied to ZnO based nanocomposites fabric and effect of LED exposure after 1 or 2 hrs. It was proposed that ZNSs with photocatalytic activity, when exposed to white light, it generated photoexcited charge carriers followed by ROS which interacted with viruses. The ROS

caused protein oxidation, RNA damage, and membrane disruption, ultimately led to deactivation of the viruses. The proposed mechanism has been shown in **Figure 12E**.

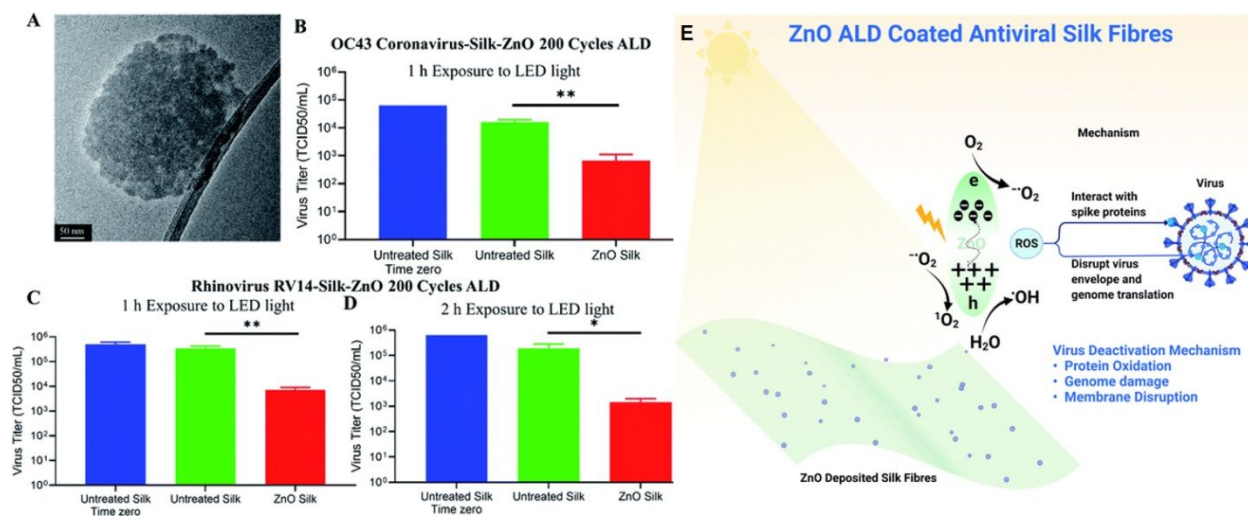


Figure 12: (A) HR-TEM image of deactivated coronavirus OC43. Approximately 1×10^5 TCID50 units of coronavirus OC43 (B) and rhinovirus (C and D) were applied to 200 cycle ZnO coated silk 6 mm discs in a 96-well plate. Input virus was quantified at time zero on untreated silk, as shown in blue bars. After 1 h (B and C) or 2 h (D) LED light exposure, silk discs and media were analyzed for remaining infectious virus according to the respective virus quantification assays. Values are the mean of three independent samples and the standard deviations are represented by error bars. * Indicates p-value < 0.05 and ** indicates p-value < 0.01 comparing light exposed untreated silk versus ZnO coated silk discs. (E) Schematic diagram showing viral deactivation mechanism of ZnO ALD coated silk patch. Adopted from Ref. [155]

As also discussed in the last section that ZNSs are promising antibacterial as well as antiviral agents. Recent reviews [2, 21, 116] indicate that thin film or coating technology using these NSs on the various surfaces provides better practical applications in indoor or outdoor locations under respective light and dark conditions. Similarly, ZNSs are effective antiviral and can be used as a protective coating in the field of biomedical i.e. coating on the surgical instruments, devices etc. It is a growing field and more fruitful results are expected in the near future after the COVID-19 pandemic.

3.3 Applications in biosensing

The biosensing i.e. detection/identification of biomolecular species either in the environment or in the human breath/body is very significant and equally important for a healthy society. Amongst various nanomaterials, ZNSs based technology has been developed in last a few years for

biosensing with different nano-architectures[156-160]. In the arena of respiratory virus detection, for example, an immunosensor based on patterned ZnO NRs networks for the detection of influenza virus (H1N1 SIV) has been developed [92]. Here, role of ZnO was extremely important for the immobilization process of the collected antibodies on the electrode. Similarly, it has been found that ZnO plays an essential role in bio-conjugation between sensing materials and biomolecular species, such as viruses [161]. In a recent work, ZnO NRs based electrochemical impedimetric biosensor for detecting antibodies against SARS-CoV-2 spike protein (in convalescent and vaccinated people) was developed by Nunez et al. [162, 163]. The immobilization of SARS-CoV-2 recombinant trimeric spike protein (S protein) on ZnO NRs modified F-doped SnO₂ substrates for COVID-19 serology testing served as the foundation for this study. Morphological investigations were carried out that showed that the smooth surface of ZnO NRs (diameters 490 nm) became fade (covered) after SARS-CoV-2 recombinant spike protein immobilization. **Figure 13** provides an overview of the work's progress [162].

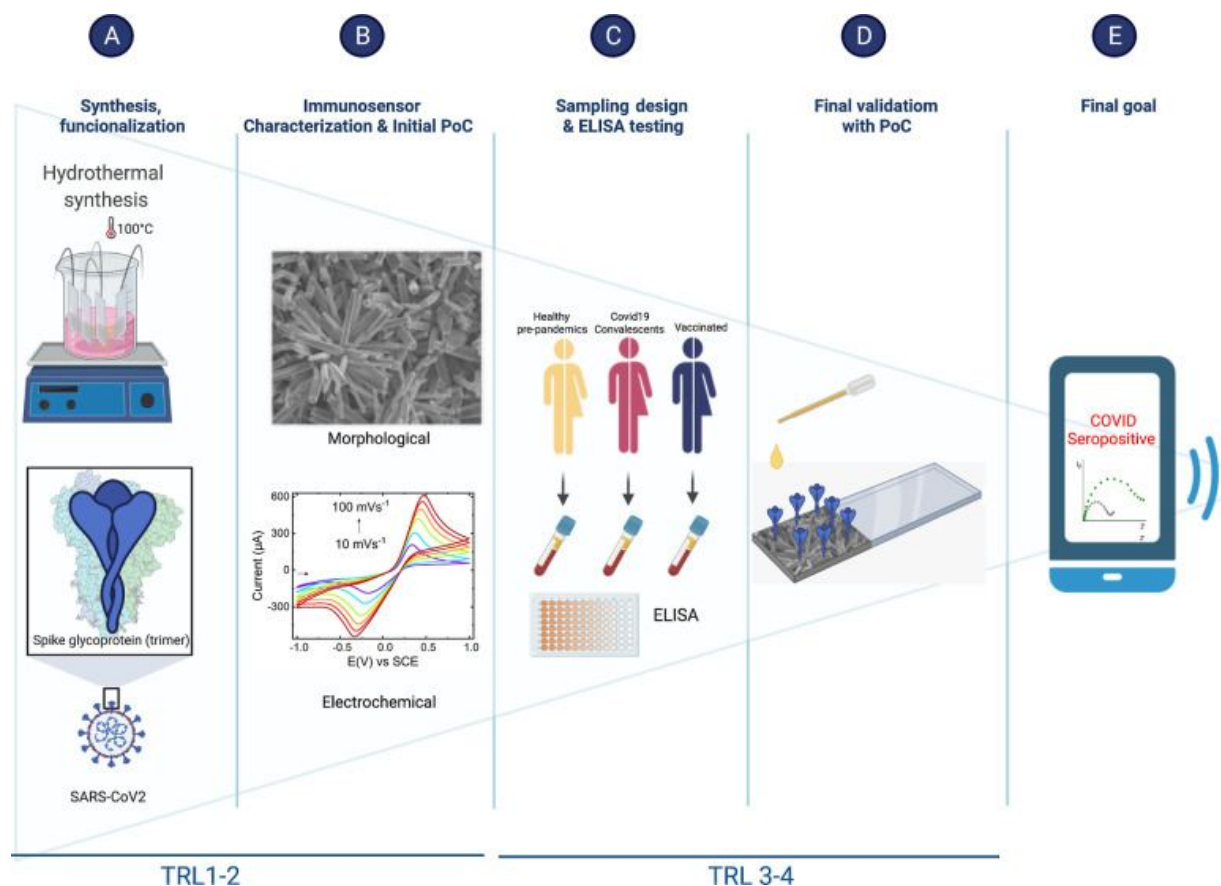


Figure 13: Development and validation of the electrochemical ZnONR immunosensors for anti-SARS-CoV-2 antibody detection. (A) Basic science research. Hydrothermal synthesis of ZnONRs, FTO (fluorine tin oxide)

functionalization with viral spike protein, and optimization of sensor architecture and (B) prototype characterization. Morphological, spectroscopic, and electrochemical characterization was performed before and after the biological modification of ZnONR-modified FTO electrodes and (C) concept validation. Sampling design, collection, and confirmation of the clinical status by anti-S IgG ELISA serological analysis. (D) Final validation with the proof of concept. Clinical serum samples from healthy pre-COVID19 individuals, convalescents, and vaccinated patients were applied on the ZnO electrode surface for anti-COVID19 antibody detection and (E) final project goal. Reproduced from Ref. [162] with permission from [American Chemical Society], copyright [2023].

Low et al. [63] described an electrochemical sensor system for detecting Avian Influenza H5 (H5N1) based on graphene/ZnO nanocomposite. In this study, a novel strategy was adopted, as the results of an amperometric analysis were compared to the performance of a conventional agarose gel electrophoresis. Finally, this comparison showed a solid validation for the use of such biosensors. Furthermore, Ji-Hoon Han and colleagues [76] described the development of an electrochemical approach for the detection of influenza viruses such as H1N1, H5N1, and H7N9 utilizing a nano-flow immunosensor based on ZnO NRs grown on a PDMS sensor. Such 1D ZNSs enabled the immobilization of a range of antibodies, which additionally led to a rise in sensitivity. Similarly, ZnO has also been used as a precursor in the development of Zn based fluorescent CdZnSeS/ZnSeS QDs and fabricated a nanocomposites with Au NPs for detecting the influenza virus H1N1 [164].

As a consequence of these efforts, an investigation into nanomaterials that are based on ZnO for their possible use in SARS-CoV-2 detection has also been carried out[165]. Such potentially beneficial technologies could pave the way for clinical diagnostics utilizing antibodies directed against the well-known spike protein S1. Recently, Xiao Li et al. [98] reported an experimental approach for improving the biosensing performance of paper-based electrochemical impedance sensing nano biosensors with working electrodes ornamented with vertically grown ZnO NWs. In human serum samples, these nano biosensors could distinguish between different amounts of IgG antibody (CR3022) to SARS-CoV-2. **Figure 14 (a)** represents a schematic illustration of microfluidic paper-based analytical devices (μ PADs) technology which are portable, accurate and robust detection systems in developing countries.

In light of the foregoing, it seems plausible that nano ZnO and its compounds could be utilized fruitfully in a biosensor platform through the application of certain functionalization procedures based on silane group immobilization. Since ZnO is an oxide, the generation of OH- groups is preferred over that of other metallic materials, which often requires more sophisticated methods.

ZnO is also one of the promising materials used in biofunctionalization [166]. Furthermore, when it comes to carrying out functionalization operations, silanization is advantageous in this case since it results in more OH- groups that are accessible for binding with the biologically recognized element. For example, Allen et al. [167] investigated the effects of treatments containing triethoxysilane on the role of silane in ZnO thin sol-gel generated films. Corso et al. [168] used two different forms of trimethoxysilanes for IgG antibody immobilization on ZnO surfaces: (3-glycidyloxypropyl)-trimethoxysilane (GPS) and (3-mercaptopropyl)-trimethoxysilane (MTS). Garcia et al. [96] investigated the effects of silanization using amino-propyldiethoxymethylsilane (APDEMS) on the hydroxylated sidewalls of ZnO-NWs. These studies revealed that the functionalization techniques demonstrated a promising technique for adapting them to Zn-based biosensing devices [169]. This approach provides the chemical modification of a surface for antibody immobilization [30] as well as an optical transduction response. As a result, it is a cost-effective option that produces biosensors by silane functionalization standards that might be used to immobilize recognition agents against the spike S1 protein.

Furthermore, it is critical to emphasize that the process of manufacturing biosensors involves an array of barriers, yet it also delivers a comprehensive image and a high degree of versatility in the assembling. Methods for antibody immobilization using crosslinkers, for example, improve orientation in diverse materials, resulting in higher sensitivity; however, this leads in a rise in total costs. Another barrier to overcome is the integration of response signals in biosensors with electronic and portable devices that must meet worldwide regulatory requirements for everyday use. Additionally, there is still a problem that must be solved in terms of validating detection limits in addition to comparing them to molecular reference methods. Random immobilization strategies, on the other hand, can alter the sensitivity of these devices. The broadening amount of information on this public health crisis has led to the idea that improved sensor surfaces be made from a variety of nanomaterials, such as zinc and related compounds, to provide a rapid detection response that is also selective and sensitive. The data generated utilizing ZnO-based biosensing platforms for different respiratory viruses might be regarded surplus and could serve as a reference guide for the development of these new prospective nano sensors for early detection of diseases. According to the databases that were examined, there are only a small number of works that have been connected to the detection of COVID-19 with micro-Zn and its derivatives. This paves the way for additional investigations and studies.

3.4 Applications in wound healing activity

The process of wound healing is a complicated one in which many different factors, including cells, chemical signals, extracellular matrix proteins, and microenvironments, interact with one another in a myriad of different ways [170]. Critical stages in wound healing includes fibroblast production, movement, and transdifferentiation into myofibroblasts [171]. After an injury, myofibroblasts are responsible for restoring the tissue's mechanical stability and integrity [172]. When tissue integrity is restored to a point where the tissue is mechanically coherent, they are eliminated via apoptosis under physiological conditions. Myofibroblasts are responsible for fibrosis through upregulated matrix production and tissue contraction in pathological wound healing processes[173]. The therapeutic possibilities for fibrotic illnesses would consequently benefit from the regulation of fibroblast activities[170, 174].

Recent investigations have concentrated their attention on the prospect of optimizing drug delivery using coated drainage devices in conjunction with applications of nanotechnology [175]. Nanomaterials have their own distinct features that are distinct from those found in materials on a larger scale; for instance, nanomaterials offer additional opportunities for chemical reactions[176]. Scarring was reduced and bleb survival was increased thanks to cationic nanocopolymers produced by Ye et al.[177]. In a separate investigation, the use of MMC-incorporated LDL NPs allowed the researchers to address activated Tenon's fibroblasts [178]. This was feasible due to the increased expression of the LDL receptor in those cells, which occurred as a result of glaucoma filtration surgery. These studies demonstrate the applicability of nanotechnology to the treatment of glaucoma filtering surgery extensively used to reduce intraocular pressure in cases of uncontrolled glaucoma in wound healing.

Dressings for wounds in today's medical practice are more than just a supplement to the whole process of wound healing. It means that, in addition to covering the wound and containing edema, they should also ideally possess mechanical properties, oxygen permeation, moisture control, secretion monitoring, antimicrobial properties, non-toxicity, biocompatibility, complete removal after complete skin regeneration, and cost-effectiveness [179]. These characteristics should be present in the ideal case. In addition to having the right mechanical qualities, wound dressings need to have enough absorptive ability to absorb wound exudates and maintain an acceptable level of moisture around the wound[180]. In most cases, the presence of moisture will accelerate the

progression of wound healing and encourage the development of new tissues. However, there is some evidence that moisture might also promote the growth of bacteria [181]. Because of this, it is necessary for wound dressings to keep the appropriate level of moisture in the surroundings surrounding wounds to encourage rapid wound healing. For instance, it was discovered that a wound dressing with the appropriate amount of moisture considerably increased the pace of re-epithelialization by fifty percent[179]. In a recent study, nanofibrous wound dressings composed from poly-lactic acid (PLA)/chitosan/starch/ZnO using electrospinning method (as shown in **Figure 14 (b-c)**) were tested to absorb in an in vitro immersion test using a PBS solution with a pH of 7.4 at 37°C[182]. Chitosan and starch were added to increase the water uptake of PLA, although zinc oxide demonstrated the most potential overall. Water uptake capacity was boosted by around seven times when ZnO was added to clean PLA, indicating that ZnO's presence greatly improved the material's ability to keep wounds moist during the healing process. Similarly, Mao et al.[183] investigated the water absorption and air permeability of PLA/gelatin/ZnO electrospun membranes and freeze-dried aerogel scaffolds. It was found that aerogel scaffolds have a 3D macro-porous structure, in contrast to the 2D structure of membranes. Furthermore, aerogel scaffolds outperformed membranes in water absorption and gas exchange because of their superior structural design. It was also reported that raising the ZnO content improved the scaffolds' hydrophilicity. It was shown that ZnO based 3D scaffolds effectively could promote wound healing of the skin infection enhancing the angiogenesis with increasing ZnO content. It was observed in vivo experiment practically as shown in **Figure 14 (d-e)**. Similarly, Rashedi et al. [184] synthesized PLA/ZnO nanofibrous nanocomposites loaded with with tranexamic acid and studied it's wound healing activities in vitro and in vivo. However, stronger absorptive characteristics may not always result from the addition of ZnO. For instance, it was hypothesized that adding ZnO NPs to poly(lactide-co-glycolic acid) (PLGA)/silk fibroin (SF) wound healing scaffolds would diminish their capacity to absorb water[14, 185]. Conflicting findings have been reported from these investigations about the impact of ZnO on the moisture absorption capabilities of wound healing scaffolds. Many experimental factors, such as the type of polymer matrix and the design of the wound healing scaffolds, are quite likely to have influenced this.

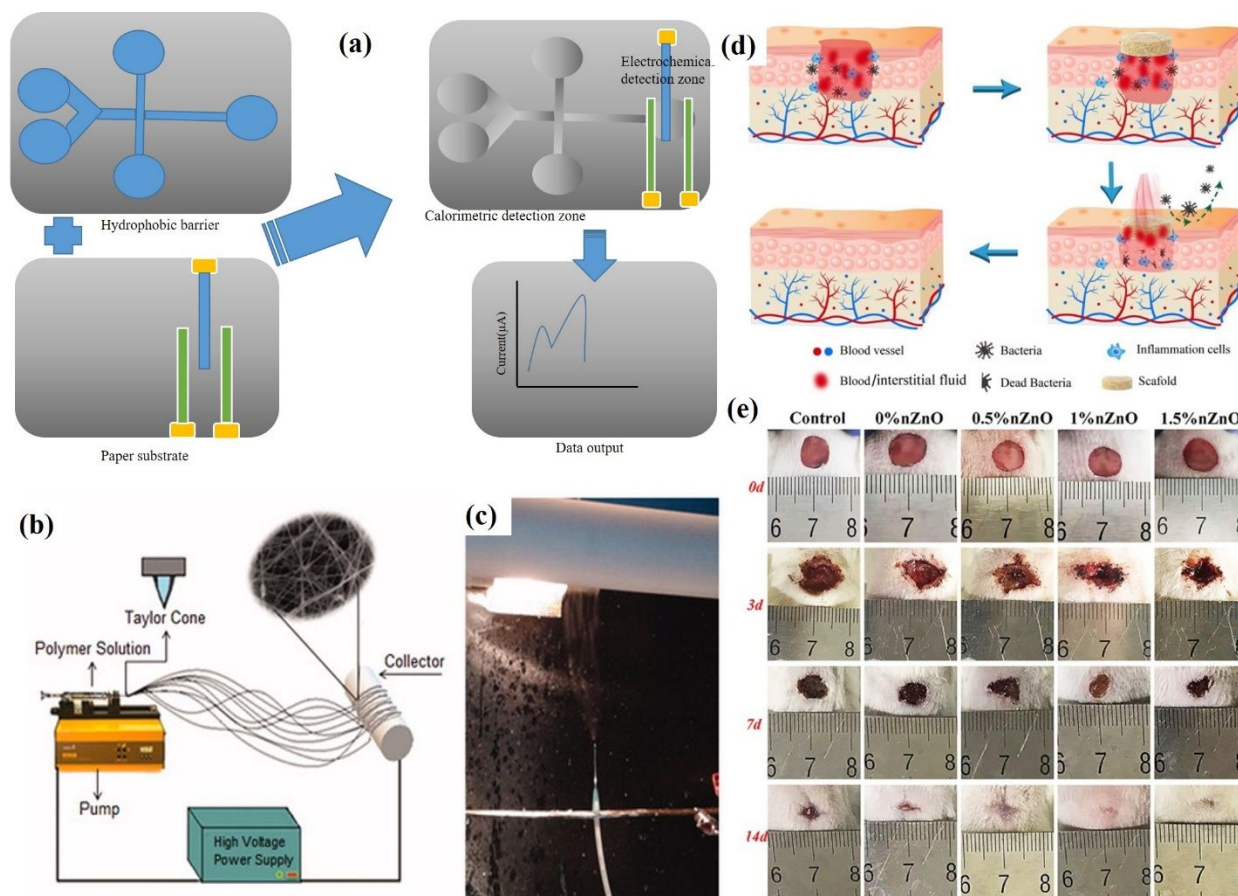


Figure 14. (a) Schematic representation of μ PAD technology (b) Schematic design of the electrospinning process, (c) Nanofibrous wound dressing production phase. Reproduced from Ref. [182] with permission from [Taylor and Francis], copyright [2018]. (d) PLA/gelatin/ZnO nanofiber aerogel scaffolds with good antibacterial properties are also good at absorbing wound exudates and allowing gaseous exchanges; (e) Digital photos of infectious wounds covered with various PLA/gelatin/ZnO nanofiber aerogel scaffolds within 14 days. Reproduced from Ref. [183] with permission from [Elsevier], copyright [2021].

Moura et al. [186] demonstrated that 1D/3D Ag-ZnO nanocomposite with NRs/nanoplatelets morphologies could heal the wounds (in the dorsal region of BALB/c mice) with non-cytotoxicity, especially on keratinocytes and collagen deposition, and increased metalloproteinases 2 and 9 activity. It was explained that Ag-ZnO based healing material healed the wound by reducing the inflammatory process, protecting tissues from damage caused by free radicals, and increasing collagen deposition in the extracellular matrix. Similarly, Le et al. [187] demonstrated that ZnO-NPs coated hydrocolloid patches are very effective in wound healing using Sprague–Dawley rat models. Recently, Rajabloo et al. [188] demonstrated the bio-fabrication of ZnO and malachite nanocomposite with excellent antibacterial and antioxidant properties and applied its coating with

chitosan in healing the infectious wounds in mice. It was found that the fabricated coating could accelerate the wound healing process and could compete with the standard ointment of polysporin. It is also suggested in this study that results pave the way for clinical studies to investigate the effects of such ZnO based nanocomposites on wounds and their uses in combination with other commercial ointments. Rayyif et al.[189] developed nanocoating dressing embedded with ZnO NPs that showed excellent antimicrobial efficiency against typical wound pathogens which are mainly involved in formation of biofilm and chronic infections.

As discussed above, ZNSs have extensively been used for wound healing and has potential of being used for clinical studies [49, 190]. In a recent article [49], it has been emphasized that ZnO based nanostructures are most promising materials for wound healing owing to its excellent microbicidal and its anti-inflammatory effects along with a source of essential Zn ions. In this field, there is a need to develop medical devices based on ZNSs that are able to improve and accelerate the wound-healing process in the patients affected by burns or chronic wounds.

3.6 Applications in anticancer activity

Cancer ranks among the top five primary causes of death among humans [191]. Immunotherapy is a form of cancer treatment that focuses primarily on boosting the body's natural defenses against the disease by stimulating the immune system[192]. However, limited therapeutic efficacy and substantial systemic toxicity have been observed with the current tumor immunotherapy employed in the clinic. Anticancer immunotherapies based on nanomaterials [193] have indeed been created to improve the body's antitumor immune response while reducing systemic toxicity, thereby overcoming the limitations of conventional medications for immunotherapy. In recent years, photo controlled nanomaterials irradiated by excitation light have found widespread application in drug delivery and photo controlled switching due to light's noninvasiveness, remote controllability, and high temporal and spatial resolution[148].

ZNSs have been found to be effective against tumor cells due to their unique chemical and physical properties. This discovery was made quite recently. According to studies [194-197], ZnO NPs have been shown to exhibit high cancer cell selectivity, as well as the ability to retain drugs with ligands attached to them and to release them in a controlled manner[198]. Due to the presence of zinc in trace amounts throughout the body, ZnO NPs exhibit less toxicity and excellent biocompatibility. When the pH is lower than 5.5, ZnO NPs break down into Zn²⁺ ions in a manner

that is analogous to the acidic microenvironment of tumors. It makes it possible for ZnO NPs to exert a lethal effect on tumor cells by causing mitochondrial malfunction, an outburst of ROS, lipid peroxidation, DNA damage, and eventually apoptosis[199, 200]. In addition, its potential as a nanocarrier for cancer treatment can be attributed to several factors, including its easy detection because of its intrinsic fluorescence, the ease of its manufacturing procedures, and its inexpensive cost. Due to the juvenile lymphatics and leaky vasculatures that are present in tumor tissue, such nanocarriers have the potential to easily extravasate and aggregate in the tumor location[201]. Because of this phenomenon, which is referred to as the enhanced permeability and retention (EPR) effect [202], it is possible for nanomedicines to be dispersed in the tumor region without using active tumor targeting. On the other hand, passive tumor targeting that is based on the pathophysiological properties (such as pH and temperature) of the tumor location also has certain drawbacks. The inability to precisely distribute anticancer medications to the site of the tumor can be hampered by the absence of tumor specificity. In addition, because of the high density of tumor cells and the high interstitial fluid pressure (IFP), nanomedicines are only able to pass through a limited number of layers, which makes it impossible to verify that they are distributed evenly and properly[203]. It is hoped that this challenge can be overcome through active tumor targeting, in which the nanocarriers can be changed by attaching some ligands that are unique to the receptors that are overexpressed specifically on tumor cells (**Figure 11**).

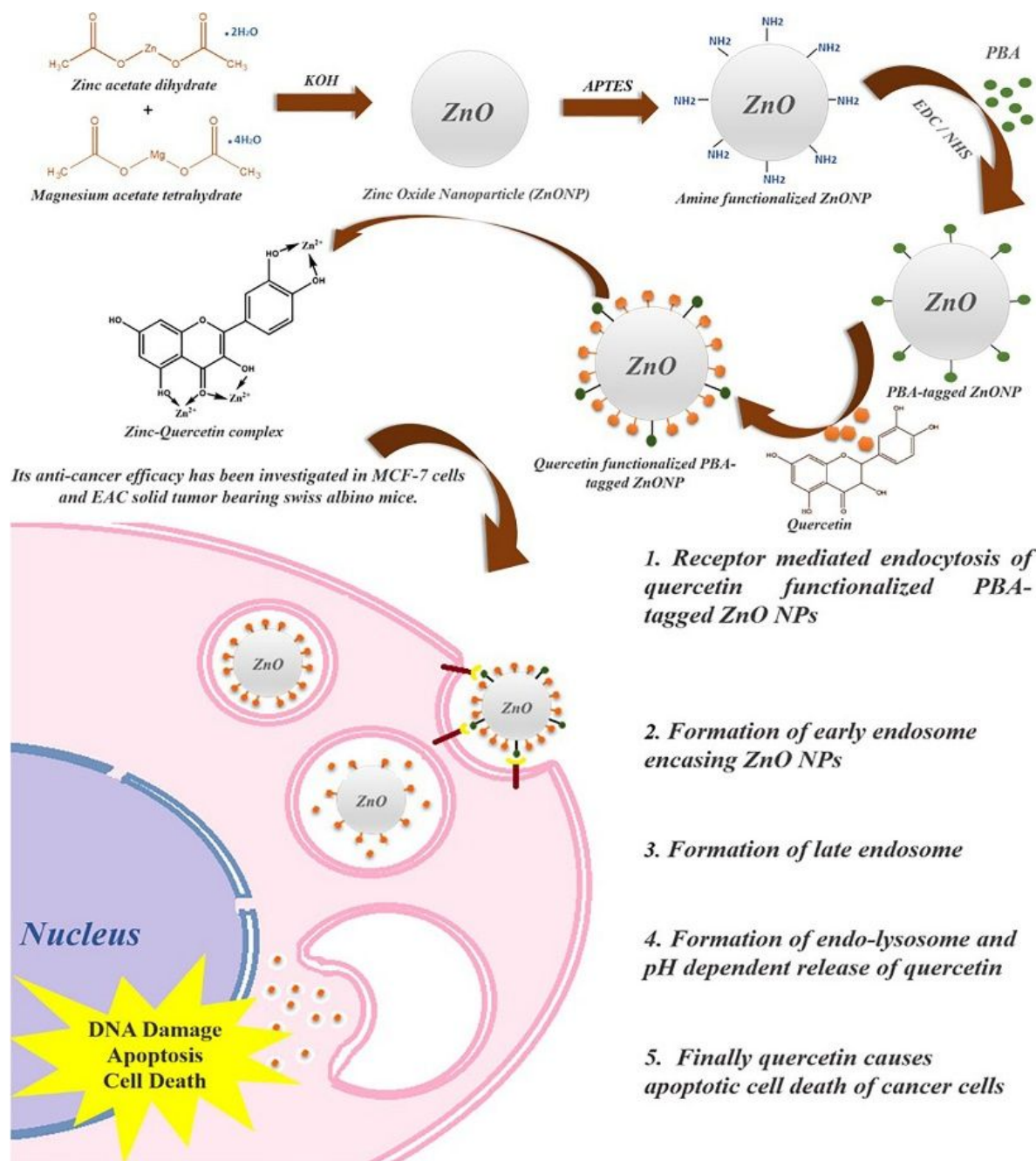


Figure 15. Scheme 1: A simplified representation of the ZnO-nanohybrid synthesis and an explanation of its likely intracellular mode of action. Reproduced from Ref. [204] with permission from [Elsevier], copyright [2019].

3.7 Application in tissue engineering

Numerous enzymes in metabolic pathways require zinc as a co-factor to be activated [202]. ZnO NPs are utilized in the scaffolds for tissue regeneration as a result of their potent antibacterial,

antioxidant, collagen production, and bio-mineralization characteristics. [205, 206]. Münchow et al. [207] used a novel ZnO NRs (65 nm) electrospun membrane to study gum regeneration. These membranes showed antibacterial activity with increasing ZnO NRs concentrations, but they did not affect human dental pulp stem cells. The researchers found that low-ZnO NRs membranes might be used for guided tissue and bone regeneration. In another study, Marycz et al. [208] investigated the effects of polyurethane/poly lactide-blend (PU/PLDL) films doped with ZnO NPs as a scaffold on human adipose stromal stem cells (ASCs) and olfactory ensheathing cells. Polymer membrane films containing ZnO NPs boosted cell proliferation. These films also inhibited apoptosis in ASCs by downregulating apoptosis-related genes. It was suggested that such polymer based membranes and films could be useful in cell recovery and regeneration. It was also suggested that for maximum tissue regeneration, antibacterial, antioxidant, and anti-apoptotic properties, ZnO should be used at lower concentrations to avoid harmful effects of greater doses.

Recently, Yousefi et al. [209] analyzed ZnO NPs/chitosan based tubular scaffold for tendon repair in a rabbit model. Eight weeks after treatment, the scaffold was completely absorbed. The scaffold also reduced tendon adhesion and prevented local infection. The scaffold's rapid angiogenesis and collagen fibril rearrangement revealed its potential application in treating tendon acute injuries. Forero et al. [210] explored chitosan/gelatin/nano-hydroxyapatite scaffold with nano-copper-zinc alloy (nCuZn) for potential applications in bone tissue engineering. The scaffolds boosted proliferation, adhesion, and osteogenic differentiation. The nanohybrid scaffolds also enhanced granulation tissue development following in vivo subcutaneous insertion. It was suggested that such nanohybrid scaffold could be potentially used in bone tissue engineering, according to findings. Chen [211] used polyvinyl alcohol/chitosan/ZnO nanofibers based sheets as a scaffold for human fetal osteoblasts and reported excellent results in view of increased calcium secretion and alkaline phosphatase activity, and promoting osteogenic mineralization along with excellent antimicrobial activity.

Shitole et al. [212] constructed a nanofibrous scaffold containing polycaprolactone (PCL), nano-hydroxyapatite (nHA), and ZnO nanofibers (318.19 nm & rod shaped) (1-30 wt. %) for bone tissue regeneration utilizing human osteosarcoma (MG-63) cells. The ZnO scaffold showed optimum cell viability, biomineralization, antibacterial activity (against gram-negative and positive bacteria), and mechanical strength. Furthermore, scaffolds containing 15 or 30% ZnO inhibited

cellular growth and were cytotoxic due to increased ROS production. The scaffold containing 10% ZnO NPs could be used to regenerate bone. Green synthesized ZnO NPs via *Artemisia annua* stem extract with improved osteoblast proliferation, differentiation, and calcium mineralization without cytotoxicity exhibited excellent bone regeneration activity for MG-63 Cells. ZnO NPs [213]. Similarly, there are number of studies including PCL/nano-hydroxyapatite scaffold with ZnO NPs [214] exhibited superior antibacterial and cell growth, nano-hydroxyapatite/ZnO and PCL/ZnO showed bone tissue regeneration [215]. These scaffolds showed excellent and greater biocompatibility and biomineralization provided with nano-porous matrix for the attachment and proliferation of cells.

According to the above mentioned literatures, ZnO NPs have the potential to rebuild bone, gum, tendon, and nerve tissues. However, the application of ZNSs in tissue engineering is very limited and need to explore in more details. Hence, the tissue regeneration property of ZNSs has to be researched further for its wide application in the field of tissue regeneration/engineering.

3.8 Applications in bioimplants

Bioimplants have been developed as a potentially effective treatment option in case of variety of illnesses, including neurological problems, visual impairments, cardiovascular disease, orthopedic concerns, disfigurement, and dental disorders, etc. [216]. Moreover, the objective of bioimplant engineering is to develop biological alternatives with a possibilities to restore/maintain, or modify the functionality of organs and/or damaged tissues. Recent studies show that functional nanomaterials have that potential to mimic the surface properties of natural tissues. It is possible in terms of modifications of surface topography, surface chemistry, surface energy, surface wettability etc. of novel functional nanomaterials to stimulate the growth of a range of tissues in bioimplants [217, 218].

A great deal of research has been followed on functionalization of bio-nanomaterial surfaces to increase cell adhesion, proliferation etc. for the purpose of developing implants with potent antimicrobial action[219]. The possible use of nanostructured materials, films or coatings over implant surface can overcome many challenging issues i.e. corrosion resistance and bacterial adhesion). These challenges are associated with conventional metallic or non-metallic implants, particularly for the purpose of optimizing implant procedures. Porous nanostructures, smart biomaterials, and 3D implants are examples of some of the emerging concepts in orthopedic

biomaterials that hold great promise for achieving the necessary qualities and structure of an implant with stimuli-responsive behaviors[220, 221]. For example, in-situ polymerization of curcumin into PU/ZnO nanocomposites was shown by Shah et al.[222] using ZnO NPs with superior hydrophilicity, higher mechanical properties and biocompatibility. A constant mole ratio of HDI: PEG: curcumin: BDO (2.5: 1.4: 0.1: 1) was used in the synthesis process of the nanocomposites along with varied contents of ZnO NPs (2-5%). The polymer nanocomposites were found to be with remarkable thermo-mechanics, elasticity, water absorption capacity, antibacterial properties and well-dispersed ZnO NPs. **Figure 16** shows antibacterial activities and synthesis process of polymer nanocomposites. It is expected that the results from this study might indicate that sufficient ZnO nanoparticles should be added to the material of the CPU in order to improve the qualities of the material, and that the material might also be suitable for use in biomedical applications.

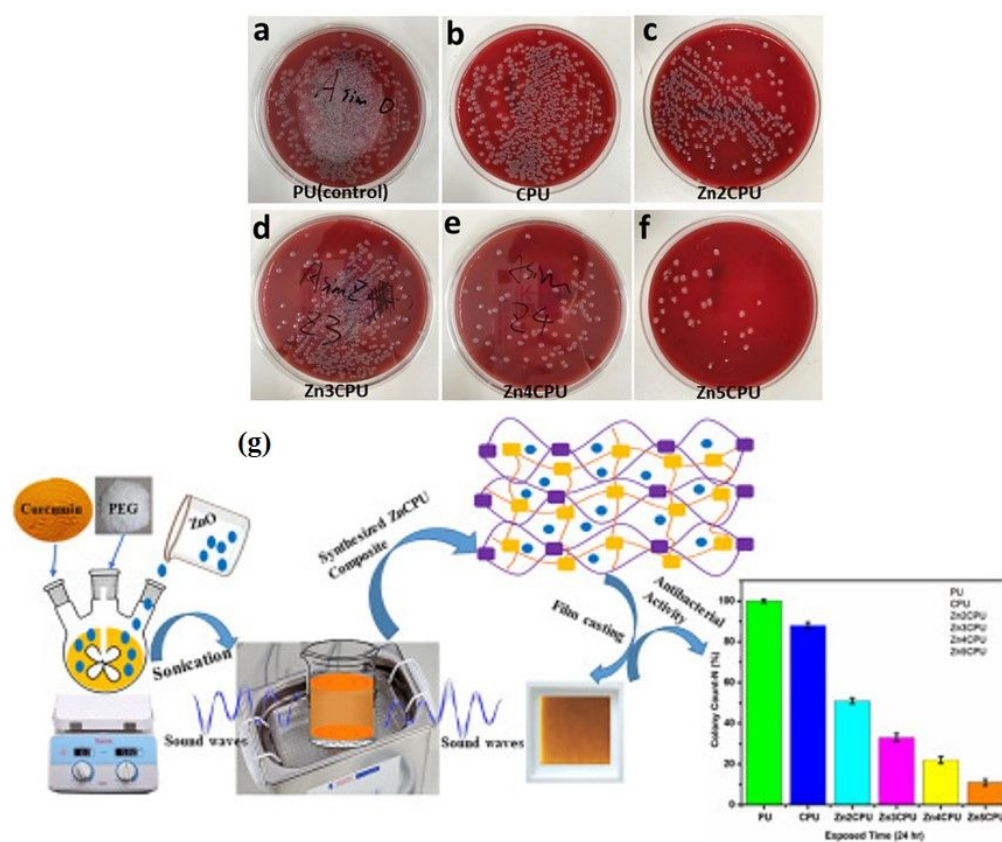


Figure 16. (a-f) Photographs of agar plates with control and different compositions and (g) Curcumin-incorporated PU/ ZnO nanocomposites synthesis with the antibacterial results. Reproduced from Ref. [222] with permission from [Elsevier], copyright [2022].

Wojcik et al.[223], recently reported biomaterials containing gentamicin and Zn-doped nano-hydroxyapatite to lower the risk of infection in wounds which exhibited bactericidal activity against *S. aureus*. Interestingly, it did not cause any toxicity when tested on human skin fibroblasts. The produced biomaterial displayed a bactericidal effect against *P. aeruginosa* in addition to other bacteria (*S. aureus*). Such biomaterials have the potential to take in germs, kill them while they are trapped inside their gel structure, and then release them. In addition, the effectiveness of gentamicin-loaded material was demonstrated by the successful treatment of an acutely infected wound in a veterinary patient. The Zn-loaded biomaterial, on the other hand, has the potential to be applied to wounds as a dressing in order to decrease and prevent microbial infection.

The relatively recent field of theranostics, which encompasses drug delivery, tissue targeting, bioimaging, and cancer therapy, has made significant use of Zn-based ceramic NPs for a wide range of applications (**Figure 17**)[224]. Such nanomaterials with distinct morphologies possess a high surface-to-volume ratio, excellent photoluminescence, antibacterial activity and good biocompatibility. For example, Zn-based organic biomaterials, i.e. metal–organic frameworks (MOFs), also possess excellent surface properties in addition to pH responsiveness, which positions them as potentially useful materials for drug administration, bioimaging, and cancer therapy.

3.9 Applications in bioimaging

As discussed above, the inherent photoluminescent properties and high compatibility of Zn-based ceramic NPs make them a more desirable choice as bioimaging agents than standard organic fluorescent dyes[225]. Most of the Zn based nanomaterials including ZnO, ZnS, ZnSe, and ZnAl₂O₄, have been investigated for their potential benefits in bioimaging[226]. In order to achieve chemical stability and high photoluminescent quantum yield in aqueous solutions, particularly in circulating blood, surface modification utilizing specific polymeric or silica ligands to construct a core-shell is a critical method [227]. Since the animal body cannot be penetrated by UV excitation when using ZnO QDs for in vivo animal imaging, a dual model imaging ZnO-based nanoprobe incorporated with radionuclide (for example, ⁶⁴Cu) or rare earth elements (for example, Gd³⁺ and Yb³⁺) were used to achieve good tumor targeting and image contrast. Measurements were shown to be comparable with ZnS, ZnSe, and ZnAl₂O₄ QDs that had been doped with Ag, In, and Cr [228, 229]. However, the biosafety of these doping elements is a major concern. As a result of their

superior biocompatibility, Fe, and Mn may be suitable alternatives [230]. Targeted bio-labeling of fluorescent ZnO nanoclusters, which were biosynthesized and preferentially aggregated in the hippocampus, was used as well in order to carry out *in vivo* bioimaging of Alzheimer's disease [231]. This was carried out to label the nanoclusters with specific biological markers. Amna et al. [100] demonstrated phase-contrast microscopy data indicated that C2C12 cells proliferated well on ZnO/TiO₂ NFs between 1 and 10 g/ml, and morphology confirmed that cellular attachments were present. This research in comparison to the titanium substrate and the control, the nanostructured ZnO/TiO₂ hybrid nanofibers exhibit improved cell adherence, proliferation, and spreading. Similar results with high spatiotemporal dual modality bioimaging (i.e., magnetic resonance and fluorescence imaging) were obtained in a subsequent study by the combined injection of ferrous chloride solution post-stomach, and Zn gluconate solution post-tail vein, into Alzheimer's model mice, as shown in **Figure 17** [230]. This was done to obtain similar results with high spatiotemporal dual modality bioimaging. These results reveal that the usage of Zn-based ceramic NPs is more suited for use in bioimaging applications than the use of standard organic fluorescent dyes and routinely utilized CdSe and CdTe QDs.

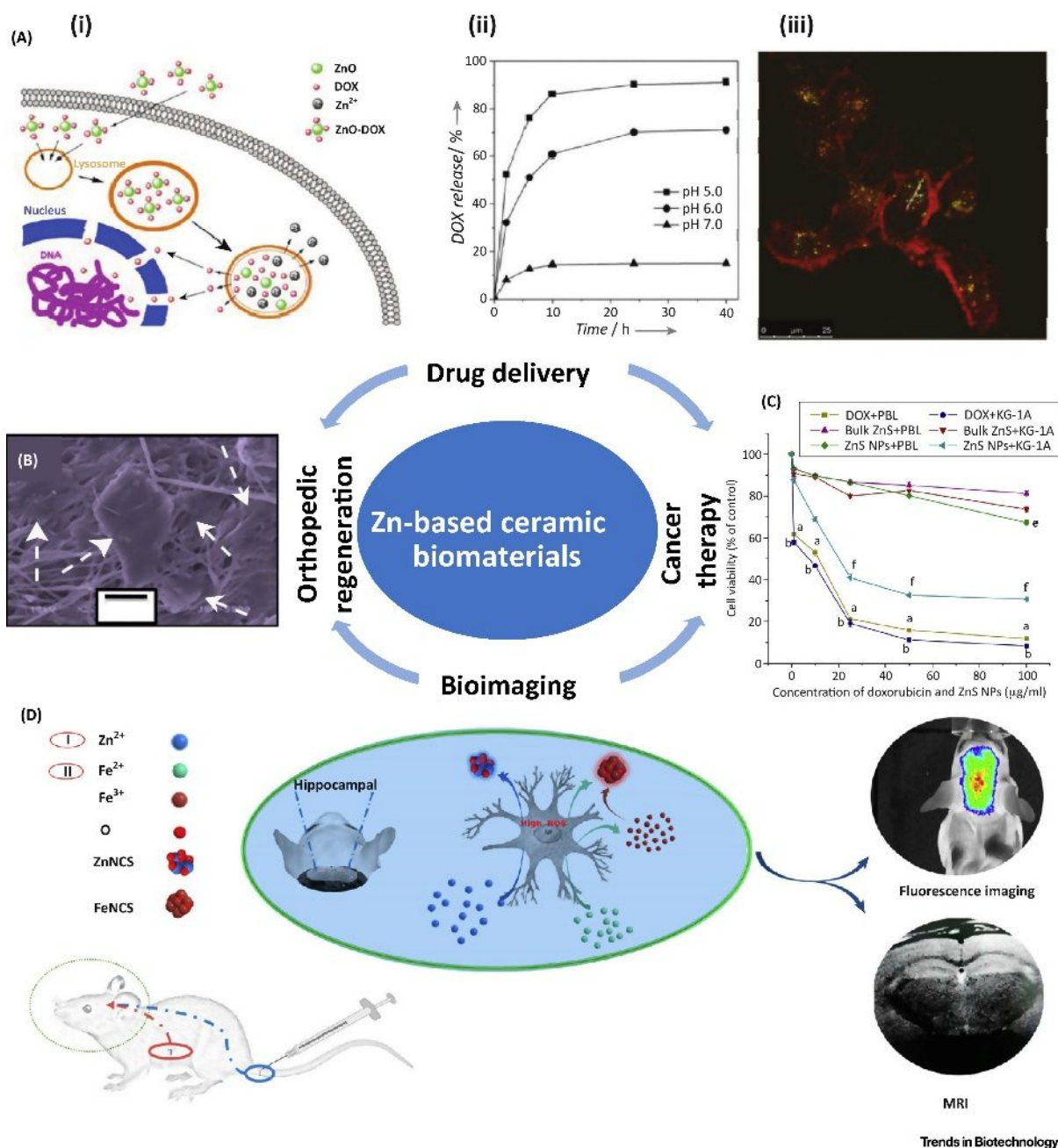


Figure 17. (A) Zn-based ceramic biomaterials potential clinical applications. Multifunctional ZnO @polymer–DOX composites for drug delivery: (i) schematic delivery mechanism into cells, (ii) drug release profiles at different pH values, and (iii) CLSM pictures of U251 cells after 3 h incubation with the composites and lysotracker. The lysotracker emits green light; composites emit red. Reproduced Ref. [224] with permission from [John Wiley and Sons], copyright [2013] (B) SEM photos of C2C12 cell spread pattern on electrospun ZnO/TiO₂ nanofibers after 72 h. Reproduced from Ref. [100] with permission from [John Wiley and Sons], copyright [2013]. (C) Cell viability assay of PBL and KG-1A cells cultured with DOX, ZnS powder, and ZnS NPs during 24 h, Reproduced from Ref. [226] with permission from [John Wiley and Sons], copyright [2014]. (D) Graphical representation of in vivo dual modality bioimaging of modelled Alzheimer's mice brains using biosynthesized zinc and iron oxide. Reproduced from Ref. [230]. with permission from [American Chemical Society], copyright [2017].

3.10 Phototherapeutic applications

Light-activated phototherapy with a suitable nanomaterial which could be activated by light irradiation or photosensitizer- may be useful in controlling cancer at high specificity and tumor selectivity [232]. Since ZnO is an excellent photocatalytic material and it generates ROS under the influence of light irradiation, therefore, ZNSs have shown great potential for phototherapeutic applications in biomedical fields [198, 233, 234]. Such ROS produced and the resulting phototoxicity are generally very effective in killing the cancer/tumor cells or tissue engineering. As compared to the traditional ways of cancer treatments i.e. systemic toxicity, radiation therapy which could also possibly damage the normal neighbouring normal cells also, phototherapeutic treatment using ZnO kind of nanomaterials does not impose any side effect of toxicity towards other biological systems [235]. For example, Zhang et al. [236] studied the phototherapeutic application of ZnO based nanomaterials as photosensitizers in photodynamic therapy (PDT) for cancer treatment. It was concluded that ZnO NPs could generate ROS within the tumor cells after UV light irradiation resulting in the inactivation of cancer cells. Similarly, a core-shell hybrid iron oxide-ZnO NPs as photosensitizer were used in PDT of human epithelial colorectal adenocarcinoma (Caco-2) cells [235]. Interestingly, under the influence of UV irradiation, ZnO based photosensitizer exhibited the photo-killig mechanism with a great reduction in Caco-2 cell viability to 6% attributed to the cellular interactions with light irradiated ZNSs. Similarly, Firdous et al. [232] et al. fabricated ZnO NRs based photosensitizers for the diagnosis and treatment of cancer using lasers as shown in **Figure 18 (a)**. It was demonstrated that such ZNSs can served as a biomarker for cervical carcinoma cell line (HeLa) through PDT due to their striking combination of optical, physical, mechanical and chemical properties. The fluorescence of the ZnO NRs was monitored for effective necrosis of the cancerous cells. The whole procedure for the cellular apoptosis and narcosis producing heat and ROS based on fluorescence imaging-guided PDT in tumor cells is shown in **Figure 18 (b)**.

Antitumor activities of photo-stimulated ZNSs have extensively been studied in recent past [237, 238]. Very interestingly, core-shell based ZNSs which contained a core of upconversion NPs, a layer of mesoporous SiO₂ with anchored ZnO nanodots along with an outer layer of polypyrrole was proposed to exhibit both photothermal therapy (PTT) as well as PDT [237]. Such ZNSs could

emit UV radiation upon irradiation with NIR irradiation due to the presence of upconversion NPs. The emitted UV radiation could trigger the ZnO nanodots to produce ROS around cancerous cells realizing the PDT function. Additionally, polymer layer could produce the heating effect due to the NIR irradiation to achieve synergistic PDT and PTT effects leading to the anti-tumor efficiency *in vitro* and *in vivo* as shown in **Figure 18 (c)**[237]. Similarly, Vasuki et al. [239] developed NIR light active ternary modified ZnO nanocomposites for combined PDT and PTT cancer therapy for *in vitro* cytotoxicity studied on human breast cancer cells (MCF-7) the human embryonic kidney normal cells (HEK 293) and results are shown in **Figure 18 (d)**.

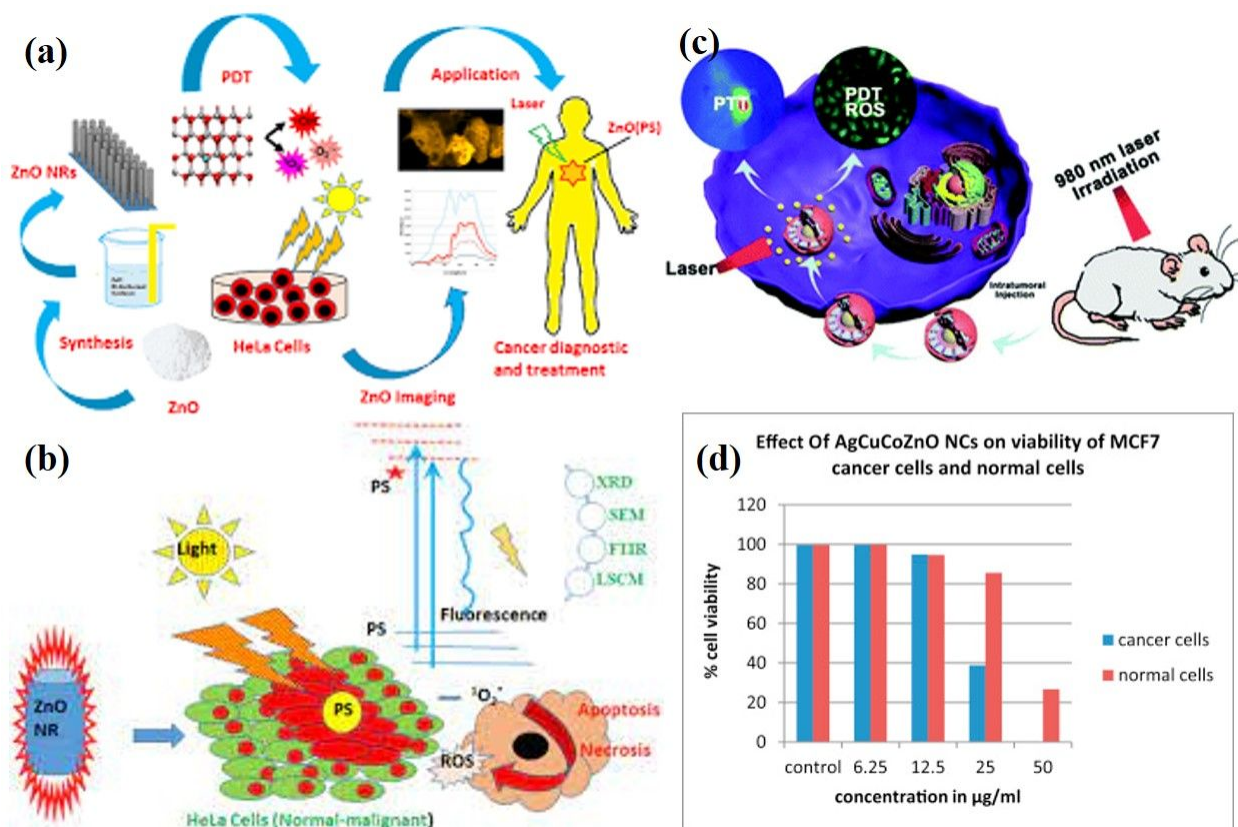


Figure 18: Schematic illustration of (a) the synthesis and application of ZnO NRs as a photosensitizer and biomarker used for the PDT of cancer cells (b) the whole procedure for the cellular apoptosis and necrosis producing heat and ROS based on fluorescence imaging-guided PDT in tumor cells. Reproduced from Ref. [232] with permission from [IOP publishing, Ltd], copyright [2018]. (c) Schematic of ZNSs based nanocomposite for combined PDT and PTT. Reproduced from Ref [237] with permission from [Royal Society of Chemistry], copyright [2018] (d) The percentage viability of MCF7 cancer cell lines and HEK 293 normal cell lines using MTT assay after 48 h exposure to AgCuCoZnO. Adopted from Ref. [239].

The ZNSs-assisted UV treatment was shown very effective with linear and quadratic positive effects on the *in vitro* bilirubin photolysis. Based on the trial of ZNSs assisted phototherapy of

hyperbilirubinemic animals, it was suggested that it could be useful for a potential treatment for hyperbilirubinemia in humans [240]. Lin et al.[241] demonstrated the photoprotection/phototoxicity on human fibroblast Hs68 cells using various ZnO nanostructures i.e. nanospheres, NRs, and nanoflowers. It was explained that such photoprotection using ZnO nanostructures might be useful in preventing photocarcinogenesis, photoaging, and photosensitivity induced in human body/skin caused by exposure to the sun[241]. Similarly, phototherapy has been developed for antimicrobial treatment [242, 243], for example, Jin et al. [244] demonstrated that dual UV-multiscale ZnO, other metal oxide NPs, their hybrids exhibited enhanced antibiotic potentials which could also be applied as a next-generation antibiotic tool in industrial and clinical fields. Studies indicate that ZNSs are the most promising next-generation photocatalyst materials for phototherapeutic applications in biomedical fields due to their unique phototoxic effect upon UV radiation which can also be tailored through doping and other processes [234]

4. Toxicological implications and clinical translation of ZnO-based nano-architectures

ZNSs have been extensively studied for their potential biomedical applications, including drug delivery, tissue engineering, and biosensing. However, concerns have been raised about their potential toxicological implications. Recent research has focused on understanding the mechanisms of ZnO nanotoxicity and developing strategies to mitigate these risks. One of the main challenges in assessing the toxicological implications of ZNSs is their diverse range of properties, which can vary depending on their size, shape, and surface chemistry. This can make it difficult to generalize findings from one study to another. Additionally, the mechanisms by which ZnO nanomaterials interact with biological systems are complex and not fully understood.

Despite these challenges, significant progress has been made in recent years in understanding the toxicological implications of ZNSs. One of the key findings is that ZnO NPs can generate ROS[245], which can damage cells and lead to inflammation. ROS generation is thought to be one of the main mechanisms by which ZnO NPs exert their toxic effects. Another important finding is that ZNSs can interact with proteins and other biological molecules, which can disrupt cellular processes and lead to cell death. Additionally, ZnO NPs can accumulate in tissues and organs over time, which can lead to long-term toxicity [246].

Despite the potential toxicological implications, ZnO nanomaterials remain a promising platform for biomedical applications. Researchers are developing strategies to mitigate the risks associated

with ZnO nanomaterials, such as by modifying their surface chemistry or encapsulating them in protective coatings [247]. Additionally, researchers are developing new ZnO nanomaterials with improved biocompatibility and reduced toxicity [248]. Here are some specific examples of recent research advancements regarding the toxicological implications and clinical translation of ZnO-based nano-architectures:

(i) A recent study published investigated the toxicological effects of ZnO nanoflowers on human lung epithelial cells. The researchers found that ZnO nanoflowers induced ROS generation and cell death in the lung cells. The study also found that ZnO nanoflowers accumulated in the lung cells over time, which could lead to long-term toxicity[249].

(ii) Chong et al. developed a new type of ZnO nanomaterial with improved biocompatibility and reduced toxicity. The researchers encapsulated ZnO NPs in a biocompatible polymer coating. The coated ZnO NPs showed reduced cytotoxicity and genotoxicity in human cells[179].

(iii) A recent study investigated the use of ZnO nanomaterials for drug delivery. The researchers developed a ZnO nanocarrier that could be used to deliver the anti-cancer drug doxorubicin to cancer cells. The ZnO nanocarrier was found to be effective in delivering doxorubicin to cancer cells and killing them [250].

5. Key issues, open challenges, and prospects

There are several key issues which are needed to address for the successful implications of the ZnO based nanomaterials in form of diverse nano-architectures, films and coatings for their practical/clinical applications in the biomedical fields: -

- Nanotechnology can revolutionize tissue regeneration and repair. However, developing nanomaterials that can signal diseased or damaged cells and tissues to regenerate is a challenge [251].
- Clinical application studies to assess side-toxicity and stability in exposed conditions in vitro and in vivo are lacking. This prevents commercialization of ZnO-based antimicrobial coatings. [140].
- It is important to place a greater emphasis on the structure–activity connection of photo-induced toxicity of ZnO NPs. This is particularly the case for forms of ZnO that are applied as thin film coatings, as these forms are not as apparent as nanoparticulate forms.

- The process of photodegradation, which is brought on by exposure to ultraviolet light, commonly has become an issue with ZnO coating and brings about structural alteration because of changes in the properties of the coating. The ZnO coating's photooxidation problem is continuously being investigated and solved[252].
- PLA biomaterials assist in advancing biomedical additive manufacturing (AM). It is noted that PLA is susceptible to typical sterilizing procedures and chemical disinfectants, limiting its use. Adding fillers like ZnO NPs to PLA can give it improved antibacterial properties. It is uncertain whether PLA-ZnO nanocomposites will stay functional following additive AM processing. Additive manufacturing is an extension of existing manufacturing methods in post-pandemic with a aim to provide consumers with safer products for a safer environment[253]. Additional research is needed to 3D print safe and practical PLA-ZnO parts.

6. Summary and conclusion

Functional nanostructured materials in form of diverse nano-architectures, thin films and coatings with desired properties are promising for potential practical applications in biomedical field. However, producing such materials and maintaining/tailoring their properties are very challenging. This review presents the nano-architecting aspects of ZnO based nanomaterials, thin films/coating and their biomedical applications. Extensive discussion was focused on the ZNSs with diverse nano-architectures, thin films/coatings, tailoring of their opto-electronic and surface properties etc. in view of the investigations made in last few years with emphasis on their promising biomedical applications. It has been found that ZNSs and thin films or coating with diverse 0-3D nano-architectures are promising for several biomedical applications including bioimaging, bioimplants, tissue engineering, biosensing, wound healing, and anticancer/antibacterial/antiviral agents etc. There are several interdisciplinary approaches to control their properties for their wider applications in several other fields of nano-biotechnology. In addition, emerging applications of ZNSs in phototherapeutic applications has been discussed.

In addition, recent development in all these directions including synthesis (brief) and engineering of ZNSs and thin films/coatings with diverse nano-architectures (0-3D) with emphasis on their multifunctional biomedical applications have been discussed. It has also been found that polymer

films embedded with ZNSs would be easier to apply from practical applications point of view in biomedical applications. Apart from this, several key issues and challenges regarding use of such nanostructures, thin films and coatings in biomedical applications have been discussed in view of their potential application in practical world. Surface engineering of ZNSs and suitable nanocomposite formation are the key parameters to enhance their functionality for their multifunctional potential applications. Eventually, the detailed discussion indicates that ZnO based diverse nano-architectures have great potential to be considered as futuristic bio-nanomaterials.

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