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Review

Advances in tannic acid-incorporated biomaterials: Infection treatment, regenerative medicine, cancer therapy, and biosensing

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ABSTRACT

Polyphenol-based materials have attracted wide-spread interest from academic and industrial communities because of their unique structure and physicochemical properties. Tannic acid (TA), as a polyphenolic phytochemical with high level of galloyl groups, interacts with various substances (proteins, polysaccharides, and metals) through several modes including hydrogen bonding, hydrophobic and electrostatic interactions. Such hybrid or hybrid-like systems allow the preparation of various advanced materials with promising applications in medicine. In this review, we highlight the recent advances of TA-incorporated materials in medical applications including drug delivery, tissue engineering, treatment of infections, cancer therapy and biosensing. We believe that this review provides further investigation and development of TA as a promising natural compound to design new versatile architectures in the field of materials science.

1. Introduction

Tannins are non-toxic and ecologically friendly polyphenolic phytochemicals found in beverages and foodstuffs, particularly in red wine, green tea, raspberries, and black-eyed peas [1]. Tannins are classified into two categories, namely condensed tannins (non-hydrolyzable) and hydrolyzable tannins [2]. Tannin, as a polyphenol, possesses a wide range of restorative, therapeutic and pharmacological properties including anti-cancer, anti-inflammatory, antimicrobial, antiviral, antioxidant, wound healing, and homeostatic characteristics [3,4]. Aside

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from the aforementioned properties, tannins neutralize free radicals, which can be employed in various medical complications such as allergies, diabetes, Parkinson's, Alzheimer's, and cardiovascular diseases [5,6]. Currently, tannic acid (TA) is being studied as an organic additive because it exposes and enhances the bioactive properties of the host materials [7].

Here, the structure and properties of TA were discussed along with highlighting its biomedical applications in drug delivery, tissue regeneration, infection therapy, biosensing, and cancer treatment. This is followed by a discussion on cytotoxicity concern for clinical translation. This review covers the capability of TA-based supramolecular materials to generate different structures with many potential medical applications.

2. Structure and properties

TA as a naturally occurring polyphenol compound exists in almost all tissues of aerial plants. The peculiar features of TA are on its unique structural characteristics. Based on structural analysis, TA has a central glucose molecule, which is connected to 10 gallic acid units through five diacetyl ester groups (Fig. 1) [8-10].

In the mid-nineteenth century, Adolf Strecker determined that TA consists of the combination of glucose and gallic acid with the molecular formula of $C_{27}H_{22}O_{17}$ [11]. Over half a century later, K. Feist discovered that TA is a blend of two ester-like molecules of glucosylgallic acid and gallic acid, as he noticed that the crystalline compounds gallic acid and glucose can be separated from Turkish nutgalls [3]. Nobel Prize winner Emil Fisher and his disciples almost contemporaneously performed a comprehensive study to identify tannins [12]. They proposed that TA is a mixture of very similar substances, for instance, a penta-(digalloyl)-glucose with a tetra-(digalloyl)-glucose or tri-(digalloyl)-di-(galloyl)-glucose. Those days, a mixture of polygalloyl glucose molecules was considered to be TA and usually demonstrated with the empirical formula $C_{76}H_{52}O_{46}$ [3]. TA has numerous features such as anti-mutagenic and anticancer properties. It shows activity against micro-organisms (bacteria and viruses) and acts as an antioxidant and homeostatic agent [13]. The physicochemical and biological properties of TA are tabulated through Table S1.

Besides their diverse biological properties, TA also possesses unique physicochemical features. In fact, the catechol and pyrogallol functional groups of TA are responsible for its interaction with various species through multiple hydrogen bonding, π–π, hydrophobic, coordinative interactions, and dynamic covalent complexation with boronate groups (Fig. 1) [14]. For example, the high number of phenolic residues in the TA's structure provides hydrophobic domains which are able to make an interaction with collagenase cleavage sites followed by preventing the protease activity of the enzyme. Collagenase breaks down the native collagen that holds animal tissues together. Such non-covalent interactions produced a tight cluster playing a barrier role against water penetration resulting in the successful suppression of the collagenase enzymatic activity [15].

Benefiting from the reducing property of TA, it could act as an anti-oxidant and ROS scavenger agent. For example, the anti-oxidant activity of manganoporphyrin-TA microcapsule as a high-performance catalyst has been demonstrated [16]. Such anti-oxidant capacity of the TA-based systems endowed them with anticarcinogenic activity as well [17]. In a study, it was indicated that TA was a selective CXCL12/CXCR4 antagonist and could inhibit tumor cell migration and angiogenesis *in vitro*. CXCL12 is a type of chemokine which is highly involved in cancer metastasis [17]. The antimicrobial property of TA relates to its direct action against bacteria and the suppression of microbial virulence factors including neutralization of bacterial toxins, prevention of biofilm formation, and restriction of host ligand adhesion [18]. It is noteworthy that the adhesive feature of TA comes from the pyrogallol or catechol groups [19]. In addition, the functional groups on the TA can coordinate with different multivalent metal ions to form metal-TA supramolecular

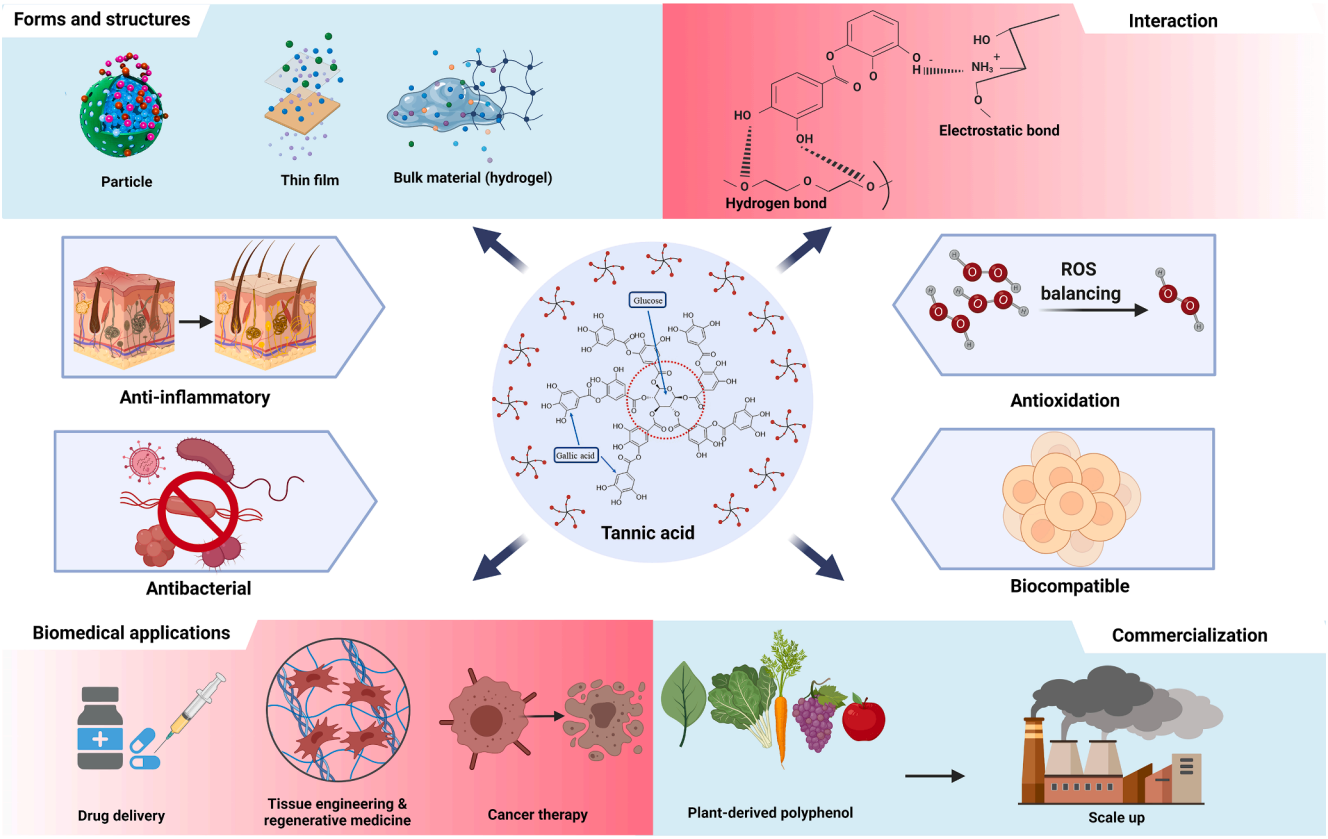


Fig. 1. Schematic illustration of various aspects of TA including structure, forms, interactions, properties, medicinal applications, and commercializations.

amorphous networks. Of note, pH of the coordination process is a key factor, so that in the basic condition the hydroxyl groups of the catechol units can deprotonate, thus largely contributing to the binding of the groups to metal ions [20,21]. Such strong interaction allows to construct a large library of metal-TA networks via self-assembly route without any use of external assistant including heat or light [22]. In addition, the self-assembly can be completed in water in the absence of organic solvents, making the process easy and environment-friendly. Therefore, diverse particles, thin films, and bulk materials (e.g., gels) have been prepared through the above-mentioned interactions and exploited in broad applications (Fig. 1) [19,23]. This unique character makes it as an excellent candidate in catalytic nanomedicine [24-26]. For example, Iron-TA network as an autocatalytic Fenton nanosystem has been used for effective tumor ablation via producing toxic •OH radicals by breaking down of intratumoral H_2O_2 [27].

Encouraged by the low cost, pH-responsiveness, multiple functions, good biocompatibility, biodegradability, and biosafety, the TA-based formulations have been widely investigated for biomedical applications including drug delivery and tissue regeneration (Fig. 1) [22,28,29]. Moreover, there are some examples confirming that scalable fabrication of TA based formulations for drug delivery applications. For example, paclitaxel-loaded TA/poly(N-vinylpyrrolidone) nanoparticles were produced by flash nanoprecipitation process using multi-inlet vortex mixer driven by strong intermolecular hydrogen-bonded interactions among the components of the formulation [30]. The same method was applied to fabricate an all-in-one nanomedicine containing an active-targeting ligand, anticancer drug, and imaging agents (Fe ions) based on iron(III)-catechol coordination interactions as a cancer theranostic [31]. Therefore, such methods open a new window to fabricate this type of formulations via simple and scalable way with composition controllability, high drug loading and minimum batch-to-batch variability. Although promising progresses have been made in this field of study, the long-term toxicity, *in vivo* fate of such formulations, the targeting ability to the tumor or inflamed tissues, *in vivo* biodegradability and renal clearance should be scrutinized. Besides, some clinically relevant indexes e.g., the reproductive toxicity, carcinogenicity, mutagenicity, and genotoxicity of the TA-containing formulations should be addressed in the near future [19].

3. Biomedical applications of TA

3.1. Drug delivery

Drug delivery systems are designed to either target specific location or release therapeutic agents controllably at a particular site. They can bypass traditional shortcomings of the administration of drugs in free-form such as chemical instability, low bioavailability, poor solubility, and systemic cytotoxicity. Without considering the carrier's composition, drug delivery systems are capable of improving the bioavailability and uptake of drugs, and release their cargo in a specific target in a controlled manner [32-34]. An ideal drug delivery system should have the following criteria: (*i*) drug loading greater than 20 % per total weight; (*ii*) preventing the cargo from degradation in physiological medium without sacrificing colloidally dispersity; and (*iii*) releasing the drug molecules with a sustained rate in the target tissue [35]. Having a glucose molecule in the center surrounded by 10 gallic acid units, TA is endowed with multiple hydroxyl groups ready to interact with different types of materials. At physiological pH, the hydroxyl groups of TA are negatively-charged as the pK_a of TA is 6–8.5, culminating in an electrostatic interaction with cationic compounds [36]. In drug delivery, TA has been used as a molecular glue for interaction with drug molecules, polymers, and proteins to form nanoparticulate carriers, hydrogels, and films [37,38]. Then, the resulting TA-based nanoparticles and hydrogels are covalently crosslinked with metal ions to improve their stability. A metal-polyphenol (Fe^{3+}-TA) framework-coated nanoscale liposome was developed for the delivery of rhodamine B, a hydrophilic dye. It was found that the metal ions (Fe^{3+}) in combination with TA were able to bridge the lipid bilayer of the liposomes [39]. This property of TA was later utilized to form depots as a high loading controlled delivery system for drug molecules with reduced dosing frequency [38]. The results demonstrated that TA serves as a barrier in liposomal delivery systems to slow the drug release rate compared to liposomes without TA. Moreover, the release rate was found to be faster in acidic medium than physiological pH [39]. A drug delivery system composed of liposome-coated TA-Fe^{3+} is shown in Fig. 2**A(a)**. In another study, TA was used as an agent for the formation of a mechanically-stable hydrogel for DNA delivery. After exposure of the hydrogel to the physiological medium, the ester groups of TA undergo hydrolysis to release the encapsulated DNA as shown in Fig. 2**A(b)** [37]. In another study, the drug doxorubicin (DOX) was conjugated to polyethylene glycol (PEG) micelles and assembeled with TA into a thin film layer-by-layer. The role of TA was to form strong hydrogen bonds with PEG to facilitate assembly into a multilayer film encapsulating the drug. The interaction between TA and the corona of PEG micelles led to sustained pH-responsive delivery of the drug, as shown in **2A(c)** [40].

As stated previously, TA is primarily used as an additive to promote interaction between different compounds in the mixture. Recently, the polyanion nature of TA has been exploited as a carrier for encapsulation and delivery of cationic drugs including colistin sulfate, gatifloxacin, and gentamicin sulfate. In this simple process, the drug and TA were prepared in separate solutions, the two solutions were added together, and the pH of the mixture was adjusted. Aside from excellent drug loading of 30–36 wt%, the TA-based carrier showed favorable stability and pH-responsiveness when exposed to an acidic medium. Fig. 2**B(a)** shows the preparation of self-assembled TA complexes with colistin sulfate, gatifloxacin, and gentamicin sulfate as cationic antibiotics and their corresponding molecular modeling with TA. Although the charge density of colistin sulfate is relatively low, its large molecular size (1267.6 Da) culminated in the formation of strong and stable bonds between TA and the drug molecule (eight hydrogen bonds). Gentamicin sulfate formed 10 hydrogen bonds with TA. The TA/colistin sulfate and TA/gentamicin sulfate complexes were in the micron size range and had stable structures. Conversely, gatifloxacin formed only one hydrogen bond with TA, resulting in a less stable structure with a smaller particle size in the range of nanometers. Interestingly, the simulation predicted that gatifloxacin would have higher energy of interaction with itself than with TA [10]. In another study, TA and poly(*N*-vinylpyrrolidone) nanoparticles loaded with paclitaxel were synthesized by intermolecular hydrogen bond interactions between TA and poly(*N*-vinylpyrrolidone). Fig. 2**B(b)** shows the 3D model of paclitaxel-loaded TA/poly(*N*-vinylpyrrolidone) drug delivery system and the interactions between TA and poly(*N*-vinylpyrrolidone). Due to the hydrophobicity of paclitaxel, they aggregate to form the nanoparticles' core, followed by uniform distribution of TA on top of the drug molecules via hydrogen bond interactions. Next, the complexation of TA with poly(*N*-vinylpyrrolidone) occurs imparting a stable structure to the resulting nanoparticles [30]. Another study reported on the synthesis of a stimuli-responsive drug delivery system comprised of DOX, TA, and indocyanine green. As DOX is a cationic drug and TA is a strong polyanion, the positively-charged amino groups of DOX and negatively-charged phenolic groups of TA interact electrostatically to form a complex, which the complex in turn interacts with the anionic indocyanine green to form a more stable ternary complex. The zeta potential of TA changed from $-$ 26.2 $\pm$ 1.55 mV to 19.64 $\pm$ 0.68 mV after complexation with DOX, and shifted again to $-$ 26.31 $\pm$ 2.61 mV after the assembly with indocyanine green, indicating the existence of strong electrostatic interactions between the three molecules (Fig. 2**B(c)**) [41].

Material factors that affect safety and effectiveness of nanoparticulate delivery systems include particle dispersity in physiological medium, biocompatibility, physicochemical properties like particle size, shape and surface charge, and route of administration. Effectiveness of injectable systems is limited by clearance of the nanocarrier from blood

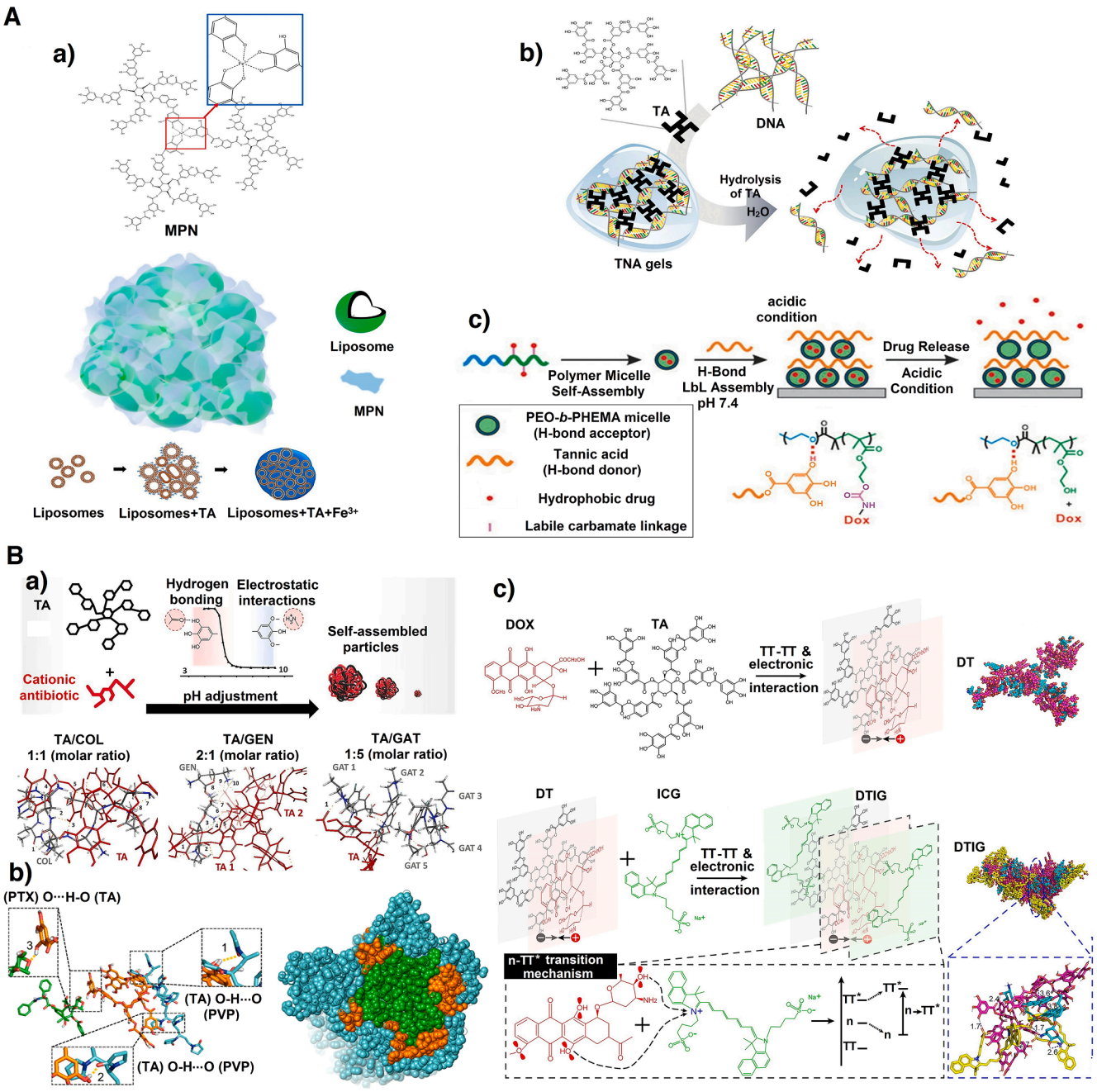


Fig. 2. (A) Incorporation of TA in drug delivery systems. a) The structure of metal-phenolic networks (MPN)-coated liposomes showing the interaction between the hydroxyl groups of TA and Fe^{3+} ions to form an MPN. Reprinted from [39] with permission from American Chemical Society. b) The formation and degradation of TA-DNA hydrogel (TNA gels). Reprinted from [37] with permission from American Chemical Society. c) A schematic showing the formation of DOX-loaded PEG micelles/TA layer-by-layer (LbL) hydrogel films and release of the drug in acidic environment of tumor. Reprinted from [40] with permission from Royal Society of Chemistry. (B) Interaction of TA with different drug molecules. a) TA complexation with colistin sulfate (COL), gatifloxacin (GAT), and gentamicin sulfate (GEN) as cationic antibiotics and the molecular modelling of TA/COL, TA/GEN, and TA/GAT complexes. Reprinted from [10] with permission from Elsevier. b) Hydrogen bond formation (yellow dashed lines) between paclitaxel (PTX in green), TA (orange) and poly(*N*-vinylpyrrolidone) (PVP in cyan) molecules. Reprinted from [30] with permission from American Chemical Society. c) The electrostatic interactions between DOX and TA (DT) as well as DT and indocyanine green (ICG) (DTIG). Reprinted from [41] with permission from American Chemical Society.

circulation, which is mediated by the formation of protein corona on the surface of the carrier. Under *in vivo* conditions, nanoparticles with a large surface-to-volume ratio interact with a wide range of biomolecules including proteins, nucleic acids, lipids, carbohydrates, and proteoglycans. Protein adsorption on the surface of these nanoparticles results in the formation of nanoparticle-protein complex [42]. Among these proteins, opsonins form special complexes that tag the injected nanoparticles for phagocytosis by phagocytic cells, leading to their premature clearance from the circulation [43]. This is similar to the process in which IgG antibodies form complexes with microbial species leading to an immune response to phagocytose microbes [44]. A common approach to circumvent opsonization is to modify the surface of nanocarriers with polymers like PEG that are capable of reducing protein adsorption on the surface of biomaterials [45]. However, PEG surface modification accelerates blood clearance of the nanocarrier by forming a bond between IgM anti-PEG antibody and PEG's -(O-CH_2-

$CH_2)_n$- subunits [46]. It is surmised that TA would be more effective in prolonging the retention time of nanoparticles in circulation [47]. It has been reported that the multitude of hydroxyl groups in TA prevent non-specific protein binding to nanoparticles in plasma, thus avoiding phagocytosis by the reticuloendothelial system, which leads to long retention time of TA-modified nanoparticles [41]. A recent study took advantage of TA and came up with a term called TANNylation which is similar to PEGylation, but for targeting protein and peptide therapeutics to the heart. The main concern with traditional heart delivery systems is their invasive essence requiring surgical procedures. TA is revealed to be easily prepared through mixing with proteins and the combination of TA/proteins-peptides is found to accumulate gradually into the heart's myocardium up to 48 h after injection (Fig. 3) [48].

For comfort, most patients prefer the oral route of administration over parenteral route [49]. Many orally administered proteins are deactivated by denaturation or enzymatic pathways as they transit through the digestive tract. There are safe and effective excipients that can protect and stabilize drug molecules transiting thorough the gastrointestinal cavity [50]. Recent studies demonstrate that covalent complexation of polyphenols like TA with proteins provide greater degree of protection to protein drugs as compared to non-covalent interactions [51]. Hence, TA is potentially a viable and cost-effective candidate for stabilization and bioavailability enhancement of protein drugs administered orally. In a recent study, the model protein β-galactosidase was modified with zein/TA and encapsulated in sporopollenin exine capsules for oral delivery of the protein. It was found that the zein/TA modification improved sustained delivery of the protein as compared to modification with zein only, which was attributed to the stronger bonding of the drug to zein/TA [52]. In another study, a hydrogel composed of salecan-g-poly(*N*,*N*-dimethylaminoethyl acrylate) and TA synthesized via microwave-assisted polymerization, was used for encapsulation of β-lactoglobulin. The encapsulated β-lactoglobulin was released from the hydrogel in a pH-dependent and sustained manner [53]. Corticosteroids are a treat option for patients with inflammatory bowel disease, which is known to cause colitis-associated cancer [54]. TA is hydrolyzed in the presence of esterase enzymes which are upregulated in inflammatory bowel disease. In one study, stimuli-responsive nanoparticles based on TA and triblock copolymers of polyoxypropylene and polyoxyethyene (Pluronic F-127 and Pluronic F-68) were developed for the delivery of anti-inflammatory drug dexamethasone (DEX). The nanoparticles based on TA and Pluronic F-68 resulted in the fastest release of DEX in simulated intestinal fluid, attributing to the faster hydrolysis of TA in the presence of esterase [55].

In a nutshell, the cooperation of TA with different materials has yielded multifunctional drug delivery systems. This plurofunctionality mainly comes from the extraordinary physicochemical properties of TA. The first one is its multitude numbers of functional groups (hydroxyl groups) which can interact with other molecules via hydrogen bond. In addition, the polyanionic nature of TA enables the TA-derived nanocarriers to load cationic drugs and proteins through electrostatic interactions resulting in higher loading capacity compared to the other type of nanostructures. Nonetheless, stimuli-responsiveness is proved to be an important feature in drug delivery systems. TA containing drug delivery nanocarriers possess the potential of being pH-responsive resulting in an improved drug targeting efficiency besides preventing premature drug leakage. As another important factor that plays a crucial role in the effectiveness of drug delivery systems, TA-coated drug delivery systems exhibit stealth behavior leading to a longer circulation time and so more efficiency and effective results.

3.2. Regenerative medicine

The scaffold plays an important role in tissue constructs as a mechanically stable structure for cell adhesion, growth, extracellular deposition and healing [56-58]. The scaffold properties that affect tissue regeneration include porosity, pore size, surface chemistry, roughness, biodegradability, and mechanical properties [59]. The scaffold properties also affect the degree of microbial infection, the host's immune response and inflammation [60]. In this regard, TA has attracted attention as a natural crosslinker to improve stability of biopolymers used in tissue regeneration [61]. The enzymatic degradation of scaffolds based on natural biopolymers (collagen or hyaluronic acid) and scaffold depolymerization by ROS generated by human tissues can be lowered through complexation with TA [62]. Besides TA's crosslinking role in the chemistry of polymers, it is endowed with incredible therapeutic and regenerative properties—anti-inflammation, antibacterial, and anti-oxidation all of which making TA a great candidate for wound healing applications. Therefore, it is not surprising to see that most of research studies about TA in the tissue and regenerative medicine have been devoted to wound healing. However, TA has been applied in other organs as well and through this section, these organs are also covered.

Wound healing process encompasses multiple stages including hemostasis to stop bleeding followed by inflammation to protect the wound bed against microbial invasion, fibroblast proliferation and migration of endothelial and keratinocytes to the injury site, and skin tissue remodeling [63,64]. Chronic wounds may remain in the inflammatory stage of wound healing for a much longer time and the process of healing may not be as orderly as compared to acute wounds [65]. Wound dressings have been used to treat chronic wounds to prevent microbial infection and accelerate healing [66]. The wound dressing stops bleeding by triggering blood clotting, absorbing the exudates, and promoting a healing response [67].

Polysaccharides are very attractive because they provide a moist environment for wound healing [68,69]. A triphasic wound dressing composed of chitosan, PEG, and TA was developed to take advantage of antioxidative and antibacterial properties of TA and the cross-linking and network formation capability of PEG. The addition of PEG improved stability of the film but decreased the rate of hemolysis [70]. In another study, the addition of TA to a chitosan-based wound dressing improved physicochemical properties of the film. Further, the hemolysis rate was elevated with increasing TA content of the film in a concentration dependent manner, which improved blood clotting capability of the film [71]. Hydrogels resemble biological tissues and they have tailorable physicochemical and biological properties. Thanks to their capacity to absorb high volume of fluids and to remove exudates while preserving the wound's moisture at a predefined level, they are widely used in clinical wound healing [72,73]. Regarding to their abundance, biocompatibility, and degradability in physiological medium, natural hydrogels have received special interest as scaffolds in regenerative medicine applications [74]. Among natural hydrogels, hyaluronic acid is a hydrophilic, biocompatible, degradable and non-immunogenic glycosaminoglycan that is abundantly found in animal tissues. However, its application in regenerative medicine is limited by weak mechanical properties and low chemical stability mostly against ROS [75]. One solution to overcome this limitation is to blend hyaluronic acid with TA to increase intermolecular bonding via TA's hydroxyl groups [76]. It is reported that the addition of TA not only improved the mechanical properties, but it also enhanced rheological behavior, enzymatic stability, and cell compatibility of hyaluronic acid-based hydrogels [62]. Silk fibroin is another promising natural-based hydrogel that can be used for regenerative applications. However, silk fibroin-based hydrogels suffer from several shortcomings including weak mechanical properties, slow gelation rate, and poor bioactivity [77]. To overcome these limitations, as shown in Fig. 4, TA has been used as a gelation agent in the production of silk fibroin hydrogels to not only improve the gelation rate, but also to impart biochemical properties like anti-oxidation, anti-inflammation, and antibacterial properties to the hydrogel. The resultant hydrogel was enriched with shear-thinning and self-healing properties as well as suitable adhesiveness, and a fast gelation rate. Moreover, the synergistic effects of antioxidation and antibacterial properties of TA were found to accelerate wound healing in TA-based dressings [78].

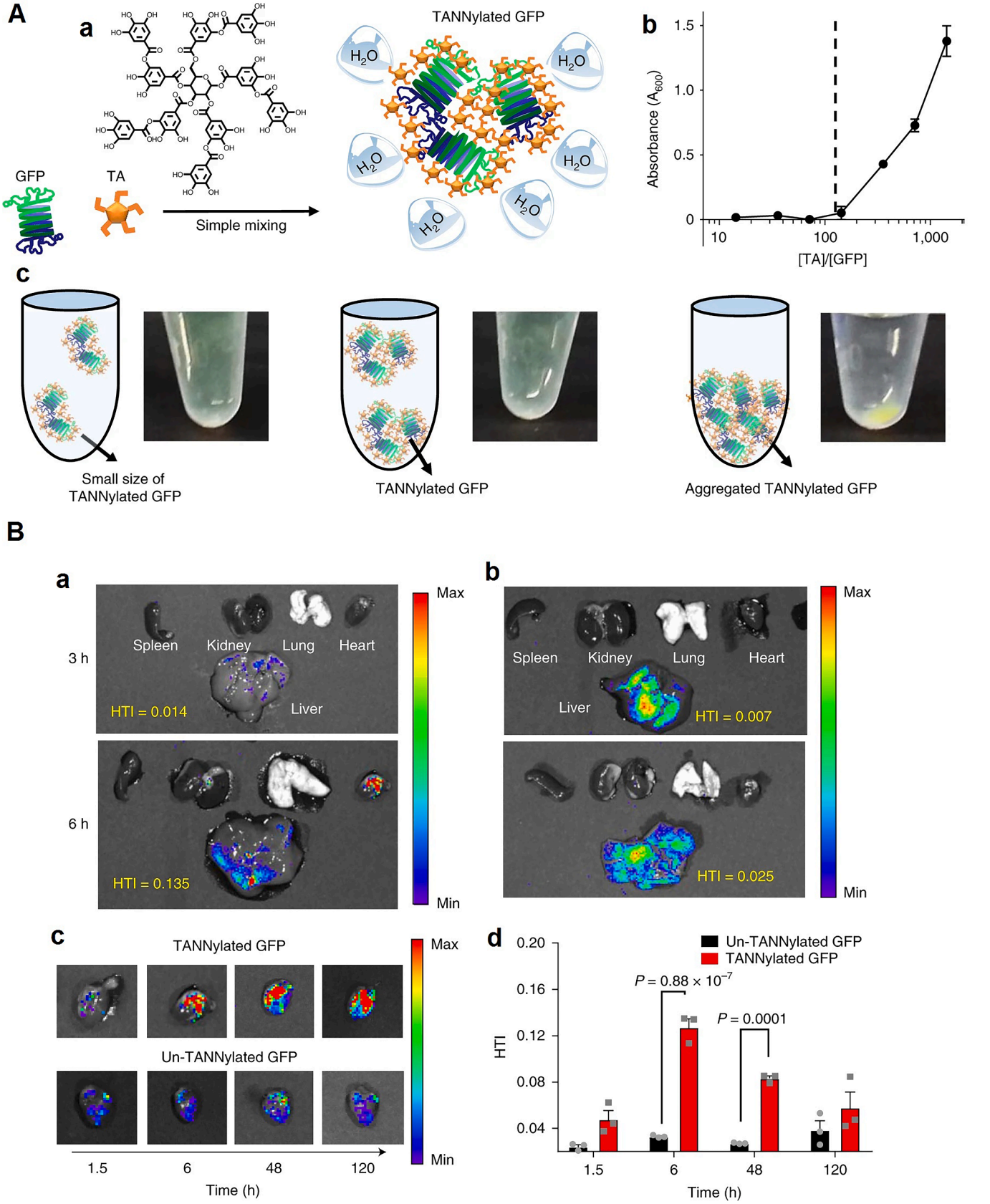
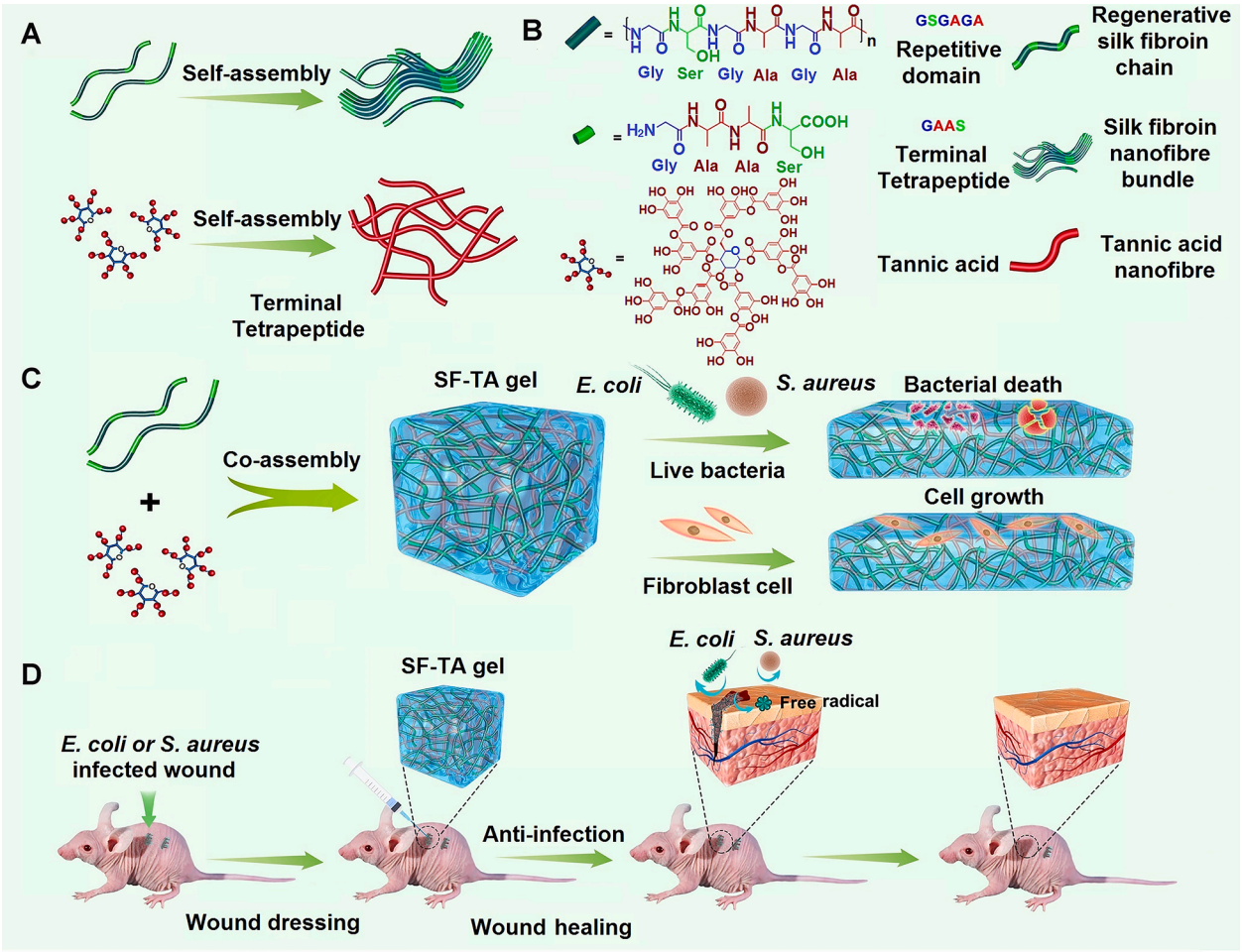


Fig. 3. Preparation process, heart-targeting, and heart accumulation of protein TANNylation. (A) (a) The preparation scheme of TA and green fluorescent protein (GFP); (b) determination of appropriate ratio of TA and GFP through turbidimetric assay; (c) the TA/GFP combination with different stoichiometric ratios including 72 (left), 143 (middle), and 357 (right). (B) The fluorescent images showing the distribution of TANNylated (a) and un-TANNylated (b) GFP through various organs at different time intervals. (c) Heart accumulation effect of TaNNylated GFP as a function of time. (d) Quantitative results related to (c) through heart targeting index (HTI) values (means ± s.e.m., n = 3). Reprinted from [48] with permission of Nature.



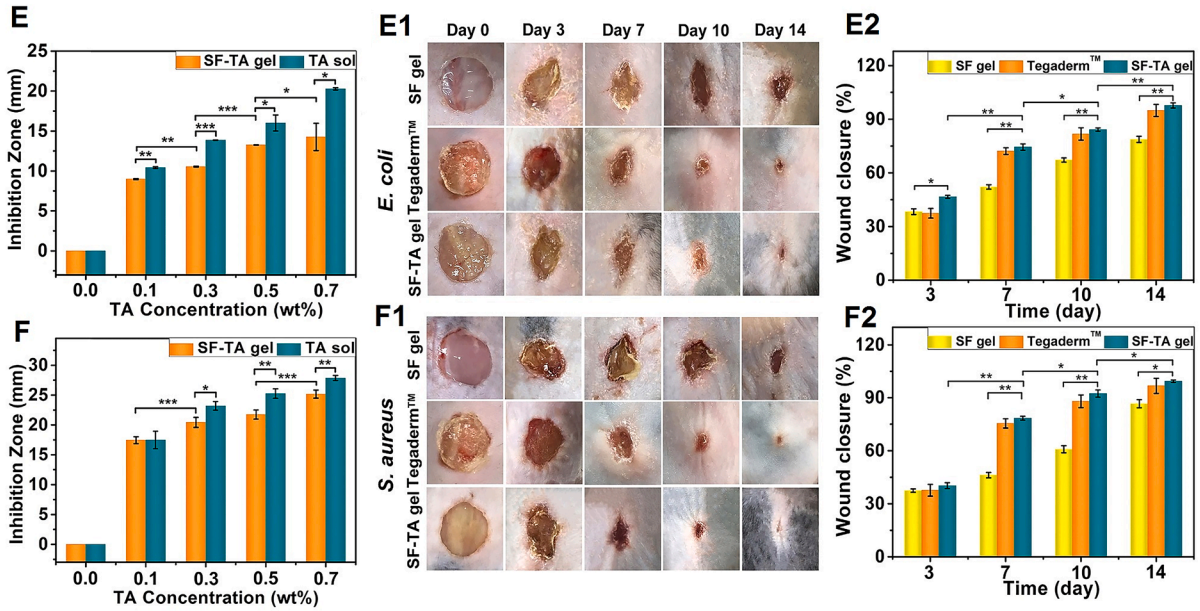


Fig. 4. The multifaceted silk fibroin (SF)-tannic acid (TA) hydrogel for wound healing applications. (A and B) Self-assembly process of SF and TA and their molecular structure. (C) Synthesis of SF-TA hydrogel. (D) Wound healing potential of as-prepared hydrogel. (E-E2) Antibacterial activity (*E. coli)* of different hydrogels including pure SF, commercial dressing (Tegaderm), and SF-TA hydrogel plus the images of infected wounds with *E. coli* (1×10^8 CFU/mL) followed by their closure rate at different time intervals after treatment with the aforementioned hydrogels. (F-F2) Antibacterial activity (*S. aureus)* of the hydrogels plus the images of infected wounds with *S. aureus* (1×10^8 CFU/mL) followed by their closure rate at different time intervals after treatment with the aforementioned hydrogels. Reprinted from [78] with permission from the American Chemical Society.

As breast cancer is the leading type in women, most of the patients diagnosed with this type choose reconstructive surgery followed by partial or complete removal of the tissue (mastectomy) [79,80]. The main post-treatments are just for cosmetic purposes through adopting conventional silicone implants or autologous fat transplants. However, the transplantation is with some problems including tissue necrosis and calcification and also there is a probability of cancer recurrence in the tissue [81,82]. Nonetheless, the occurrence potential of infection is another problem as about 20 % of the patients, who have received the reconstructive surgery either the transplantation or silicone implants, are found with post-operative infection [83,84]. Therefore, an implant with not only regenerative potential to restore the already removed tissue, but also anticancer property to prevent the cancer recurrence is required. For the mentioned issues TA has very promising potential as besides its regenerative properties to accelerate the repair rate, it is capable of inducing apoptosis in breast cancer cells at a specific concentration impeding the cancerous cells return [85]. An injectable bead implant material based on TA and collagen type I was recently developed as a potential strategy to replace lipofilling. The *in vivo* results implied that neither infection and inflammation nor tissue necrosis was observed thanks to TA. After 12 weeks of implantation, the beads were found to completely incorporated into the tissue as the sign of bioactivity without being encapsulated by fibrous tissues all of which proof the reconstructive potential of TA/collagen type I for adipocyte tissue regeneration [86]. Somewhere else, a 3D-printed PCL scaffold coated with the combination of human serum albumin and TA was fabricated for breast reconstruction to address the post-surgery bacterial adhesion on the implant. Human serum albumin was observed to induce a reduction of *Staphylococcus aureus* colonization by about 70 % which has been increased up to nearly 100 % when TA had been combined with it. The binary surface coating effectively inhibited the growth of both *Staphylococcus aureus* and *Pseudomonas aeruginosa* two well-known

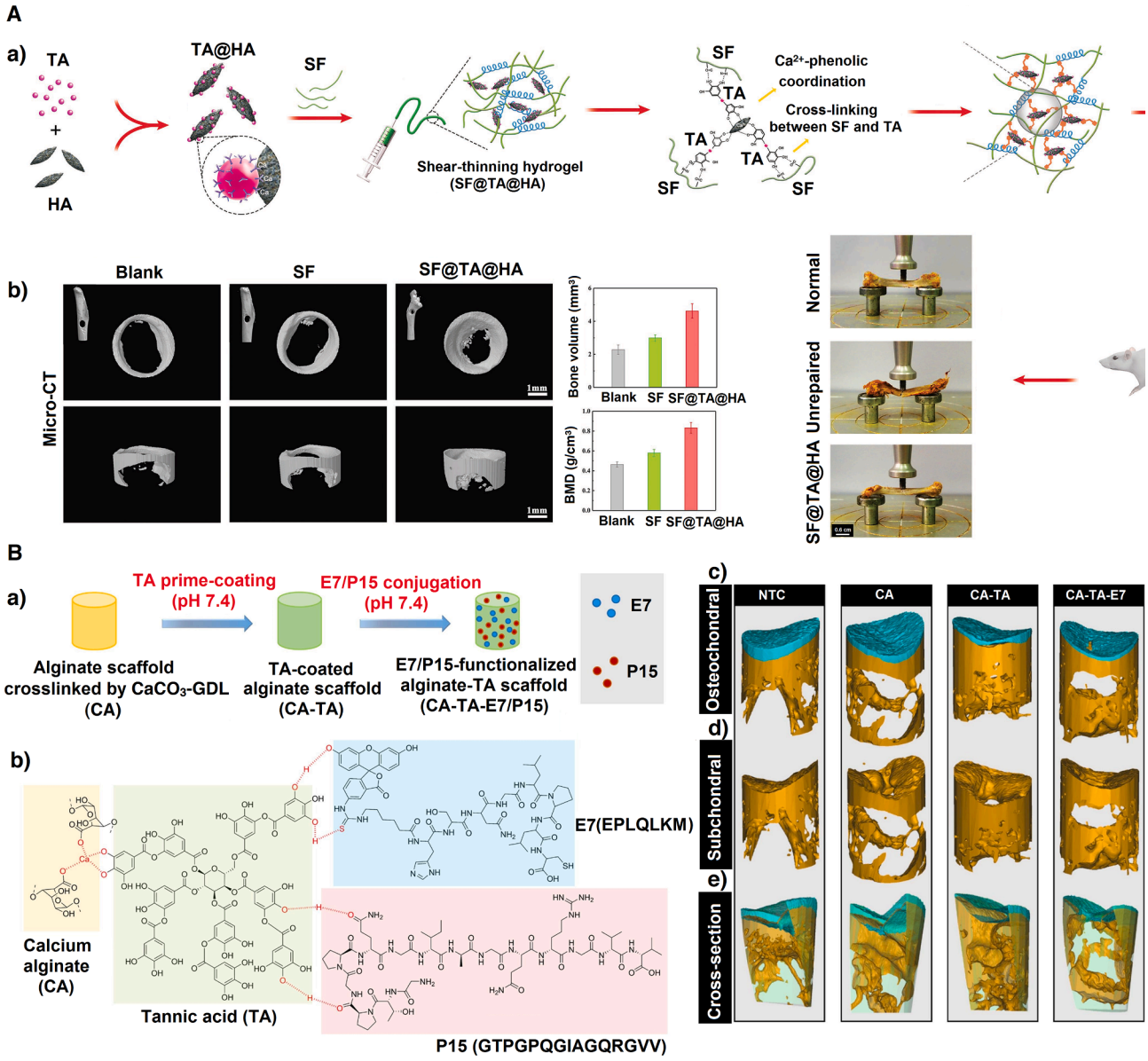


Fig. 5. (A) The adhesive composed of silk fibroin (SF), TA, and hydroxyapatite (HA) (SF@TA@HA) for bone tissue regeneration. a) A schematic showing the process for the production of SF@TA@HA followed by its implantation in a rat femur defect. b) Micro-CT and quantitative results of axial and radial new bone formation after 8 weeks. Reprinted from [91] with permission from Wiley. (B) The peptide-functionalized TA-coated calcium alginate scaffold for cartilage and bone tissue regeneration. a) A schematic on the fabrication process of the ternary scaffold and b) the possible interactions between each component. The micro-CT 3D images of c) osteochondral, d) subchondral, e) and the cross-section view of osteochondral tissues after 12 weeks' implantation for each sample. Reprinted from [90] with permission from Elsevier.

pathogens causing infection in breast implants. Although this study has come up with an efficient solution for potential infection, it is still vague if the surface coating is cytotoxic to the host cells as there is no *in vivo* study [87].

Aside wound healing applications, TA has been widely used in bone tissue regeneration as a surface coating for bone scaffolds and implants, bone adhesives, hydrogels, etc. [88-90]. A hydrogel based on TA-silk fibroin has been recently designed as a bone adhesive [91]. The hierarchical structure of bone is formed through the assembly of hydroxyapatite nanocrystals and collagen nanofibers. In one study, TA as a phenolic glue was mixed with hydroxyapatite nanoparticles followed by co-assembly with silk fibroin to mimic the bone structure [66]. The strong affinity between silk fibroin and TA led to *in situ* hardening of the mixture in the bone defect with superior mechanical properties. It is known that phenolic compounds like TA crosslink with proteins to form water-resistant adhesives with superior physicochemical and biological properties [92]. The ternary silk fibroin/TA/hydroxyapatite hydrogel bone adhesive was evaluated *in vivo* in a rat femoral defect, and the results were promising for the treatment of critical-bone defects [91]. Fig. 5**A** illustrates the chemistry of the ternary hydrogel, its application, and its performance *in vivo* in a rat femoral defect model. There are other studies which adopt TA as a surface modifier for bone tissue regeneration stemming from multiple reactive chemical groups of TA. 3D-printed PCL scaffolds were coated with TA followed by immobilization of bone morphogenic protein-2 on the scaffolds. The TA coating controlled the bone morphogenic protein-2 release rate culminating in the scavenging of excess ROS in cells and increasing in the osteogenic activity of osteoblast cells [93]. A very recently published study reported the development of a cell-instructive scaffold for osteochondral and bone tissue regeneration. The aim was to deliver E7/P15 peptides into the defect area and TA played a key role here; TA was used as an intermediate layer between calcium alginate scaffold and the peptides and improved the scaffold's stability and mechanical properties. Moreover, the TA coating facilitated the conjugation of peptides and took control over their release rate without affecting the peptides' bioactivity in a negative manner. Therefore, the peptide-loaded scaffold stimulated the concurrent bone and cartilage regeneration *in vivo* (Fig. 5**B**) [90].

The pH of the wound is affected by the type of wound and infection. In this regard, pH-sensitive hydrogels can be used to deliver therapeutic agents in a controlled manner to infected wounds [94]. Moreover, thermosensitive injectable hydrogels are promising for the delivery of therapeutic agents in wound healing due to their ability to harden *in situ* after injection to fill any irregularly-shaped defect [95]. In an attempt to design a pH-responsive hydrogel, a ternary system composed of carboxylated agarose, TA, and zinc salts was developed in which TA was released in a sustained rate from the composite matrix. In the presence of TA and zinc salts, the hydrogel's mechanical properties, antioxidation, anti-inflammation, and antibacterial activities were significantly improved [96]. In another work, a pH-sensitive hydrogel for wound healing was produced using a green chemistry approach, in which gelatin and TA were mixed to form a hydrogel via hydrogen bonding between their functional groups. The porous structure of the resultant hydrogel allowed the delivery of therapeutic hydrogels to the wound bed. Allantoin is a plant-derived compound used as a powerful moisturizing agent in wound healing and skin tissue regeneration. The allantoin-incorporated TA/gelatin hydrogel showed superior performance *in vivo* as compared to a commercial wound dressing. With regard to stimuli-responsiveness of the hydrogel, the TA release rate was sustained and lasted up to 350 h at pH = 7.4 whereas the release was very low in amount and slow at pH = 5.5. The TA in the hydrogel experiences a charge repulsion at higher pH and released in a sustained manner, whereas the TA molecules form electrostatic bonds with gelatin as the number of carboxyl and protonated amine groups increase at lower pH [97]. It is well-known that chronic and infected wounds have a pH in the range of 7–8.5 while the healthy skin has a pH of approximately 5.5 [98]. It should be noted that the allantoin release from the hydrogel did not follow the release pattern as TA. Allantoin underwent protonation similar to the gelatin due to the presence of amine groups in its structure, therefore its release was not pH-dependent [97]. Fig. 6**A** shows the process for synthesis of allantoin-loaded gelatin-TA hydrogel and its use in wound healing.

A more efficient strategy is to design a bifunctional hydrogel responsive to both heat and pH. A novel injectable hydrogel composed of hydroxypropyl chitin, TA, and Fe^{3+} with dual thermal and pH responsiveness was synthesized by a self-assembly process. In this approach, TA not only functioned as a crosslinker to enhance the hydrogel's mechanical properties, but it also provided the hydrogel with its antioxidation and antibacterial properties. The thermo-responsive behavior of the hydrogel was important here; the hydrogel precursor was liquid at ambient condition, but underwent gelation and filled the irregularly-shaped wound site after injection at the body temperature (Fig. 6**B**) [99].

Based on the composition, bone implants are with some disadvantages leading to their failure as a bone substitute. The main concern is their integration with the surrounding tissue and another one is attributed to the potential infection rising in the implant's site [100]. Moreover, some of these implants like magnesium suffers from a fast corrosion rate in the biological media [101]. The others are observed to release toxic ions which cause an undesirable cytotoxic effect in the adjacent tissues. A potential solution to those problems can be found through an effective surface coating to not only equip the implant with improved bioactivity, biocompatibility and antibacterial activity, but also decreasing the degradation rate based on the intended application [102,103]. The potential of TA as an inhibitor of corrosion on the different metallic substrates has been assessed; based on both the TA concentration and soaking number in the polymer solution the corrosion resistant can be determined [104,105]. TA in combination with different compounds have been coated on different substrates for bone tissue regeneration through layer-by-layer technique. Versatility, simplicity, low cost, and effectiveness are the main reasons why this technique is of particular interest. Recently, a few studies have assessed the combination of TA with lysozyme for bone tissue regeneration [88,106]. First, the TA-lysozyme ability to induce antibacterial activity, antioxidation, fast cell attachment, and improved osteogenic activity was assessed *in vitro* [88]. The same group then added graphene oxide to the former composition as it is capable of stimulating mesenchymal stem cells to differentiate towards osteogenic cells [107]. The multilayer ternary coating (TA-graphene oxide-lysozyme) has been applied onto silicon-based substrates for dental applications. The multilayer coating exhibited strong antibacterial activity along with enhanced osteogenic activity [108].

Metal nanoparticles due to their multifunctional nature have been used extensively in medical applications [109]. Phenolic compounds like TA tend to form strong bonds with metal nanoparticles resulting in materials with superior mechanical properties [110]. Among different metal nanoparticles, silver and gold nanoparticles have attracted more attention for wound healing as these nanoparticles tend to promote regrowth of skin cells (fibroblasts and keratinocytes) and restore surface characteristics of the skin [111]. In this regard, silver nanoparticles with average sizes in the range of 30–50 nm promoted wound closure, epithelialization, angiogenesis and granulated tissue formation *in vivo*. The adhesion of the hydrogel to the tissue to seal the bleeding wound and accelerate blood clotting are important factors in skin tissue regeneration [112]. The incorporation of TA in polyacrylamide-kaolin hydrogels increased tissue adhesion and coagulation properties of hydrogel. The increase in adhesion property of the hydrogel was related to the formation of hydrogen bonds and electrostatic interactions between TA and the porcine skin surface [113].

3.3. Infection therapy

The prevalence of multidrug-resistant antimicrobial species like

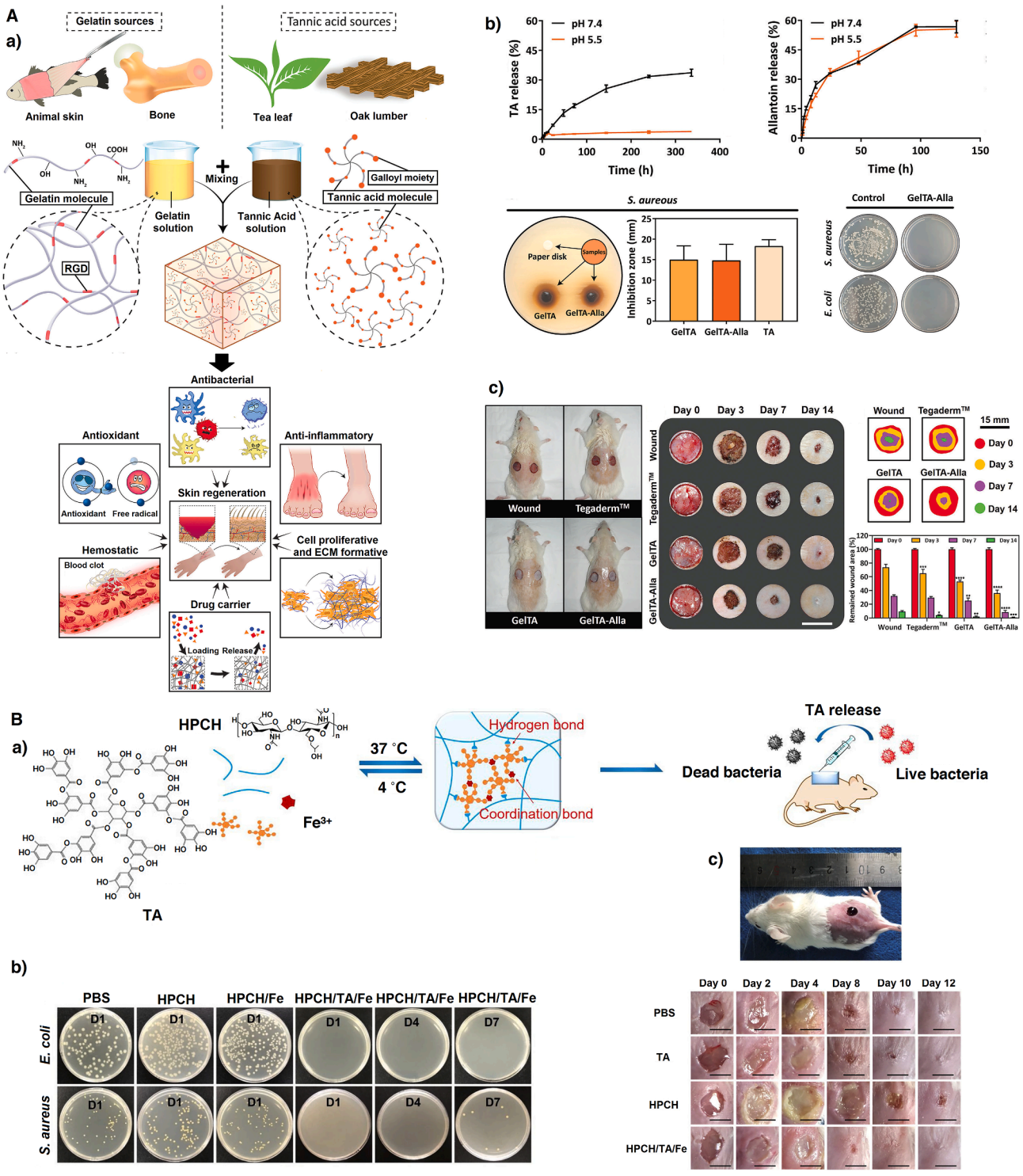


Fig. 6. (A) The multifunctional allantoin (Alla)-loaded gelatin (GEL)-TA hydrogel and its use in wound healing. a) The process of synthesis; b) TA and Alla release profiles from the hydrogel structure in neutral and acidic environments and the antibacterial activity of samples against *E. coli* and *S. aureus* bacteria. c) The *in vivo* study up to 14 days. Reprinted from [97] with permission from Wiley. (B) Thermosensitive and pH-responsive injectable hydrogel for wound healing. a) A schematic showing the production of hydroxypropyl chitin (HPCH)/TA/ferric ion (Fe). b) Antibacterial activity of the hydrogel against different bacteria. c) *In vivo* evaluation of the hydrogel at different time intervals. Reprinted from [99] with permission from Elsevier.

bacteria has heightened the demand for more effective antibacterial agents with direct bactericidal actions [114-116]. Resistance to antibiotics for a growing list of infections including pneumonia, tuberculosis, gonorrhea, and foodborne infections has led to higher medical costs, longer hospitalization, and higher mortality for patients. There is a need to develop innovative natural-based antibacterial compounds and to better understand their mechanism of action against microbial species [117]. It is envisioned that such compounds would be used in the form of dietary supplements or applied as raw materials in packaging. Due to their antibacterial and antiviral activities, polyphenols such as TA have attracted attention as a natural antimicrobial agent over the past decade [78,118]. The possibility of the TA to synthesize metal–organic

nanosheets and nanoclusters can be employed to fabricate the antimicrobial compounds (e.g., Cu-TA nanosheets in combination with acrylic resin) with excellent antibacterial activity against *E. coli* and *B. subtilis* bacteria as well as algicidal properties [119,120]. For instance, TA has been utilized as a reducing agent to produce metallic nanoparticles (e.g., Ag-NPs) with strong antibacterial activity using a one-pot environmentally-friendly process [119].

Li *et al.* developed a multi-layer coating for medical products based on TA, graphene oxide (GO) and lysozyme (Lys), abbrevaietd as TA-GO-$Lys_{n\text{-}pH}$, using a layer-by-layer technology. In this coating process platform, *n* is the number of dipping cycles in TA-GO solution to reach a desired multilayer film thickness and pH is an important variable in the fabrication process. The compounds TA, GO and Lys are integrated into the coating without losing their respective individual functions to provide a synergistic effect in eliminating bacteria. The data in support of TA-GO-$Lys_{n\text{-}pH}$ multilayer composite was *in vitro* data. Further research needs to be done to evaluate the composite for antibacterial activity *in vivo* for clinical applications, such as coating of the dental implants [121]. In another study, a smart antibacterial hybrid film was designed based on TA, Fe^{3+}, and poly(*N*-isopropylacrylamide) (PNIPAAm) that could be deposited on different substrates, as shown in Fig. 7. These hybrid films prevented adhesion of pathogenic bacteria, which in turn prevented bacterial colonization and biofilm formation. The TA/Fe^{3+} complex showed excellent bactericidal activity by serving as an anchor for surface modification, as an agent for photothermal ablation of attached bacteria, and as a linker for immobilization of NH_2-terminated PNIPAAm on the surface. This antibacterial film coating could be applied to a wide range of applications, in particular to medical devices and public hygiene products [122].

TA in combination with silver nanoparticles (Ag-NPs) have shown excellent bactericidal properties against a variety of microorganisms [123]. Ag-NPs increase permeability of the bacterial cell membrane, produce ROS, and interrupt the replication of bacterial DNA by releasing Ag^+ ions [124]. These properties of Ag-NPs combined with those of TA produce a synergistic bactericidal effect against microorganisms. In one study, Ag-NPs were deposited *in situ* on TA-coated viscose textiles without adding any reducing agent. The TA in the coating process of the textile surface provided many catechol groups with the ability to reduce and convert Ag^+ ions into Ag-NPs. Then, the surfaces were subjected to hydrophobic treatment under mild reaction conditions to generate durable superhydrophobic and antibacterial viscose textiles [123]. To produce a superhydrophobic surface, the Ag/TA-coated viscose textiles were immersed in 97% perfluorodecanethiol overnight. The HS-terminated functional groups facilitated the self-assembly of perfluorodecanethiol through metal-thiol coordination, Schiff-base and Michael-addition reactions on the surface of textiles [125,126]. Experimental results showed that the original and TA-treated viscose fabrics had no antibacterial activity against *E. coli* and *S. aureus*. Conversely, the Ag/TA-coated textiles formed by reduction of Ag^+ ions with TA demonstrated high antibacterial activity. These multifunctional textiles with super hydrophobicity and long lasting antibacterial properties can potentially be used in biomedical bandages or protective clothing for extreme environmental conditions [123]. In another work, biocompatible and antibacterial coatings were developed using TA and collagen (TA/COL) for implant-correlated anti-infection applications using layer-by-layer assembly. The TA/COL films were created in acetate or citrate buffer with pH = 4.0. The buffer type influenced the physicochemical properties as well as antibacterial activity of the films. For instance, citrate-created films exerted an antibacterial effect against *S. aureus* without causing any cytotoxicity against human gingival fibroblasts [127].

Polysaccharides undergo coacervation and form nanoparticles by crosslinking with biopolymers with opposite charges through electrostatic interaction [128]. In this regard, a novel self-healing composite hydrogel with antioxidant and antibacterial activities was developed using cellulose nanofibrils and TA as functional components. The antibacterial performance of the composite hydrogel could be adjusted by varying the TA content. Rheological measurements demonstrated that the incorporation of cellulose nanofibrils and TA in PVA and sodium borate noticeably affected the viscoelasticity of the hydrogel. Due to its self-healing ability, antioxidant and antibacterial properties, and simple production process, this coacervate-based coating is a model system for the design of intelligent self-healing medical devices and surface coatings [118].

3.4. Biosensors

Biosensors are portable analytical devices for rapid identification of biological agents such as pathogens, proteins and glucose [129,130]. Biosensors are evolving toward the concurrent identification and analysis of multiple analytes. Biosensors often consist of three parts, namely a bio-receptor, a transducer, and a signal processing unit [131]. Early diagnosis and treatment of diseases like cancer is very important in improving the quality of patients' life. Each disease may possess its specific signature structure, which is called biomarker [132]. Biosensors can be applied for the early diagnosis of the disease. The advent of nanotechnology has begun a new era in biosensor design.

TA with its many functional groups has been used in the design of biosensors. TA can serve as a chelator agent, hydrophilic factor, reducing agent, and electroactive factor. This section reviews recent advances in TA-based biosensor technologies. In one work, a biosensor based on polydopamine, Fe^{3+}-mediated TA, and four-arm polyethylene glycol was developed for quantification of breast cancer type 1 (BRCA1) DNA biomarker. Fe^{3+} acts as a mediator to form coordination bonds between the multiple hydroxyl groups of TA and the catechol functional groups in polydopamine [133]. In this process, polydopamine was first deposited on the glassy carbon electrode by cyclic voltammetry. Next, the polydopamine coated electrode was coated with Fe^{3+}-mediated TA and four-arm polyethylene glycol, which interacted hydrophilically with polydopamine layer. The TA in the coating acts as a chelator for scavenging Fe^{3+} ions via galloyl groups and glucose molecules from the environment [134,135]. This layer-by-layer deposition is called coordination driven multistep assembly [21]. The TA's functional groups in the coating not only served as a chelating agent but also enhanced the reaction response of the sensor for glucose measuring [136]. In another work, a biosensor based on poly-TA doped polyaniline was developed as an antifouling biomaterial for *in vivo* monitoring of dopamine in the mouse brain. Polyaniline as a conductive/nanoporous polymer was selected to enhance the hydrophilicity and electroactivity of the microelectrode whereas the poly-TA functioned as a dopant for polyaniline to enhance its electrochemical activity in physiological pH. The performance of the carbon fiber electrode modified with poly-TA doped polyaniline was measured using potential-controlled amperometry and fast-scan cyclic voltammetry. The selectivity of detection of dopamine was affected by ascorbates and other negatively charged compounds present in the brain. To mitigate the selectivity issue, nafion or a similar negatively charged polymer was coated on the electrodes. The combination of physical and chemical antifouling approaches resulted in excellent performance for *in vivo* analysis [137]. TA can serve as an electron transfer agent in electrochemical systems by oxidation of its hydroxyls; it can be oxidized in more positive potentials to quinone groups during the application of cyclic voltammetry. In this regard, a glucose biosensor was developed based on TA to reduce graphene oxide and Au^{3+} to gold nanoparticles. In this technology, TA attached to the surface of the reduced graphene oxide, and served a suitable substrate for immobilization of glucose oxidase enzyme through hydrogen bonding between the nitrogen-containing moieties of enzyme and hydroxyl groups of TA [138]. TA has also been applied as a template for the synthesis of mesoporous TiO_2; the template left mesoporous structure leading to an increase in the adsorption of Au nanoparticles and glucose oxidase in a photoelectrochemical glucose sensor (Fig. 8**A-D**) [139].

To produce switchable biosensors (like on–off mode), the sensor

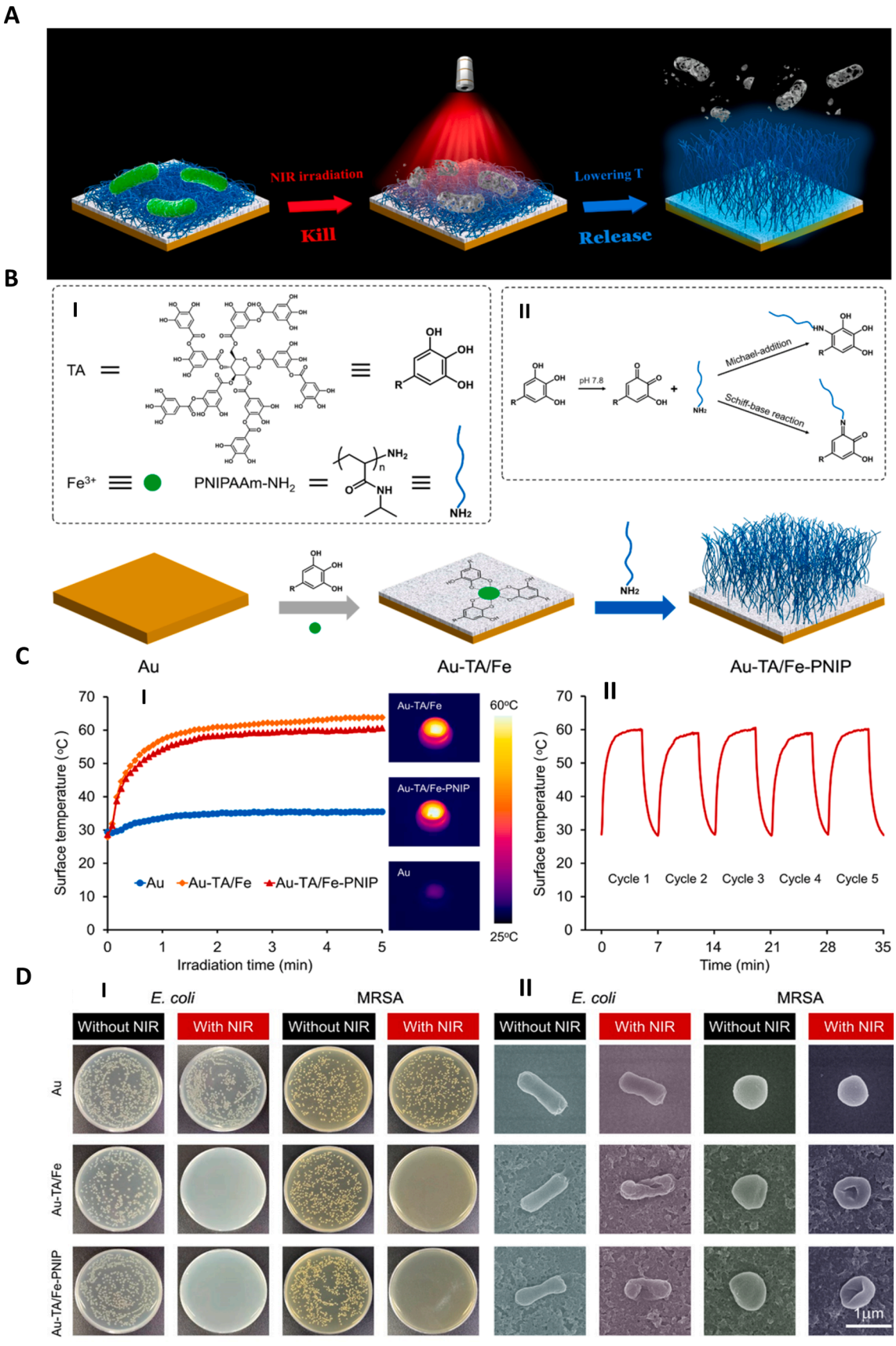


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Fig. 7. (A) Schematic diagram of a smart antibacterial surface with dual photothermally activated bactericidal and thermally triggered bacteria-releasing functions. (B) Schematic illustration of the preparation of Au-TA/Fe-PNIP surface: (I) Chemical structures of TA and PNIPAAm-NH_2; (II) Proposed mechanism of the reaction between TA and PNIPAAm-NH_2. (C) (I) The surface temperature of different substrates in PBS as a function of near infrared irradiation time (2.2 W/cm^2) with the corresponding thermal images shown on the right. (II) The temperature of Au-TA/Fe-PNIP surface under alternating on/off near infrared irradiation (2.2 W/cm^2) over five cycles. A single cycle consisted of irradiation for 5 min followed by cooling at ambient condition. (D) (I) Representative images of bacteria (*E. coli* or MRSA) colonies formed on agar plates after detachment from different surfaces and (II) representative SEM images of the attached bacteria (*E. coli* or MRSA) on different surfaces with/without near infrared irradiation (2.2 W/cm^2, 5 min). TA: tannic acid, PNIP: poly(*N*-isopropylacrylamide). Reprinted from [122] with permission from the American Chemical Society.

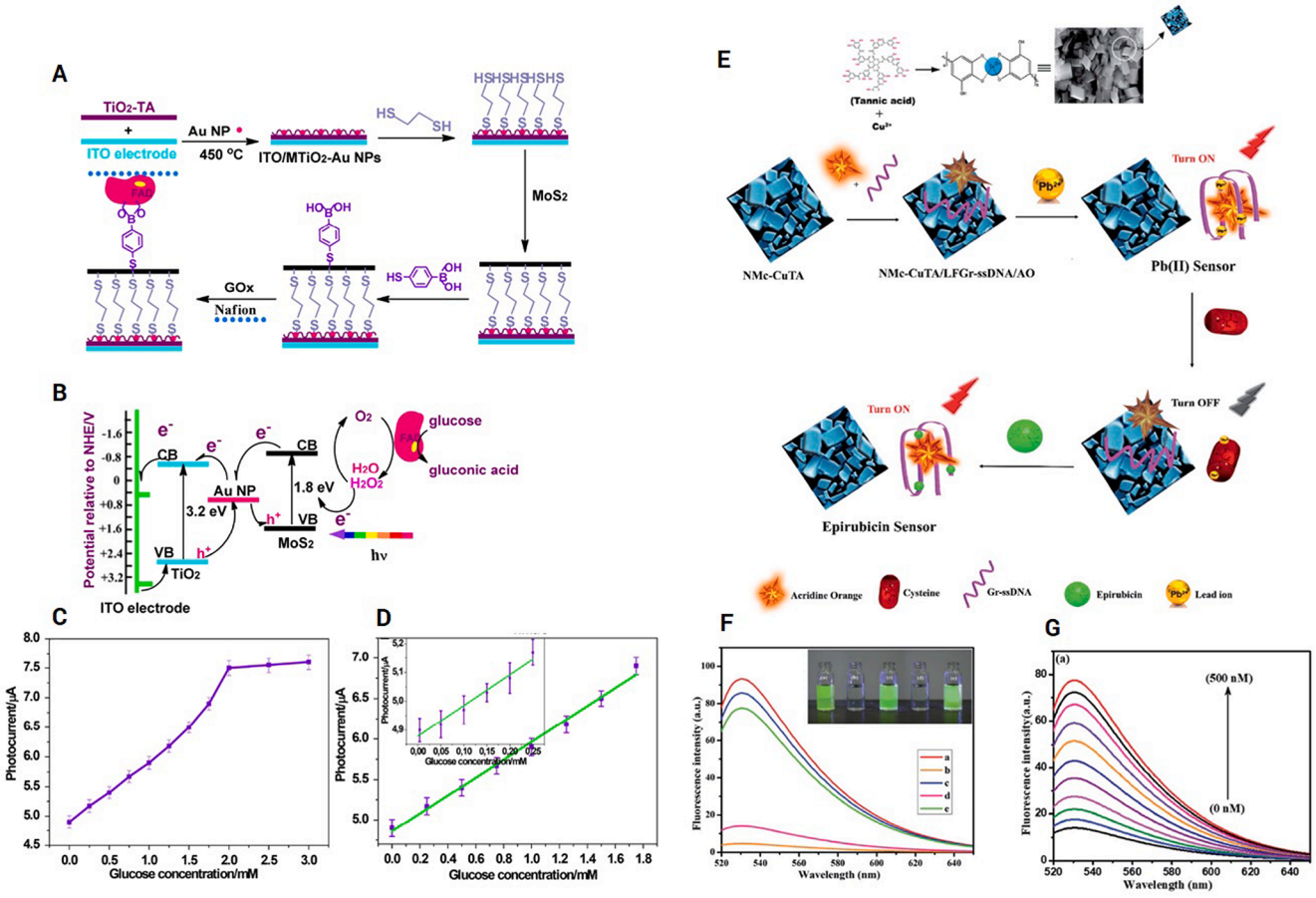

Fig. 8. (A) Schematic illustration of an indium tin oxide/mesoporous TiO_2, Au nanoparticles, and molybdenum disulfide photoelectrochemical glucose sensor. (B) The (ITO/MTiO$_2$-Au nanoparticles-MoS_2) photoelectrochemical biosensing mechanism for glucose. (C) Photocurrent responses vs. glucose concentration graph, (D) The linear part of the graph (inset: measurement between 0 and 0.25 mM glucose). Reprinted from [139] with permission from Wiley. (E) schematic illustration of the fluorescence detection of Pb^{2+} ions and the anti-cancer drug epirubicin using the nano-monoclinic Cu–TA/LFGr-ssDNA/ acridine orange sensing platform. (F) The fluorescence emission spectra and UV properties (inset) of acridine orange alone (a), the platform-acridine orange complex (b), the platform-Pb^{2+}-acridine orange-G4 complex (c), the platform-acridine orange/LFGr-ssDNA/Pb^{2+}-cysteine complex (d), and the platform/epirubicin-acridine orange-G4 complex/Pb^{2+}-cysteine complex. (G) Fluorescence spectra of the optimized sensor in response to different concentrations of epirubicin in the range of 0–500 nM. Reprinted from [140] with permission from Wiley.

surface should have the ability to respond to an external actuator like a change in temperature or pH. TA can be utilized as a green and natural reducing agent to modify the surface of graphene oxide via π-π interactions [141]. Further, TA as a polyphenol interacts with proteins via hydrogen or Schiff base bonding for enzyme immobilization. In this regard, the glassy carbon electrodes have been modified by TA-reduced graphene oxide and platinum nanoparticles. Such modified electrodes can be developed as sensors with switchable temperature or pH functions [142]. TA can be complexed with polymers such as poly(*N*-isopropyl acrylamide) as well as other polyamides through hydrogen and hydrophobic interactions to generate a thermosensitive drug delivery system. In addition to complexation, TA facilitates the formation of multilayer thin films with polyamides using a layer-by-layer assembly process. These thin films are generated without using polycations which can potentially reduce toxicity issues. The selection of different temperature and pH levels allows the sensor to increase its selectivity and improves its output response [143,144].

Another reported application of TA and its ligands is in the synthesis of complexed metal-polyphenolic nanomaterials. TA with polydentate ligands coordinates with metal ions such as Cu^{2+} ions and form a metal/TA nanocomplex (Cu^{2+}/TA) which has many advantages including high quenching yield, high surface area, tailorable composition and biocompatibility. The surface of these monoclinic-like nanomaterials is occupied with sp^2-hybridized carbon atoms and paramagnetic metallic ions (with a fluorescence quenching nature). The biosensing mechanism of these nanocomplexes is based on strong absorption of both label-free guanine-rich ssDNA (LFGr-ssDNA) and acridine orange as a fluorescence probe on the surface of the metal–phenolic nanomaterials via π–π

stacking or electrostatic interactions (off-mode) leading to the formation of G4 complexes. In the presence of Pb^{2+} ions, a stronger interaction occurs between LFGr-ssDNA and Pb^{2+} ions in competition with metal/TA nanomaterial, and the release of LFGr-ssDNA from the surface causes restoration of fluorescence (on-mode). The subsequent addition of epirubicin to the solution results in the intercalation of LFGr-ssDNA with epirubicin, thus once again forms a G4 complex and increases the fluorescence intensity, as shown in Fig. 8**E-G**. Therefore, such TA-based nanomaterials can easily be applied in biosensors for measuring the concentration of cancer drugs, heavy metal ions, and biomolecules [140].

A unique ability of TA is to serve as a cross-linker between some -metal ions (such as Fe^{3+}, Al^{3+}, Cu^{2+}) and various substrates such as DNA, protein, metallic/metal oxide nanoparticles and cells. TA plays a bifunctional role as a crosslinker and as a reducing agent in the formation of metal–ligand complexes and metal nanoparticles. For instance, TA in the form of TA–Fe^{3+} complex was used in producing a biosensor, in which Au nanoparticles were used as nanoprobes. The nanoprobes were formed in the presence of TA as a reducing agent. The modified nanoparticles were employed for the fabrication of electrodes via powder processing of gold with α-Al_2O_3. The produced electrode was treated using target peptide solutiin to form Au-S bonds by immersion. Afterwards, the electrode was incubated in tryspin solution to form the acetylated peptide and immersed in Au nanoparticles/TA-Fe^{3+} nanoprobe solution. The developed electrode was used to monitor the electrogenerated chemiluminescence response for the detection of histone acetyltransferases activity. Such fabricated biosensors are potentially useful in clinical diagnostic applications, drug discovery, and chemotherapy [145].

In cancer therapy, TA-metal complexes including Fe^{3+}, $Ru^{3+-}$and V^{3+} adhere to different polymeric templates such as nanospheres, nanovesicles, and mesoporous silica nanoparticles regardless of their surface morphology. These TA-metal complexes produce strong absorption in the near infrared range which would be applicable in the design of multimodal image-guided theranostics for cancer photothermal therapy [146].

3.5. Cancer therapy

Cancer is the second leading cause of death in the United States. Despite significant efforts to find more effective therapies and eradicate cancer, limited success has been achieved to date [147-149]. TA is a promising anticancer agent that affects many signaling pathways involved in oncogenesis [150]. This section reviews the anticancer mechanism of TA and targeted tumor delivery systems based on TA. The potential anticancer properties of TA against several cancer types including lung [151], breast [152], liver [153], prostate [150], ovarian [154], and colon [155] cancers have been reported. TA plays a role in down-regulation of multiple signaling pathways involved in oncogenesis including JAK/STAT, EGF/EGFR, and TGF-β1/TGF-β1R axes. TA also activates tumor suppressor proteins p53, p21, p18, and p27, as shown in Fig. 9**A**. The intracellular proteins targeted by TA in different cancer types are summarized in Table S2. Taken together, the inhibition of proliferation and induction of tumor cell death by TA through different mechanisms are dependent on cancer cell type and TA concentration.

Although conventional cancer therapies like surgery for tumor resection, targeted chemotherapy, and radiation therapy have made significant progress, cancer patients still suffer from undesirable side effects of cancer therapeutics [156]. Although considerable progress has been made to steer chemotherapeutic agents towards the tumor tissue, the adverse effects of these drugs on healthy cells continue to persist because cancerous cells are often intertwined with normal cells. In addition, targeted chemotherapies and ionizing radiation therapies are hampered by multidrug resistance and radiation insensitivity of hypoxic tumor cells, respectively [157]. In this regard, TA has the potential to reduce the undesired side effects of cancer therapies because of its innate anticancer effect, ability to encapsulate both hydrophilic and hydrophobic drugs, and capability to enhnace drug targeting by both passive and active delivery.

As a practical demonstration, a double-core shell magnetic nanocarrier based on Fe_3O_4, SiO_2, and TA (Fe_3O_4/SiO_2/TA) was developed for pH-responsive, co-delivery of DOX and methotrexate. This nanocarrier showed satisfactory results for cancer therapy due to the nontoxic and biocompatible nature of TA, its chemical stability, high surface area, antitumor activity, and high drug loading capacity [158]. In another work, nanocomplexes based on pectin and TA were used to improve encapsulation efficiency and bioavailability of a range of anticancer drugs from 5-fluorouracil to gemcitabine and irinotecan. The pectin-TA nanocomplex showed promising results for targeted delivery of cancer therapeutics, especially in pancreatic cancer [159]. The assembly of TA with proteins in the lung fluid was investigated for its application as an effective pulmonary drug delivery system to cancer cells. It was shown that TA interacts with proteins as well as cancer cells in the lung fluid, thus the TA-protein assembly could potentially be utilized for encapsulation and targeted delivery of drugs like gemcitabine, carboplatin, and irinotecan to lung cancer cells [160].

In another work, thin sheets composed of nanocomplexes of TA-Fe were produced for encapsulation of bioactive moelcules and microbial species [161]. The TA-Fe nanoparticles were shown to be pH-responsive and improved stability in aqueous medium [162]. Further, TA-Fe nanoparticles coated with PEGylated PLGA showed reduced systemic toxicity, targeting to the tumor tissue, pH-responsive release, enhanced cellular uptake, and enhanced tumor cytotoxicity [163].

One approach to non-invasively remove the tumor tissue is photothermal ablation therapy. In this approach, near infrared radiation localized to the tumor tissue is converted to heat using a photothermal agent. The localized generation of heat destroys the tumor tissue as tumors due to oxygen deficiency and acidic environment, are more vulnerable to heat compared to normal tissues [164]. In one work, paclitaxel nanocrystals were coated with TA for combinational photothermal and chemotherapy. The compound in combination with radiation therapy increased cytotoxicity of paclitaxel against mouse 4 T1 breast tumor cells as compared to the nanoparticles without radiation therapy. The *in vivo* studies showed more intense photothermal effect and stronger tumor inhibitory effect of nanoparticles under laser irradiation as compared to photothermal or chemotherapy alone [165]. A stimuli-responsive nanoparticulate drug delivery system with the capability to undergo reversible hydrophobic-hydrophilic conversion was developed to address the nanoparticles short circulation time in blood stream, weak tumor penetration and cellular uptake. The drug delivery system is called nano-transformer composed of DOX, TA, and indocyanine green in which DOX and TA were first assembled through electrostatic interactions followed by indocyanine green assembly on DOX-TA complex as a photothermal agent, as shown in Fig. 9**Ba**. The ternary hydrophilic system was reassembled into a ternary hydrophobic system when exposed to the acidic tumor microenvironment, which facilitated its uptake by the tumor cells (Fig. 9**Bb)**. The reassembly continued in the lysosomes as the pH decreased to 4.5, causing the particle size to increase to as much as 1.5 μm, thus facilitating the particles' escape to the cytoplasm. Interestingly, as the complex escaped into the cytoplasm, it reassembled into a hydrophilic nano delivery system. An important advantage of the nano-transformer was its ability to synergistically enhance photothermal and chemotherapies. Upon laser irradiation, the nano-transformer underwent disassembly, which increased the local tumor temperature and the release rate of DOX payload in a controllable manner. Further, the combination of photothermal and chemotherapy reduced the chance of drug resistance which increased the effectiveness of the treatment [35]. The cytotoxicity of the ternary complex was evaluated with MCF7 human breast cancer cells *in vitro* at pH 6.5 and incubation time of 4 h. The complex can be seen in the image of Fig. 9**Bc** at the cell's edge trapped within the lysosomal vesicle with a size of approximately 750 nm after 0.5 h of incubation. After

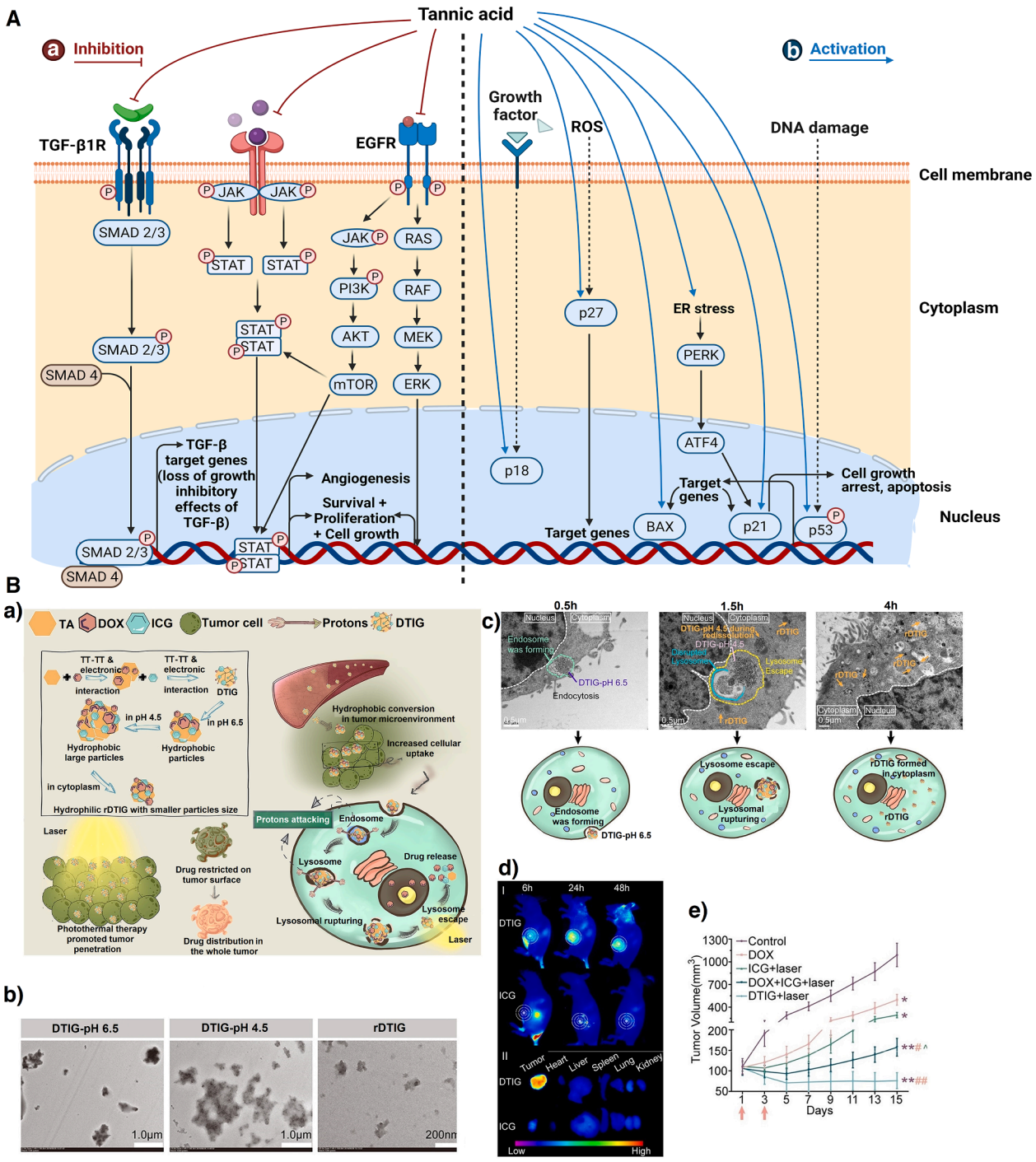

Fig. 9. (A) Proposed intracellular pathways involved for anticancer action of TA. a) TA is a potent inhibitor of many oncogenic signaling pathways hampering cell growth and proliferation of cancer cells. TA hinders TGF-β-induced Smad-dependent gene transcription. TA suppresses JAK/STAT and EGF/EGFR signaling pathways. b) TA induces tumor suppressor proteins, contributes to apoptosis and cancer cell death. TGF-β1, transforming growth factor β1; EGFR, epidermal growth factor receptor; JAK/STAT, Janus kinase/signal transducers and activators of transcription; BAX, BCL2-associated X protein; ATF4, activating transcription factor 4; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; PERK, protein kinase R-like endoplasmic reticulum kinase; mTOR, mechanistic target of rapamycin. (B) Multifunctional ternary drug delivery system (DTIG) composed of DOX, TA, and indocyanine green (ICG) for cancer therapy. a) A schematic on the synthesis procedure and treatment mechanism of DTIG (in the cytoplasm DTIG changes to hydrophilic DTIG nanoassembly which is abbreviated to rDTIG). b) The TEM micrographs of the samples. c) The TEM micrographs plus schematics related to MCF7 cells which were treated with DTIG up to 4 h. d) *In vivo* fluorescence images including the accumulation of DTIG and ICG in (I) the tumor site (the circle represents the tumor's site) and in (II) the different organs. e) the tumors volume treated with different samples up to 15 days, $^{*}p < 0.05$ vs control, $^{**}p < 0.01$ vs control, $\#p < 0.05$ vs DOX, $\#\#p < 0.01$ vs DOX, $\hat{}p < 0.05$ vs ICG + laser, $\hat{}\hat{}p < 0.01$ vs ICG + laser, $@@p < 0.01$ vs DOX + ICG + laser. Reprinted from [41] with permission from American Chemical Society.

incubation for 1.5 h, a ruptured lysosomal vesicle can be seen in the image and size of the complex increased up to 1.5 μm, which was attributed to the lower pH = 4.5 of the lysosome. After incubation for 4 h, the complex can be seen in the cytoplasm. These results demonstrate that the transformations of the ternary complex during intracellular drug delivery are triggered by pH changes from the interstitial space to lysosomal vesicle and cytoplasm. The cumulative release of DOX and indocyanine green increased when the pH values decreased and the laser irradiation was applied. *In vivo* fluorescence imaging (Fig. 9**Bd**) showed that the ternary complex was not instantly cleared from the circulation due to the abundance of hydroxyl groups on the surface that inhibited protein binding and accumulated in the tumor tissue for 48 h. However, the free indocyanine green without complexation with DOX-TA failed to reach the tumor tissue and it was removed completely after 24 h. Photothermal studies (Fig. 9**Be**) showed the highest shrinkage in tumor volume with the use of ternary complex and laser irradiation, culminating in the release of DOX and an increase in the local tumor temperature [41].

4. Toxicity and signaling pathways

Cytotoxic chemotherapy drugs employ a variety of pathways to inhibit survival and cell division [147,166]. The drugs are not able to distinguish between normal and malignant cells but inhibit cell division, to kill cancer before the host [167]. Then, cells may become necrotic (loss of cell membrane integrity, lysis, and cell death), actively stop growing and dividing (reduced cell viability), or cells may control the cell death genetic program activation (apoptosis) [168].

Induction of apoptosis occurs through the external pathway (death receptors) and the internal pathway (mitochondrial) [169]. Various death ligands [TNF-related apoptosis-inducing ligand (TRAIL), Fas (FasL, CD95L), and tumor necrosis factor alpha (TNF-α)] and their respective death receptor signaling pathways play essential roles in tumoral cell apoptosis-inducing. Fas ligand and TNF are processed by metalloproteinases, whereas TRAIL is cleaved by cysteine proteases at the cell surface to yield a soluble cytokine [170]. The surface of the cells contains death ligands, which are responsible for transmitting apoptotic signals. These receptors are divided into six groups (DR1-DR6) [171]. Apoptotic promoter proteins play an essential role in increasing the permeability of the outer mitochondrial membrane, which ultimately leads to the release of cytochrome *c* into the cytosolic space [172]. The apoptosome is an Apaf-1, cytochrome *c* complex that activates procaspase 9. Within the apoptosome, procaspase 9 was broken to activate caspase 9 and then stimulated apoptosis via the caspase 3/7 activation (Fig. 10) [172]. Various compounds can activate apoptotic pathways, TA being one of them.

TA plays an essential role in regulating TGF-β1, JAK/STAT, RAS/RAF/mTOR, TGF-β1R axis, CXCL12/CXCR4, and VEGF/VEGFR oncological signalling pathways that presented in **Section 3.5**.

TA can modulate the response to chemotherapy through pathways involved in drug withdrawal. For instance, the concentration above 50 μM of TA decreased the DOX-induced keratinocyte toxicity [173]. Besides, TA has cytotoxic effects on cancer cells and prevents metastasis, angiogenesis, and migration of cancer cells. The activity of TA as a CXCL12/CXCR4 (as chemokines involved in tumor growth and angiogenesis/ receptor) inhibitor, may illustrate its anti-inflammatory and antitumor properties [17].

Cell viability is an important parameter that determines the cell's ability to proliferate in contact with materials [174]. In one research, thin films based on a mixture of chitosan and TA were fabricated in the

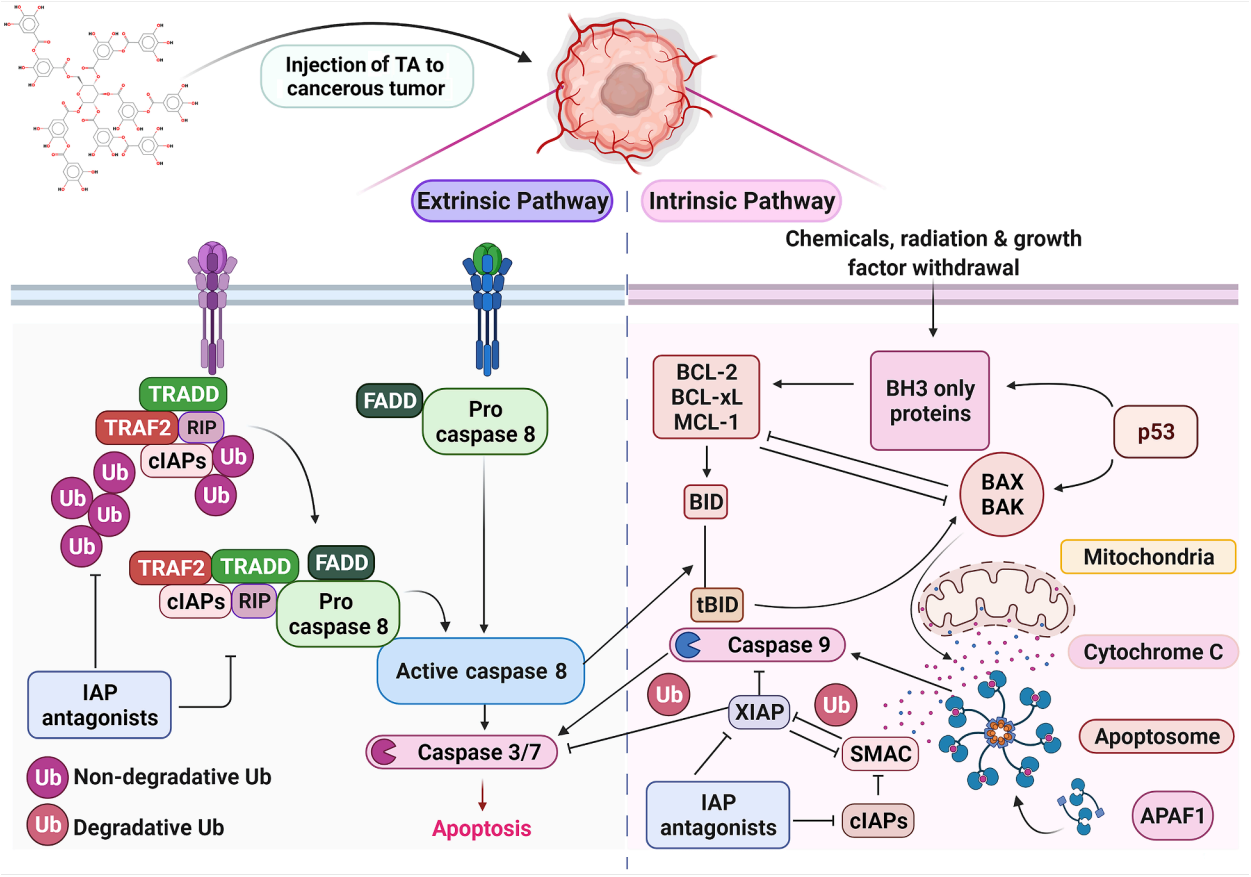

Fig. 10. The mitochondrial pathway of apoptosis is induced by TA. Apoptosome forms via reacts cytochrome *c* with the Apaf-1, adenosine triphosphate, and procaspase 9. Within the apoptosome, procaspase 9 is degraded and activated by caspase-9, activating caspases 3 and 7, and inducing apoptosis.

ratio of 80:20, 50:50, and 20:80. Their cell viability was investigated through utilizing some various cell lines including MNT-1, SK-MEL-28, Saos-2, HaCaT, and BMSC. The highest cell viability effect was observed for MNT-1 cells, while the lowest related to BMSC cells [175].

In a study, TA/Au nanoparticles demonstrated higher cytotoxic activity against various HCT116, MCF7, and HepG2 cancer cell lines than TA free form. TA/Au nanoparticles decreased IC_{50} by increasing in ROS level generated from the Au nanoparticles in cells compared to inherent ones [176]. TA has a high affinity to repress the expression of Akt and, through this pathway, inhibits the survival of cancer cells by increasing cytotoxicity. Moreover, in paclitaxel-loaded TA/polyvinylpyrilidone nanoparticles, quick-release of the drug was assessed at higher pH values (6.8 or 7.4) that pH sensitivity could protect acid-sensitive drugs like paclitaxel [176]. As there are few specialized studies on the cytotoxic effects of TA, it is a supplement to increase the effectiveness of drugs in cancer therapy [177]. Table S3 represents the examples of TA used in combination with anti-cancer agents for cancer therapy.

Nowadays, TA is employed in combination with nanoscale carriers for the treatment of cancers [178]. Nanostructures containing chemotherapeutic drugs and TA offer more significant benefits than free drugs (such as increased cytotoxicity effect, synergistic inhibitory effect, improved anticancer effect, good cytocompatibility, reduced IC_{50} & increased cellular uptake of the drug, preventing drug resistance, and enhanced drug availability for tumor sites) [179,180]. Therefore, they have great potential to inhibit migration and cell invasion and limit metastatic death for clinical applications [179,180].

5. Conclusion and outlook

With rapid developments in bionanotechnology, several plant-based polyphenol compounds have attracted attention in advanced materials design and applications due to their chemical, biological and therapeutic properties. Tannic acid (TA) as a polyphenol compound like other natural polyphenols, has many biological properties, is safe, biocompatible, non-toxic and well-tolerated. The present review shed light on the most recent investigation of TA for different bioapplications. TA is intrinsically considered as a multifunctional material. For instance, it has radical scavenging capability, antibacterial activity, anticancer property, and regenerative potential. Besides them, its unique structure is able to make different interactions with wide variety of materials culminating in the innovative plurofunctional composites with improved physicochemical and biological properties.

TA has numerous phenolic and carbonyl functional groups making it an excellent H donor followed by forming strong hydrogen bonds with different non-ionic polymers. Moreover, TA can make an electrostatic interaction with other ionic polymers through ionization of its galloyl phenol groups. In another word, these functional groups facilitate the incorporation of TA in the structure of a wide range of biomaterials by coordination and supramolecular chemistry through hydrogen bonding, electrostatic and van der Waals interactions, and π–π stacking. However, the interaction of polyphenols specially TA with various ionic and non-ionic polymers should be further investigated to yield multifunctional systems for various applications. TA self-polymerising mechanism must be conducted in details. Accordingly, it is essential to have more experimental results to acquire a typical rule for the self-polymerizing.

The antibacterial and antioxidation effects of TA are very useful and attractive in tissue engineering and regenerative medicine. Normally, these two properties are provided in various scaffolds through two or more agents, but TA alone can give these properties to a scaffold making it also cost-effective from commercialization point of view. However, its release rate *in vivo* must be further assessed to exclude the potential cytotoxicity. The multifunctionality of TA in tissue regeneration is clear to the research community, but more *in vivo* studies are in need to assess these properties together and find out if the local release of TA from the implanted biomaterial can induce antioxidation and antibacterial activities without leaving toxic effects behind.

TA in combination with other conventional chemotherapy drugs such as 5-fluorouracil or mitomycin C [181], cisplatin [182] and DOX [183] showed an increased synergistic anti-cancer effect, toxicity effect, and chemical sensitivity in several resistant cases. Unlike most chemotherapeutic drugs, TA as a hydrolyzable tannin has no side effects on the cells growth of normal human breast [184], ovarian [185], bronchial [186], and liver [187]. Since the use of chemotherapy drugs is recognized as a promising strategy in the cancer therapy, TA increases the cytotoxicity, synergistic effect of chemotherapy drugs by enhancing drug-induced apoptosis, and decreasing drug resistance in cells. Moreover, TA can regulate membrane pumps, inhibits cell cycle progression, and modulates cellular efflux pathways [181]. TA leads to a reduction of drug resistance by inhibiting the increase in P-glycoprotein and the multidrug resistance proteins 1 and 2 (membrane pumps) [181]. However, the extensive clinical use of TA in cancer therapy is yet to take place rooting in its weak lipid solubility, low bioavailability, and short half-life. Therefore, designing novel drug delivery systems is of profound significance to deliver TA to the targeted site followed by increasing its anticancer activity.

In summary, the recent advances in the designing and bioapplications of natural TA and TA-based compounds were highlighted. We hope that the present review paves the TA journey as a multifunctional, cost-effective, abundant, naturally occurring polyphenol towards clinical applications. The true potential of TA is yet to be fully understood and we are confident that the researchers in the field will discover the full potential of TA in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cej.2021.134146.

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