Progresses in conductive polyaniline-based nanocomposites for biomedical applications: A review

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Abstract

Inherently conducting polymers (ICPs) are a specific category of synthetic polymers with distinctive electro-optic properties, which involve conjugated chains with alternating single and double bonds. Polyaniline (PANI), as one of the most well-known ICPs, has outstanding potential applications in biomedicine because of its high electrical conductivity and biocompatibility caused by its hydrophilic nature, low-toxicity, good environmental stability and nanostructured morphology. Some of the limitations in the use of PANI, such as its low processability and degradability, can be overcome by the preparation of its blends and nanocomposites with various (bio)polymers and nanomaterials, respectively. This review describes the state-of-the-art of biological activities and applications of conductive PANI-based nanocomposites in the biomedical fields, such as antimicrobial therapy, drug delivery, biosensors, nerve regeneration and tissue engineering. The latest progresses in the biomedical applications of PANI-based nanocomposites are reviewed to provide a background for future research.

Keywords: Conductive polyaniline nanocomposites, biological activities, biosensor, drug delivery, tissue engineering, antimicrobial activity, antioxidant activity.

1. Introduction

Most polymers are insulators since they are made by covalent bonds without free moveable electrons or ions; some polymers can nevertheless form a conductive path under an electrical stress. These polymers have different tendencies to form a conductive path under various conditions. Some properties such as resistivity, arc resistance, dielectric constant, and dissipation factor are used to express the electrical properties of polymers [1].

Inherently conducting polymers (ICPs) are a specific category of synthetic polymers with distinctive electro-optic properties. These polymers have conjugated chains with alternating single and double bonds [2]. The π-electrons in the ICPs, which are highly delocalized and simply polarizable, show an imperative role in the electro-optic properties of ICPs. Furthermore, the physiochemical properties of ICPs, such as structural, electrical, and optical properties are affected by the nature of the inherent quasi-one-dimensional and the level of both intra- and inter-chain delocalization of π-electrons [3].

The first conducting polymer, iodine-doped polyacetylene, was discovered by Alan Heeger, Alan MacDiarmid, and Hideki Shirakawai in 1977. They were awarded the Nobel prize in chemistry for this discovery in 2000 [2]. Polyacetylene (PAs), polypyrrole (PPy), polythiophene (PTh), polyfuran (PFu) and polyaniline (PANI) are examples of

ICPs [4]. These ICPs are extensively used in the biomedical fields including tissue engineering and biosensors because of their smart response to the electrical fields [5].

Among ICPs, polyaniline has received considerable attention in various industrial and biomedical fields due to their facile preparation, low cost, high electrical conductivity, biocompatibility, low toxicity, and environmental stability [3]. However, PANI has some disadvantages, such as low solubility or insolubility in the most common solvents, infusibility, and weak processability. Also, its electrical conductivity decreases over a long cycle time [6]. A number of approaches, such as re-doping with the functionalized organic acids, copolymerization with PANI derivatives or other polymers, and the preparation of the blends and nanocomposites with various materials have been developed to diminish the aforementioned disadvantages [7].

Polyaniline nanocomposites are one of the most promising ICPs nanocomposites showing an electrical conductivity by combining the PANI matrix with the conducting or insulating nanofillers. These nanocomposites with improved properties are extensively used in the biomedical fields, such as tissue regeneration and antimicrobial therapy. Also, they have been applied in the industrial sectors (e.g. in electronics and water purification) [8].

The current review describes a state-of-the-art update on the biological activities (i.e., biocompatibility, cytotoxicity, antioxidant and antimicrobial activities) and biomedical

applications (i.e., antimicrobial therapy, drug delivery, bone regeneration, nerve regeneration, wound healing, and biosensor) of conductive PANI-based nanocomposites to provide a background for future research.

2. Synthesis

Polyaniline, or more specifically "aniline black", is one of the oldest ICPs which was discovered in the mid-nineteenth century [9]. The molecular structure of PANI may possess either benzenoid or quinonoid units or both types at different proportions [3,10].

The PANIs are synthesized using both chemical and electrochemical oxidative polymerization in an acidic medium (**Fig. 1**). The most widely used initiators for the chemical polymerization of aniline are ammonium persulfate (APS) and potassium persulfate (KPS) [3,10]. Usually, the electrochemical method is used for the small scale synthesis, whereas the chemical method allows large-scale preparation of the polymer and/or the corresponding nanocomposites [11]. The electrochemical methods include the electrode coating and co-deposition approaches. In the electrode coating method, reference, working, and counter electrodes are used in a one-compartment cell containing the electrolyte and the monomer solution [12]. In the co-deposition method, an insulating polymer host is dissolved in an electrolyte solution comprising the monomer of the conductive polymer [12].

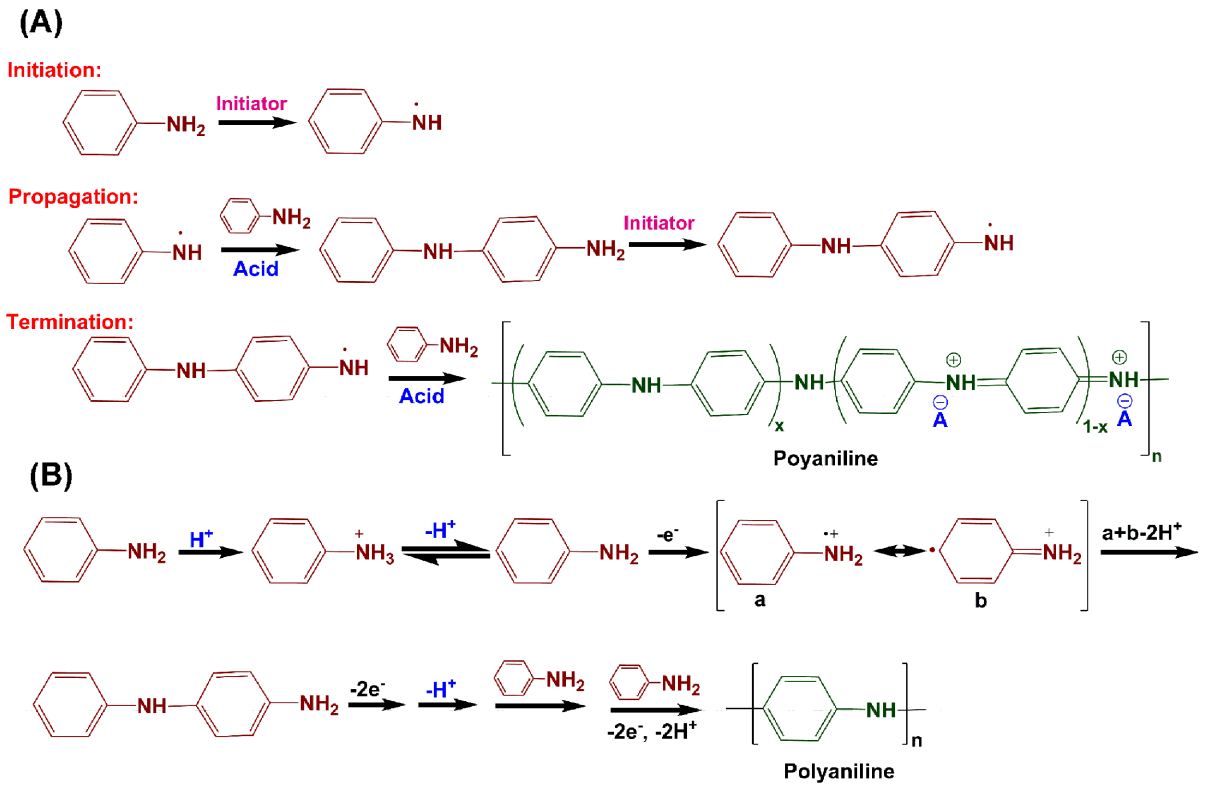

Fig. 1 Chemical (A) and electrochemical (B) polymerization mechanisms of polyaniline. Chemical polymerization of polyaniline is carried out in acidic medium by using a common initiator such as ammonium persulfate and potassium persulfate, while the electro-polymerization of polyaniline is carried out in the electrolyte solution of aniline and acid through applying a potential difference between the working and counter electrode.

Polyanilines containing various nanostructures with different properties have been reported by many research groups. Different nanoarchitectures show additional advantages because of their high surface-to-volume ratio, which leads to the improvement of the properties of their nanocomposites [13]. Therefore, the optimization of the synthesis conditions of PANI with specific morphologies and sizes for high-performance applications is very important.

Several procedures such as solution, self-assembling, heterophase interfacial, and electrochemical polymerizations have been used for the design and synthesis of PANI nanostructures, such as nanospheres, nanogranules, nanorods, nanoflowers, nanofibers, and nanotubes [7,13–19]. In addition, many parameters and processes including the initiator or oxidant,

pH, temperature, solvent, chemical additives (oligoaniline and π bonding compounds), chemical oxidation process (interfacial reaction), template (hard or soft), electrochemistry, radiochemistry and sonochemistry for the design of unique PANI nanostructures should be taken into consideration [14]. **Fig. 2** shows the scanning electron micrographs of various PANI nanostructures synthesized in various conditions.

As mentioned before, a number of researches have been devoted to the preparation of PANI nanocomposites to overcome some weaknesses of the pristine PANI. There are three main procedures for the fabrication of ICPs nanocomposites including:

1. *Solvent casting*: It is one of the very first and simplest processing methods for the fabrication of the polymer composites. In this technique, a polymer is dissolved in a proper solvent and a desired nanofiller is then added to the solution under stirring [20]. In fact, the main advantage of the solvent casting method is its simplicity of manufacturing without the need of specific apparatus. There are numerous factors that can affect the solvent casting method, including the polymer molecular weight, polymer structure, stoichiometric amount, composition, filler, solvent type, and processing conditions (temperature, rate of drying, agitation rate, and frequency of stirring) [21].

2. *In-situ polymerization in the presence of nanofillers*: In this method, a nanofiller surface is modified and then the monomer and initiator are added to form a polymer nanocomposite. Some polymer properties are improved in this method because of the strong interactions between the polymer matrix and the nanofiller [22].

3. *In situ nanoparticle formation in the presence of polymers*: In this approach, an appropriate solvent is used to dissolve polyaniline and then a nanofiller precursor is added, followed by thermal or electrochemical treatment to form the polymer nanocomposite. The formed nanostructures in this method are uniform in various morphologies within the polymer matrix [23].

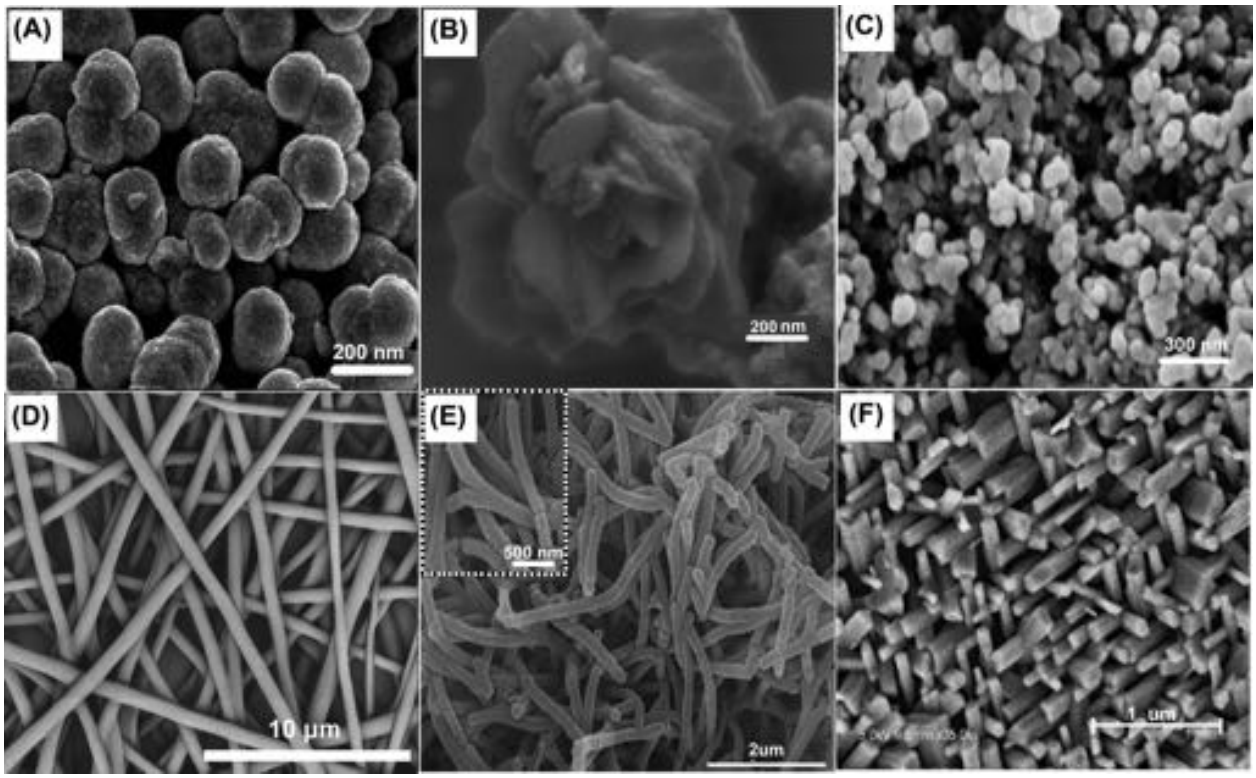

Fig. 2 Scanning electron microscopy images of different shapes of polyaniline nanostructures; (A) polyaniline nanospheres synthesized in the acidic sodium carboxymethyl cellulose (CMC) solution. Reprinted with permission from ref [15]. Copyright 2015 Royal Chemical Society. (B) polyaniline nanoflowers synthesized by the interfacial polymerization in toluene solvent. Reprinted with permission from ref [13]. Copyright 2018 Elsevier. (C) polyaniline nanogranules synthesized by the sonochemistry method in the acidic aqueous solution. (D) polyaniline nanofiber synthesized by the oxidation polymerization of aniline monomer at 0 ºC in the acidic aqueous solution followed by the electrospinning in 50 ml of $CHCl_3$. Reprinted with permission from ref [24]. Copyright 2017 Hindawi (E) polyaniline nanotubes synthesized by the micelle soft-template procedure in the oxalic acid solution as a dopant. Reprinted with permission from ref [18]. Copyright 2015 Royal Chemical Society. (F) polyaniline nanorods synthesized by the ultrasonication. Reprinted with permission from ref [16]. Copyright 2014 Royal Chemical Society.

3. Structure and properties

3.1.Structure

Polyaniline structure consists of reduced (x) and oxidized (1-x) blocks ($0 \leq x \leq 1$) [10] (**Fig. 3A**). According to the redox state of the polymer structure, PANI can be observed in one of three oxidation forms, i.e., leucoemeraldine (LE, yellow, for x= 1, **Fig. 3B**), pernigraniline (PG, purple, for x=0, **Fig. 3C**) and emeraldine (EM, dark green and blue, for x=0.5, **Fig. 3D and E**). The emeraldine form of PANI can be found in the emeraldine-salt (EM-S, dark green) and emeraldine-base (EM-B, blue) forms depending on the acidic and basic conditions, respectively [25]. The oxidation forms of PANI have different colors, conductivities and stabilities. The EM-S is the conducting form of PANI. The electrical conductivity of PANI is related to several conditions, such as the redox state, protonation degree, temperature and dopant type [3,10].

The electrical conductivity of PANI enhances with the doping of the EM-B (insulator form, $\sigma \leq 10^{-10}$ S/cm) and formation of the EM-S (conductive form, $\sigma \geq 1$ S/cm) [2]. Inorganic acids, such as HCl, H_2SO_4, $HClO_4$ and H_3PO_4, and organic acids, such as camphorsulfonic acid, *para*-toluene sulfonic acid and dodecyl benzenesulfonic acid are used for the doping process of PANI, while the

ammonium hydroxide base is responsible for the undoping process of PANI [10,26,27]. In addition, it is well known that the electrical properties of PANI-based polymers depend on the microscopic (i.e., level of doping, conjugation, length of polymer chain) and macroscopic (i.e., materials compactness and molecular orientation) properties [28].

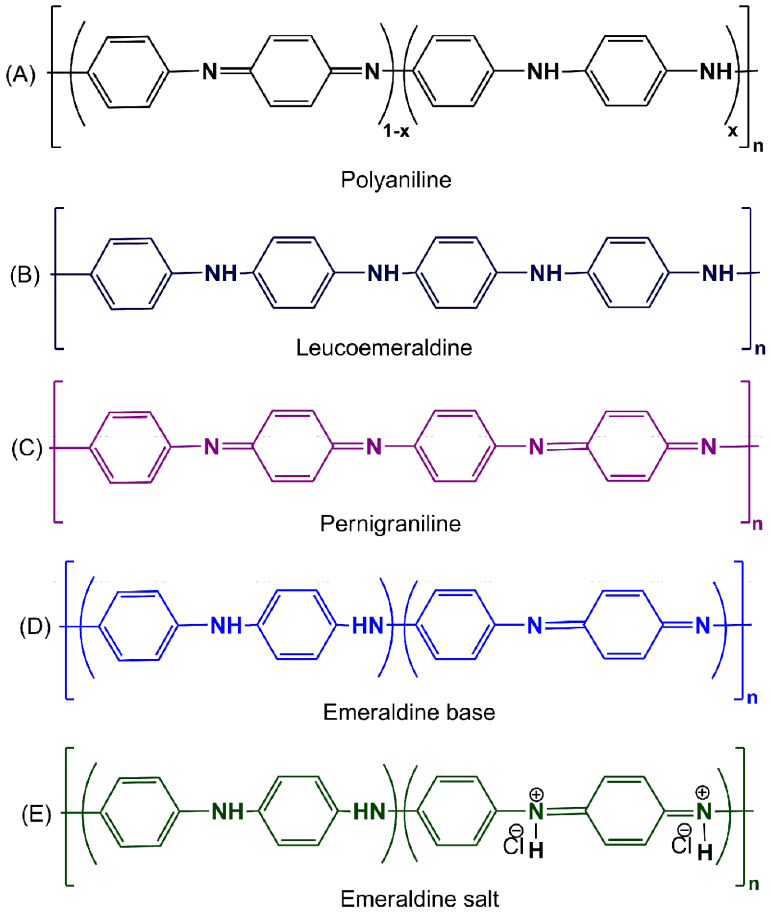

Fig. 3 Structure of polyaniline (A), leucoemeraldine (B), pernigraniline (C), emeraldine base (D) and emeraldine salt (E).

3.2.Physiochemical and mechanical properties

Polyaniline is chemically stable and demonstrates high chemical and structural resistance in acidic and alkaline solutions without undergoing any chemical reaction or degradation [10]. Depending on the redox states, PANI has different solubility in the common organic solvents. In general, PANI in the doped form (PANI-EM-S) is insoluble in the common organic solvents

including dimethyl sulfoxide (DMSO), *N*-methyl-2-pyrrolidone (NMP), dimethylformamide (DMF) and tetrahydrofuran (THF), whereas in the undoped form, PANI-EM-B is soluble in the aforementioned organic solvents [10,28].

Polyaniline pellet shows a good mechanical strength due to good compactness of the PANI powders. Moreover, a significant improvement in the physical and mechanical properties, such as Young's modulus and heat resistance, has been seen in the PANI nanocomposites [29]. Polyaniline in blends and nanocomposite forms prepared using polyurethane, natural rubber, chitosan, carbon nanotubes, and montmorillonite operates as a conducting component in a proper matrix to provide the needed mechanical properties. Indeed, the increased toughness and decreased elongation at break can be achieved in blends and/or nanocomposites by enhancing the amount of polyaniline ratio.

The rheological properties of PANI and its composites are very important for their processing in industrial and medicinal applications. For instance, the rheological parameters of the injectable PANI nanocomposites should be evaluated before being injected to animal and human organs. Indeed, the rheological properties provide information about viscosity, modulus, and gelation temperature of the injectable PANI-based nanocomposites. The size, shape, and distribution of nanomaterials have considerable effects on the rheological parameters of the PANI-based composites

As earlier mentioned, one of the main problems of PANI is its insolubility in common organic solvents. This problem has been solved successfully by developing various approaches for the synthesis of soluble PANI, such as the synthesis of PANI by the micro-emulsion polymerization or in the presence of oleic acid [30–32]. On the other hand, combination of PANI with various polymers/nanomaterials to form blends or composites can be a facile method for the

improvement of its mechanical properties [30,33]. For example, Bilal et al. studied the rheological properties of polyaniline-poly (ethylene oxide) (PANI-PEO) and their composites with KNO_3 and $NaNO_3$. They reported that pyridine is the best solvent for the rheological measurements. Their results showed that the nitrate salts of Na and K added to the PEO-based composite tend to decrease the hydrodynamic volume of the polymer molecule, which results in the decreasing the intrinsic viscosity of the composites. In addition, when the inorganic salts such as KNO_3 and $NaNO_3$ were added, the composites showed somewhat higher values of viscosity. The temperature change has a profound effect on the viscosity as well. For instance, at low temperatures, e.g. 10 °C, the pure PANI-PEO has a lower viscosity than the PANI-PEO-KNO_3 composite, and the viscosities of both composites drop by increasing the temperature to 20 °C [30].

Apart from organic solutions, the rheological properties of the aqueous PANI blends, e.g. polyaniline-poly(vinyl pyrrolidone) (PVP) dispersion have also been investigated. The PANI-PVP dispersion is stable enough showing no precipitates gelation. It was shown that the rheological behavior of this system are not governed by any of the polymeric materials. In fact, the hydrogen bonding between the PVP and PANI is the key for determination of the viscoelastic properties of this suspended blend [31].

Polyaniline has also been used in the thermoresponsive injectable hydrogels. *In-situ* injectable hydrogels can be easily administrated and match any shape of damaged tissue. These hydrogels can reduce the suffering of patients as a minimally invasive method, and therefore, their easy handling is an optimal choice for the clinicians. Thermosensitive hydrogels containing conductive PANI has drawn much attention due to their conductivity, antioxidant and antimicrobial activity. For instance, quaternary ammonium chitosan-*g*-PANI shows antibacterial activity and conductivity along with biodegradability due to the presence of chitosan. These *in situ* forming

gels undergo a sol-gel transition upon the injection into the human body. In fact, in the ambient condition or low temperature, such hydrogels act as liquid (elastic modulus < viscous modulus) and can be easily injected. In contrast, at the body temperature, their rheological properties change and they become gels (elastic modulus > viscous modulus). This alteration of temperature also enhances the viscosity properties of the thermoresponsive hydrogels [34–36]. Apart from temperature-sensitive materials, polyaniline and its composite particles, due to the conductivity features, can be used in electrorheological (ER) fluids. The ER fluid is a sort of smart electro-responsive system showing transition characteristics from a liquid-like to a solid-like state in the presence of an external electric field. For instance, PANI has been used as a coating for SiO_2 nanoparticles to impart electrorheological properties [37,38]. The summary of the physicochemical properties of PANI are listed in Table 1.

Table 1: Physicochemical properties of polyaniline.

Redox state structure	Leucoemeraldine (yellow), pernigraniline (purple) and emeraldine (dark green and blue)[25]
Electrical conductivity	Leucoemeraldine (insulator), pernigraniline (insulator) and emeraldine salt (10^{-2}-10^{0} S/cm)[2,9]
Common dopants	Inorganic acids (HCl, H_2SO_4, $HClO_4$ and H_3PO_4) and organic acids (camphorsulfonic acid, para toluene sulfonic acid and dodecyl benzenesulfonic acid)[10,26]
Solubility	Emeraldine salt (insoluble in the common organic solvents), emeraldine base soluble in NMP, DMSO, DMF and THF [10,28]
Mechanical property	Young's modulus 1.91Gpa; strength at breakpoint 89.5 Mpa; Elongation 5.88 % [29]
Stability	High chemical and structural resistance in the acidic and alkaline solutions [10]
Crystallinity	Depending on the synthesis conditions and dopants can be semi-crystalline or amorphous[22,39]
Morphology	Depending on the synthesis conditions can be nanosphere[15], nanoflower[13], nanogranule[7], nanofiber[24], nanotube[18], and nanorod[16]

Thermal	Glass transition temperature (T_g) for uncross-linked PANI 70 °C and cross-linked PANI 250 °C; thermal degradation in air atmosphere near 500-600 °C[10]

3.3.Degradability

Non-biodegradability of some scaffolds still poses a limitation in biomedicine. Therefore, degradable PANI, as an electrically conductive polymer, is preferred for the biomedical applications. In recent years, the carbohydrate biopolymers (i.e., chitosan, gelatin, heparin, and collagen) and biodegradable aliphatic polyesters (i.e., polylactide, polycaprolactone, polyglycolide and their copolymers) have been employed for the fabrication of PANI blends/composites to prepare degradable scaffolds for tissue engineering [40,41]. As discussed earlier, one of the methods to overcome the drawbacks such as the non-degradability of PANI is the preparation of blends and composites based on PANI and degradable naturally occurring polymers including carbohydrates such as dextrin (**Fig. 4A**), starch, and gelatin [22,39,40]. Consequently, the final composites/blends can be degraded by microorganisms in environmental conditions. For instance, Zare et al. evaluated the soil biodegradability of PANI/dextrin nanocomposites at various weight ratios and reported that the maximum degradation ~74.5% after two months was seen for the nanocomposite with the weight ratio 1/3 of PANI/dextrin. Moreover, the biodegradability of the PANI/dextrin nanocomposites improved considerably with the content of dextrin natural polymer [22].

Recently, a research conducted by Xia et al. revealed an excellent *in vitro* and *in vivo* biodegradability and biocompatibility of a PANI-porous silicon hybrid nanocomposite (PANI-PSi NPs). They found that the presence of the biocompatible and biodegradable PSi NPs resulted in higher biocompatibility and biodegradability of the nanocomposites as compared with the pristine PANI[42]. The biodegradable blends of PANI with poly(ethylene glycol) (PEG) and polycaprolactone (PCL) for the tissue regeneration applications have been also reported [43,44]. The

applications of the degradable PANI blends and composites in tissue engineering will be discussed in Section 6.3.

4. Biocompatibility and cytotoxicity

Polyaniline and its nanocomposites are quickly developing as promising materials for the biomedical applications. Therefore, the health risks related to PANI and PANI nanocomposites are of great importance. The biocompatibility is the ability of the materials to coexist with living things and tissues without damaging them [45]. On the other hand, the cytotoxicity depends on the chemical composition, size and shape of the nanomaterials in the nanocomposites [46]. For instance, the cytotoxicity of the globular polymers is different from that of the polymer nanoparticles. Thus, the structures of PANI and its nanocomposites can affect the biocompatibility and cytotoxicity.

It is well-known that the deprotonation–reprotonation sequences undertaken on PANI result in the decrease of cytotoxicity. However, PANI can hardly be toxic since it is fully insoluble and stable in an aqueous solution. Hence, the cytotoxicity reported on the biological entities is related to the low-molecular-weight compounds. Two types of these low-molecular-weight compounds are available; (I) reaction of by-products with oligomers of aniline [47,48] and (II) the acids that form the PANI salts. As a result, the modification of PANI with regard to the aforementioned materials is of significance [49].

According to the ISO 10993 standards, PANI shows biocompatibility properties in terms of dermal irritation and sensitization. It was reported that both PANI-EM-S and PANI-EM-B have outstanding biocompatibility properties in the duration of dermal irritation. Moreover, the cytotoxicity of the PANI-EM-S is lower than that of the PANI-EM-B due to the reprotonation-deprotonation cycle and the presence of the low-molecular-weight impurities [45]. The cell

biocompatibility of the PANI film prepared through electroless surface polymerization with PC12 cells was also reported. The results showed that the PANI film enhances the cell proliferation, revealing promising potentials of this compound as a surface coating to cultivate neuronal cells which can be used in tissue regeneration [50].

In a study, Humpolicek et al. used different cell lines, such as mouse embryonic fibroblast (NIH/3T3) cell lines and embryonic stem cells to evaluate the biocompatibility of PANI. In contrast to their previous findings, it was found that the correlation of the cytotoxicity with the impurity contents is not always strictly linear. They reported that the cytotoxicity of PANI-salts and PANI-based compounds are similar (**Fig. 4B**) [46].

The biocompatibility of the macroporous PANI cryogel prepared in the frozen poly(vinyl alcohol) solution was investigated by the examination of its cytotoxicity on the mouse embryonic fibroblasts as well as by the examination of the embryo-toxicity based on the production of beating foci inside spontaneous differentiating embryonic stem cells. It was reported that the PANI cryogel with the low contents of low-molecular-weight impurities has a good biocompatibility [51].

The cytotoxicity of the colloidal PANI on the human keratinocyte (HaCaT) and mouse embryonic fibroblast (NIH/3T3) cell lines through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was investigated and the results showed that the cytotoxicity of the colloidal PANI is low [52]. In another research, the cytotoxicity of PANI salt in the globular and nanotubular morphologies decreased after reprecipitation from NMP compared to the primary polymer. Also, no cytotoxicity on the NIH/3T3 cells was seen at 5 and 10% of the extract concentration in the case of globular and nanotubular polymers, respectively [49].

The cytotoxicity evaluation of the PANI nanofibers on the rat celiac macrophages (at the concentrations ≤1 mg/ml) showed that the PANI nanofibers did not have a considerable impact on

the level of cellular ROS and the loss of mitochondrial membrane potential (MMP) of the macrophages; while a higher amount of PANI nanofibers (at the concentrations ≥10 mg/ml) caused cell death, alterations of ROS level and MMP. It was found that the cytotoxicity of PANI nanofibers was originated by the production of the oxidative stress and change of the intracellular MMP [53].

In other researches, the teratogenic and eco-toxicity impacts of PANI nanoparticles and nanofibers in *Rhinella arenarum* larvae and embryos were reported (**Fig. 4C**). The results revealed that there is a low-risk potential after exposing *R. arenarum* to both PANI nanofibers and nanoparticles [54,55].

The difference in the biocompatibility of the PANI composites is because of the various factors such as, chemical composition, size and shape of the nanomaterials in the nanocomposites, dopants and preparation methods [56]. The biocompatibility of the PANI biocomposites such as starch/PANI increases with the increase of the naturally occurring polymer content [57]. It was proposed that the starch/PANI biocomposite be used in the tissue engineering. Surprisingly, in another research, the polyaniline-coated cotton fabric showed high cytotoxicity on the NIH/3T3 cell [58], which is because of the existence of the low-molecular-weight toxic impurities in the PANI. These entrapped impurities in the PANI cotton structure are released during the extraction of the coated cotton prior to the cytotoxicity tests [58]. The aquatic toxicology of PANI and CuO/PANI nanocomposites through acute (ISO 6341) and chronic toxicity (ISO 10706) tests with microcrustaceans *Daphnia magna* and *Vibrio fischeri*, a marine bacterium, were evaluated by Rossetto et al. According to their report, the PANI had no acute toxicity to *D. magna* (EC50,48 h, 99.21 mg/L), while the CuO/PANI nanocomposite had the EC50 value of 0.48 mg/L [56].

Regarding carbon-based nanocomposites of PANI, the *in vitro* cellular toxicity of the nanodiamonds-PANI (NDs/PANI) composite on the human embryonic kidney (HEK) cells showed that at low concentrations (0.1 to 1 μg/ml) the NDs/PANI composite can be applied for the biomedical applications without a negative effect on the cells life activities [59]. It was reported that its application in bioscience depends on the determination of the proper concentration under the *in-vivo* condition. The cellular biocompatibility of the poly(*N*-isopropylacrylamide)–carbon nanotube (CNT)–PANI nanocomposite for tissue engineering applications using the mouse L929 fibroblast cells showed very good cells growth and viability along with the cells detachment function [60]. This nanocomposite was first fabricated via the combination of coupling and electrospinning and then applied for the woven microfabric scaffolds construction.

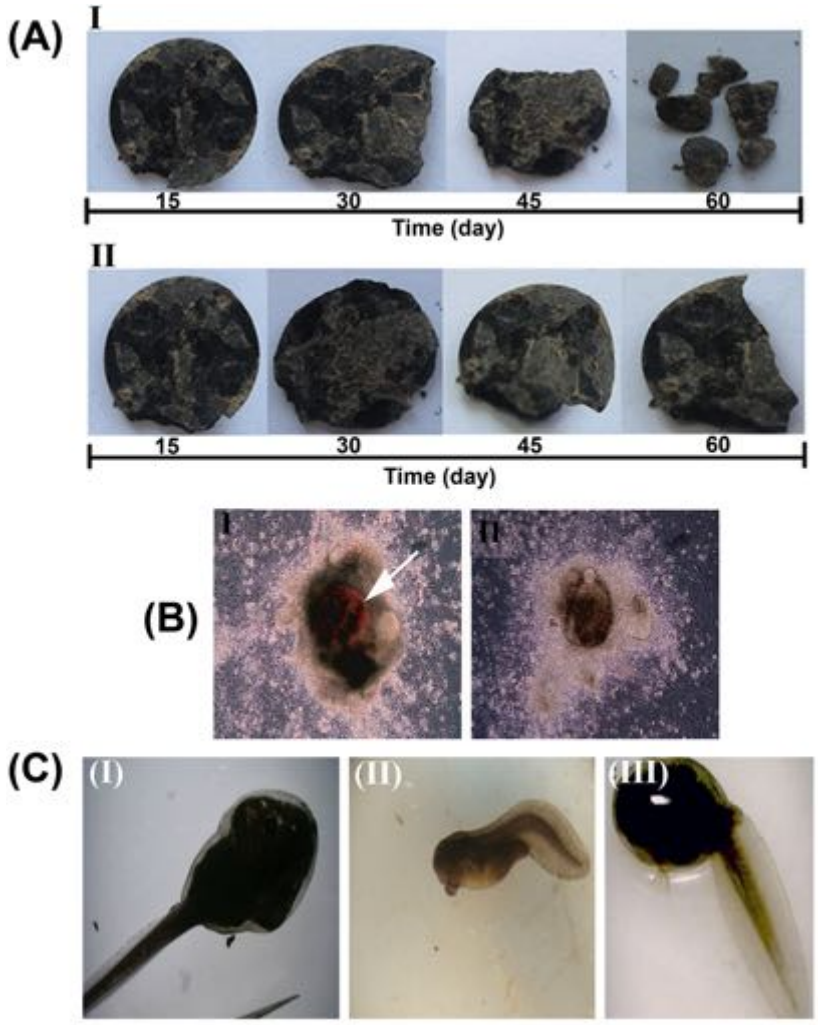

Fig. 4 (A) The soil degradability of polyaniline/dextrin nanocomposite tablets with the diameter of 14 mm for I [polyaniline:dextrin (1:3)] and II [polyaniline:dextrin (2:1)] buried in soil (pH:7.5) in the relative humidity of 60–70 % at 28–30 ºC for 60 days. Reprinted with permission from ref [22]. Copyright 2014 Springer. (B) The formation of the erythroid clusters (the red clusters marked with an arrow) within the embryoid body. (I) positive reference and (II) absence of the red erythroid clusters after cultivation in the presence of 25% extracts of PANI-salt Reprinted with permission from ref [46]. Copyright 2018 Elsevier. Photographic recording of malformations detected in the embryos treated with 400 mg/L polyaniline nanofibers, (I) the control test without any treatment, (II) embryo with incurvated body axis and (III) embryo with underdeveloped gills. Reprinted with permission from ref [55]. Copyright 2012 Elsevier.

5. Biological activity

5.1.Antimicrobial activity

The infection caused by microbes affects the human life severely. Hence, a number of studies have been devoted to prepare new antimicrobial agents to fight pathogens. The advent of new compounds containing antimicrobial properties continues unabated. Polymers with antibacterial and antifungal activities are widely used in the biomedical applications since the pathogens become resistant to the existing drugs. Conducting polymers, such as PANIs, are appealing in biomedicine because of their high cellular response [61]. In this regard, the PANI-based compounds have been synthesized to control the microbial contaminations [62]. The antimicrobial activity of PANI towards the Gram-negative and Gram-positive bacteria have been reported [63,64]. However, a number of various nanomaterials, polymers and other compounds have been added to PANI to enhance the antimicrobial activity, conductivity, and photocatalytic activity [65,66]. Hence, the PANI-based nanocomposites consist of different nano-architectures such as rods, spherical particles, tubes and sheets have been exploited for the biomedical applications. For instance, the PANI/zinc-aluminum layered double hydroxide nanocomposite prepared by the free radical emulsion polymerization has been reported to show antibacterial activity [67]. Other architectures, such as PANI decorated Au nanorods, have also shown high antibacterial properties toward *Escherichia coli* and *Staphylococcus aureus* [68]. Nanofibers of PANI/silver NPs showed antibacterial properties against *E. coli* and *B. subtilis* strains, while neat PANI did not show any antibacterial activity[69]. The application of PANI/silver nanocomposites is not limited to antimicrobial purposes. For instance, the use of Ag functionalized PANI-based biosensor has been reported for the determination of anticancer drugs [70].

The PANI nanocomposites containing microbicidal nanomaterials, such as zinc oxide and Ag nanocompounds, have shown synergistic antimicrobial effects [64]. Silver NPs and carbon nanotubes

incorporated PANI showed higher antibacterial activity than PANI-carbon nanotubes and PANI-Ag nanocomposites because of the synergistic effect of the fillers [71]. In another study, the antibacterial effect of the ZrO_2 NPs-PANI nanocomposite against *E. coli* and *S. aureus* was determined to be higher than that of the pure PANI [72].

The polymers containing quaternary ammonium compounds have high antibacterial and antifungal activity [73,74]. Therefore, copolymers of PANI with the biopolymers containing quaternary ammonium salts, such as chitosan, have been employed to improve the antibacterial activity with enhancing the biocompatibility of PANI [75]. With this in mind, quaternized chitosan-graft-PANI injectable hydrogels have been used as the biocompatible scaffolds for tissue regeneration (**Fig. 5**). The *in situ* forming biodegradable conductive hydrogels have *in vitro* and *in vivo* antibacterial properties and can improve the proliferation of the C2C12 myoblasts in comparison with the quaternized chitosan hydrogel [35]. The microcapsules of poly(lactic-*co*-glycolic acid) have been applied as a carrier for the delivery of ginseng/PANI for the implant restoration. The presence of PANI enhanced the antibacterial efficacy up to 88% [76]. Apart from releasing antimicrobial agents, non-leaching antibacterial and antifungal compounds, which have a chemical linkage to the polymer matrix is another option to form an antimicrobial surface. For instance, poly(3-aminobenzoic acid) and PANI have been applied to form an antibacterial surface [77].

The antimicrobial mechanism of PANI includes the production of H_2O_2 that causes the oxidative stress characterized by the perturbation of iron homeostasis (Fenton reaction). In fact, free iron can propagate H_2O_2 stress by participating in Fenton reaction which accelerates the formation of hydroxyl radicals leading to the microorganism destruction and, subsequently, cell death. Polyaniline is more active against Gram-negative bacteria, such as *E. coli*, in aerobic

conditions compared with the anaerobic environments. Higher antibacterial property in aerobic conditions supports the role of reactive oxygen species [78].

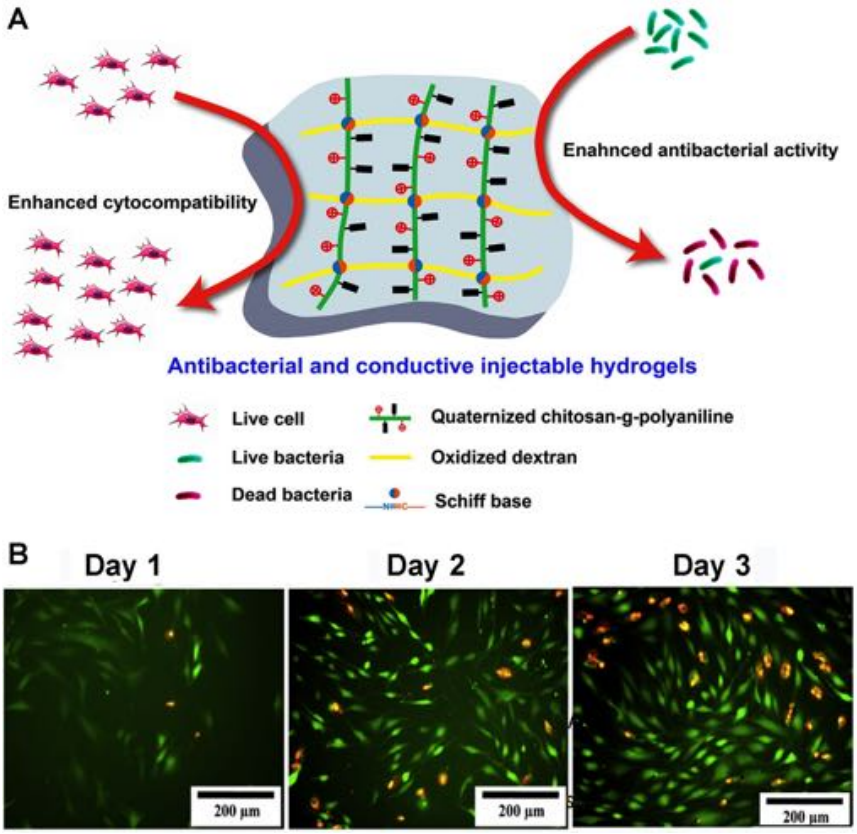

Fig. 5. (A) Schematic presentation for the antibacterial activity of injectable conducting hydrogels. (B) Live/dead staining of adipose-derived mesenchymal stem cells at successive culture periods for the quaternized chitosan-*graft*-PANI crosslinked by oxidized dextran using the Alamar Blue and Live/Dead Viability/Cytotoxicity assay. Scale bar: 200 μm. Reprinted with permission from ref [35]. Copyright 2015 Elsevier.

5.2.Antioxidant activity

Free radical intermediates lead to the tissue damage and diseases progression such as inflammation, heart disease, cancer and premature aging [79]. Antioxidant materials are compounds that prevent the oxidation of other materials. They play an

important role in foods and tissues as a health protective factor and decrease the risk of the chronic diseases [79]. The antioxidant activity of ICPs has important consequences for their applications in the biomedicine. It is particularly useful in the tissues suffering from the oxidative stress, where the capability to lower excessive stages of the reactive radical species (RRS) is appropriate [80]. The ICPs, such as PPy and PANI, have shown good antioxidant activities in the presence of 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenger [80]. The swift heavy ion irradiation of PANI and the nature of the dopant acids have shown a significant role in the antioxidant activity of the PANI nanostructures [81]. The HCl-doped PANI nanofibers induced by the swift heavy ion irradiation showed the best antioxidant activity compared to other undoped PANI structures [82]. It was reported that the observed antioxidant activity of the PANI nanofibers is related to the decrease of the size of PANI nanofibers after the swift heavy ion irradiation, which points the access of more reaction sites for DPPH scavenging [82]. On the other hand, the antioxidant activity of the materials depends on their capability to donate hydrogen to reduce DPPH, and therefore, the chemical structure of the materials are important for their antioxidant activity [22].

There are a few studies on the antioxidant activity of PANI nanocomposites to be developed in the biomedical applications. The antioxidant activity of PANI/starch biocomposites was improved upon increasing the PANI ratio. This can be related to the fact that the PANI, because of its redox active nature, is effective as a DPPH free radical scavenger [57]. The antioxidant activity of other polysaccharides/PANI composites, such as PANI/dextrin nanocomposite, prepared by *in-situ* polymerization of aniline and dextrin biopolymer, increased up to 72 % with the aniline content.

This antioxidant activity of PANI can have substantial effect on the tissues and organs suffering from the oxidative stress [22].

Regarding polyaniline containing metal nanomaterials, the maximum antioxidant activity of the PANI/polyxanthonetriazole/Fe_3O_4 nanocomposite fabricated *via* an *in-situ* emulsion polymerization was evaluated to be PANI 58% at an interval of 10–120 min. This amount of antioxidant activity is because of the presence of a higher number of electrons and hydrogen atoms [79].

The effect of the supporting electrolytes, such as *para*-toluene sulfonic acid (*p*-TSA) and KCl with different molar ratios on the antioxidant activity of PANI/reduced graphene oxide (r-GO) has also been investigated. Accordingly, the antioxidant activity of the PANI/r-GO nanocomposite in the *p*-TSA supporting electrolyte increased with the *p*-TSA molar ratio. It was also found that the protonation of the PANI/r-GO nanocomposite by *p*-TSA donates hydrogen to reduce DPPH as an antioxidant [83].

As mentioned earlier, the antioxidant activity of ICPs, which comes from their capability to decrease the levels of RRS, is possibly helpful for the suffered tissues from the oxidative stress. Thus, the antioxidant activity of polyaniline may be important, especially for the diseases that cause excessive levels of RRS. Furthermore, the PANI composites, such as the PANI/starch, may have the capability to decrease the oxidant produced *via* the chemotherapeutic drugs which can assist in neutralizing or at least decreasing the side effects of the chemotherapeutic cancer therapy. According to the literatures on this subject, a schematic illustration for the proposed mechanism

of antioxidant activity of PANI in the presence of the DPPH radical scavenger is shown in **Fig. 6**.

Fig. 6. The proposed mechanism for the antioxidant activity of polyaniline in the presence of DPPH radical scavenger.

6. Biomedical applications

Among ICPs, the PANI has outstanding potential applications in different fields such as super-capacitor, gas sensor, water treatment, anti-corrosion coating, drug delivery, biosensor and tissue engineering [84-86].

In the following sections, the applications of PANI nanocomposites in the biomedical and clinical fields are addressed. It should be noted that according to our knowledge, based on ClinicalTrials.gov international database, PANI-based medical devices has not yet reached the clinical stage, and consequently has not gained the certifications to enter the market. PANI is indeed extremely promising and interesting, but they have not yet reached a sufficient stage of maturity to allow a safe translation

from bench to bedside . In addition, the regulatory framework has not yet well defined the borders for the applications containing nanocomponents.

6.1.Antimicrobial therapy

Antimicrobial conducting PANI has been applied in biomedicine including electrotherapy, antimicrobial clothing, and electromagnetic devices for monitoring health [87]. Infections in the treatment of diseases are still challenging; for instance, during or post scaffold transplantation which reduces the efficacy of bone healing. PANI nanocomposites have been developed in combination with various antimicrobial agents including silver NPs, TiO_2, releasable drugs and biomolecules, and the non-leachable compounds, such as quaternary ammonium salts, to prepare a number of antimicrobial devices [42,62,69,88].

PANI nanofibers combined with mupirocin, a topical microbicidal compound, have been prepared *via* a self-assembly approach for their potential applications as a wound healing dress [89]. It was shown by the agar diffusion method that the antibacterial activity of the PANI-mupirocin was higher than that of the neat PANI due to the release of mupirocin [90]. Fiber-highly porous scaffolds based on poly-ε-caprolactone-PANI were fabricated by electrospinning approach for their potential applications in electrically stimulated cell growths and cytoprotection of cells against oxy-radials. The nanostructured bioactive scaffolds revealed both antibacterial and antioxidant activities (free radical-scavenging capability) with no cytotoxicity against L929 cells on the scaffolds [91].

Colloidal aqueous dispersions of PANI showed low bactericidal effects (3500 g mL^{-1}) against *B. cereus* and *E. coli*. Although the PANI dispersion has low cytotoxicity, the toxicity effect depends on the cell line and PANI dose; for example, the human keratinocyte cells were less

sensitive than the mouse embryonic fibroblast cells. In addition, the neutrophil oxidative burst assay revealed that 150 g mL^{-1} is the critical concentration of the PANI colloid dispersions for the biologically safe applications [52].

Thermosensitive gels possessing electrical conductivity and self-healing capability are of great interest as cell carriers for tissue engineering [92,93]. In a study conducted by Dong et al., an injectable and biodegradable hydrogel with antibacterial activity was synthesized by mixing dibenzaldehyde-terminated poly(ethylene glycol) (PEG-DA) and chitosan-*graft*-aniline tetramer (CS-*g*-AT) to be used for the repair of the damaged cardiac tissue. The electroactive and antibacterial hydrogels showed good viability and proliferation with rapid self-healing capability because of the cross-linking network made through the Schiff-base reaction of aniline (**Fig. 7**) [92]. The cell growth and proliferation was also reported for hard tissue regeneration using TiO_2 nanotubes-PANI nanocomposites [94].

The PANI-polyurethane foam (PANI/PUF) was employed as an antibacterial dress for the wound healing applications. The PANI/PUF film was fabricated by using *in-situ* radical polymerization of aniline monomer in the presence of usnic acid (UA, as a dopant) and PUF. The UA improved the bactericidal property of PANI toward *E.coli* and *S.aureus* strains[95]. Other bandage dressings, such as antimicrobial membrane composed of aniline tetramer/siloxane terminated polyurethane (AT/STPU), have also been suggested. The AT/STPU membranes were fabricated *via* the sol–gel method using the STPU prepolymer and AT. The presence of polysiloxane-linked PU chains improved the dimensional stability even at the high hydrated condition. It was also reported that the AT led to the improvement of the cells viability and antimicrobial activity for both bacteria and fungal strains[96].

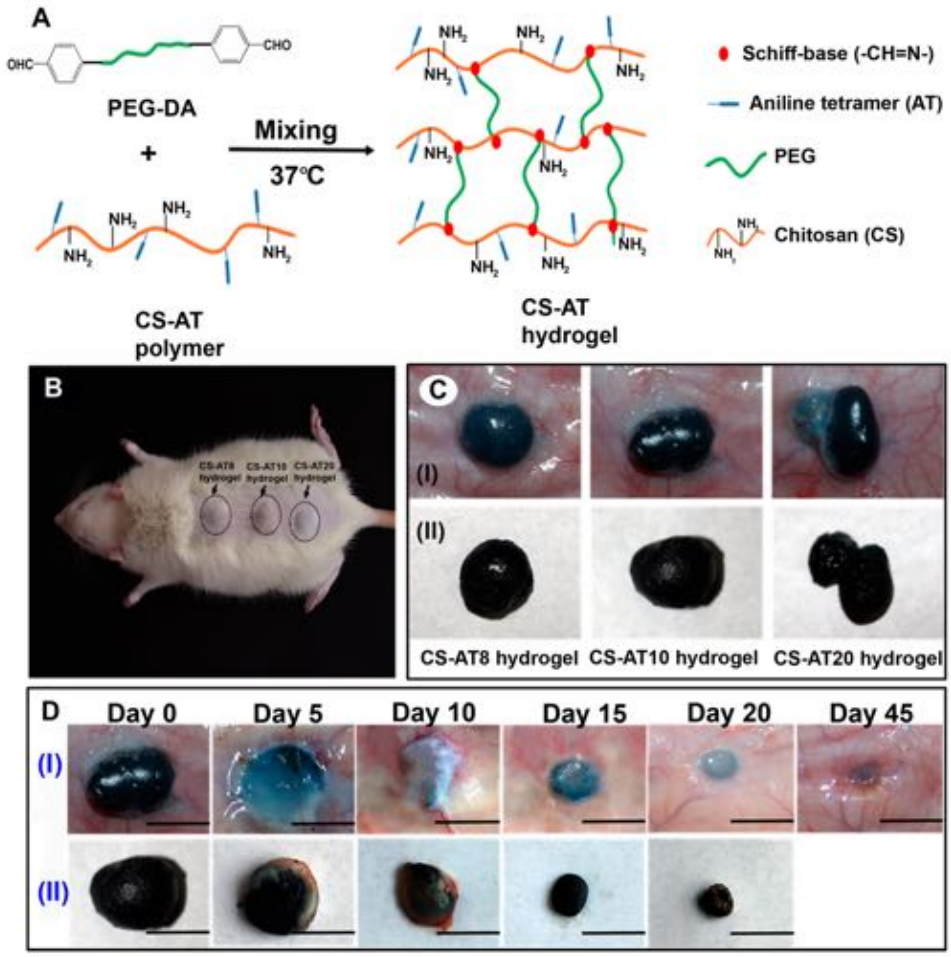

Fig. 7 ((A) Schematic procedure for the synthesis of thermosensitive chitosan-graft-aniline tetramer (CS-*g*-AT) hydrogel. (B) CS-*g*-AT hydrogels after subcutaneous injection. (C) CS-*g*-AT hydrogels wrapped in the rat's skin (row I) and the hydrogels peeled from the rat's skin (row II). The hydrogels with different aniline tetramer (AT) contents, including CS-AT8, CS-AT10 and CS-AT20, were prepared. (D) Degradation properties of the hydrogels in vivo. Row I shows the hydrogel under the skin and row II displays the hydrogel that peeled from the skin. CS: chitosan, AT: aniline tetramer. Reprinted from ref [92]. Copyright 2016 American Chemical Society.

PANI and its composites not only target the human body for the antimicrobial therapy but also are suggested to be used in places (e.g. hospitals) and devices (e.g. medical devices) that are prone to the microbial growth. For instance, Robertson et al. evaluated the antimicrobial activities of PANI and poly(3-aminobenzoic acid) (P3ABA) as the effective agents to fabricate bacteria-

resistant surfaces. The antimicrobial activities of PANI and P3ABA against *E.coli* and *S.aureus* were seen in both absorbent and non-absorbent surfaces. It was proposed that these surfaces could be applied as the wall coating in hospitals [77]. PANI coated modified polypropylene (MPP) has been prepared by using dip-coating technique as an anti bioaerosol filter. The PANI NPs were synthesized by micro-emulation polymerization and then coated onto the polypropylene filter. The antibioaerosol property of the PANI/MPP was investigated against *S. aureus*, *E. coli*, and *B. subtilis* bioaerosols. It was shown that the water absorption property, stability and antibacterial efficiency of the PANI/MPP were meaningfully improved as compared to the unmodified PP filter [97].

Metal nanomaterials embedded PANI nanocomposites have also been applied to improve the antibacterial and antifungal activity of the nanocomposites. For instance, the conductive polyaniline containing silver showed higher antibacterial activity than the neat PANI [88,98]. Though the mechanism of antimicrobial activity of nanomaterials against different microorganisms varies for the types of metals, ions and, species, the dissolution of nanomaterials into ions is often the first step and a common reason for the toxicity of metallic nanostructures (**Fig. 8**). For instance, the metal ions can produce hydroperoxide radicals, whereas zinc oxide can form hydroxyl radicals [99].

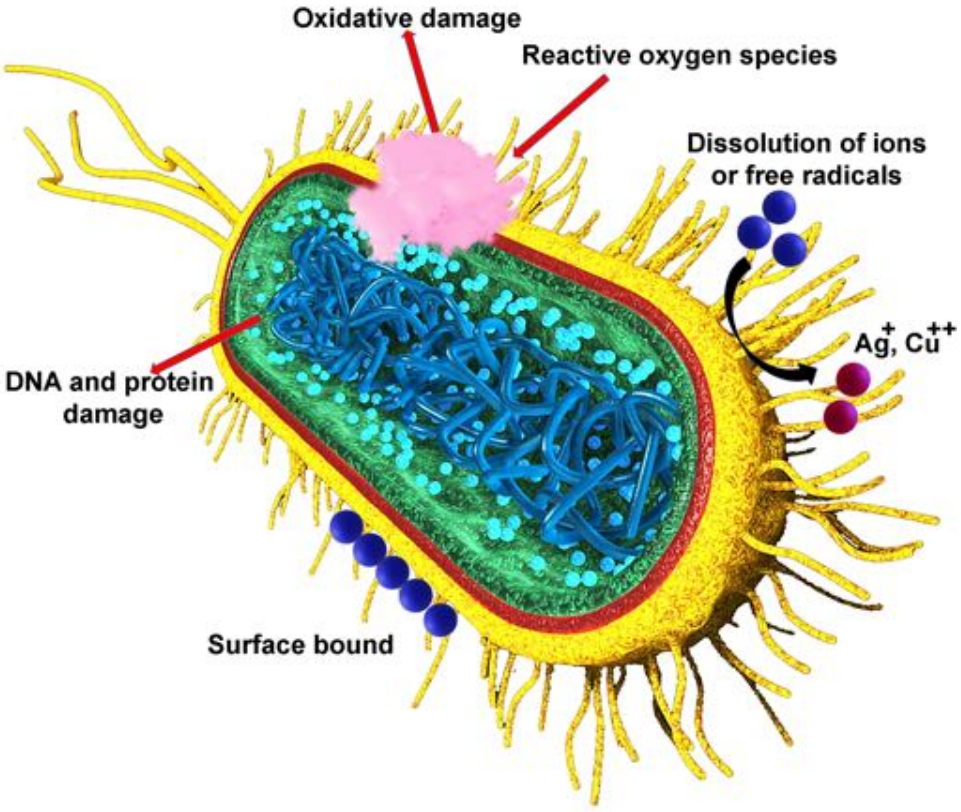

Fig. 8 Illustration of potential interactions and modes of toxicity when engineered nanoparticles targeted at different parts of a generic bacterium: capsule, cell wall, cell membrane, and cytoplasmic contents. Numerous nanoparticle shapes may reduce the bactericidal toxicity by one or some of these mechanisms. These mechanisms include the cell membrane disruption, disruption of electron transport chains, ROS production, and damage of proton efflux pumps.

6.2.Drug delivery

It is widely accepted that the kinetics by which a drug is released presents a high impact on its efficacy [100]. Traditional approaches for delivering a drug or biomolecule through oral or injection lead to the accumulation of drugs/biomolecules(concentration peak) in the human body.[101] Accordingly, to reach the therapeutic levels, the initial concentration of the biomolecules must be more than the threshold level which causes the biomolecule accumulation; however, this concentration peak is gradually reduced to an ineffective level over time. Thus, the most important objective behind the sustained and controlled drug delivery systems is to offer an optimal drug

delivery adjusting drug level to avoid under- and overdosing and preserve the released amount within a certain period. This approach leads to the reduction of the number of drugs administration per day [102]. These strategies often called smart drug delivery systems or devices (SDDS), are based on multidisciplinary approaches that combine pharmaceutics, materials science, and molecular biology together with the engineering skills [103]. The main aim is to release a certain amount of a drug, loaded within carriers, to a specific target site for a prolonged period of time with a sustained kinetics. The drug delivery device can be either inert (and so the device works only as a drug carrier) or an active part of the therapy. Following the second strategy, due to the intrinsic conductivity of PANI, PANI derivatives can be used as the drug carriers with the electric-driven release [104]. A common issue of those devices is their very low mechanical strength [105]. A good strategy to improve the mechanical properties is represented by using supramolecular nanofibers self-assembled from the sorbitol derivatives [106]. PANI is also a good candidate to be a photothermal converting material for the theranostic applications. Therefore, it can be used for diagnosis and simultaneously delivering a drug. In this regard, the biocompatible graphene and Au NP core PANI shell nanocomposites have successfully been fabricated. These nanocomposites showed high biocompatibility, good stability, strong near-infrared (NIR) absorbance, and suitable drug loading efficiency. This light-sensitive system has NIR/pH-responsive drug-releasing capability, which promotes the practical applications in the chemo-photothermal therapy [107].

Chemo-phototherapy is the incorporation of a therapeutic agent within a material that is responsive to NIR irradiation inducing anticancer activity. Of organic NIR-responsive materials, PANI emerged as an extremely promising material [42,108–111]. This strategy has attracted great attention in recent years in view of its enhanced drug accumulation and controlled release, while the side effects were relatively decreased [112]. For instance, Nguyen et al. [108] embedded a

chemotherapeutic agent, methotrexate and PANI (a photosensitizer material) within hybrid polymer NPs that can target cancer cells after conjugation with lanreotide, a synthetic analog of somatostatin. The synthesis and structure of these multifunctional hybrid polymer NPs together with the mechanism of their anticancer activity are schematized in **Fig. 9**. In addition, the efficacy of the composite systems to kill the cancer cells could be improved using the PANI derivatives, such as the PANI impregnated with the magnetic (Fe_3O_4) nanoparticles [113].

The use of PANI nanocomposites in cancer therapy is also reported by Gao et al. [114] with the development of folate-based particles functionalized with PANI. The decorated nanoparticles were able to efficiently target the cancer cells and selectively accumulate within them to achieve the NIR-triggered localized release of their content (cisplatin). It was also shown that the gold nanorods could be coated with the PANI in order to reduce the cytotoxicity and instability. After the incubation of the nanorods with HeLa cells and exposure to a NIR laser, the threshold energy to kill the cancer cells was found to be significantly lower compared with the previous studies [115].

Apart from the metallic nanostructures, the PANI chains with various lengths have been attached onto the surface of the spherical particles of hollow mesoporous silica using *in situ* chemical oxidative polymerization. The encapsulated anti-cancer drug (doxorubicin) exhibited an acidic pH-responsive release behavior; while indomethacin showed an alkaline release. The effect of the length of PANI chain-gate in the drug encapsulation capacity was also studied. Indeed, the long PANI chains decreased the loading capacity due to the blocked mesoporous channel [116]. In the field of photothermal chemotherapy, PANI was also exploited to cover inorganic [117] and organic [118] NPs as a functionalizing compound to improve their performance. Table 2 represents the use of polyaniline and its nanocomposites in drug delivery and bioimaging applications.

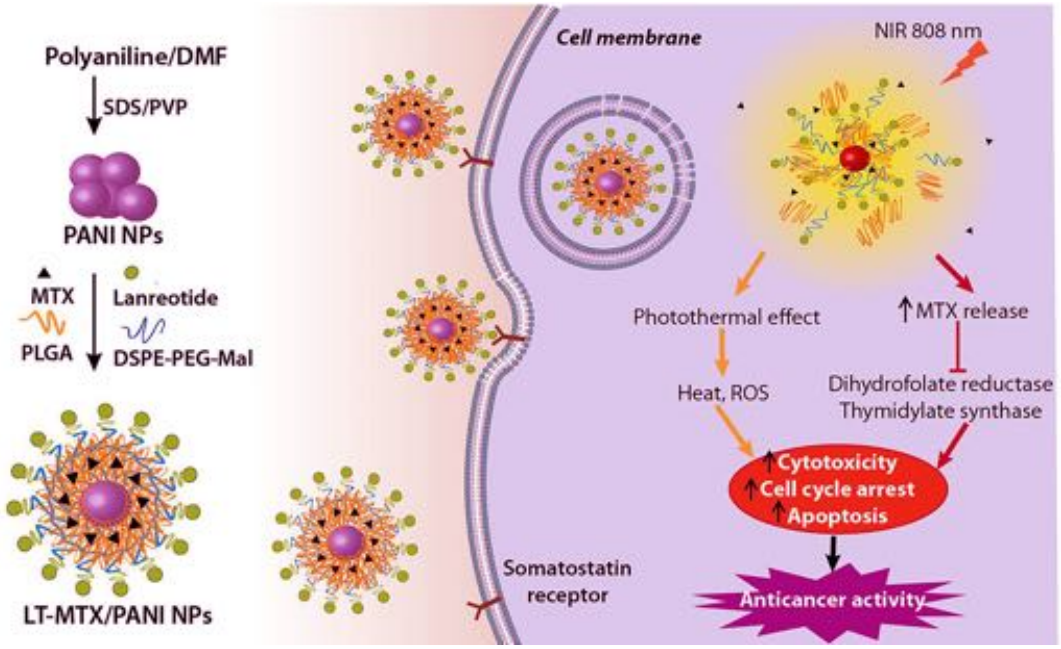

Fig. 9. Schematic illustration on the preparation of multifunctional hybrid polymer nanoparticles along with their anticancer activity mechanism. Reprinted with permission from ref [108]. Copyright 2018 Elsevier.

Table 2. Polyaniline nanocomposites used in drug delivery, photothermal therapy, and bioimaging applications.

Nanocomposites	Nanomaterial size (nm)	Structures	Drug	Applications	Reference
Polyaniline/porous silicon	10-20	Porous silica particles	Doxorubicin hydrochloride	Cancer therapy	[42]
Polyaniline	90	Nanorods	Cisplatin	Photothermal cancer therapy	[112]
Polyaniline tubes	800-1500	Rectangular shaped hollow tubes	Acid Red 8 as model drug	Drug delivery	[119]
Polyaniline/silica nanoparticles	200	Hyaluronic acid decorated silica fluorescent NPs	-	Near-infrared light responsive (bio-imaging)	[120]
Poly(ethylene glycol) with poly(ϵ-caprolactone) block copolymer/polyaniline NPs	83	Core-Crosslinked Polyaniline NPs	Cisplatin	Breast cancer cells	[118]
Polyaniline/MoS_2 Quantum Dot	5	Quantum Dot	-	Bioimaging (tomography)	[121]
Surface modified PANI NPs by F127	48	Functionalized NPs	-	Near-infrared (NIR) photothermal therapy	[122]
Graphene and Au NP core PANI shell nanocomposites	10	Core-shell NPs	Doxorubicin	Photothermal cancer therapy	[107]
Lanreotide-methotrexate/Polyaniline	180	Lanreotide-functionalized NPs	Methotrexate	Photothermal cancer therapy	[108]
Polyaniline with zeolite imidazole frameworks	200	Functionalized NPs	5-fluorouracil	Photothermal cancer therapy	[109]
Lipid-polyaniline	100	Lipid-functionalized NPs	Rapamycin	Photothermal cancer therapy	[110]

$CaCO_3$/polyaniline	1200	L-cysteine-functionalized microparticles	-	Photothermal cancer therapy	[111]
Polyaniline/Pluronic F127	50 nm	Nanoparticles	-	Photothermal cancer therapy	[122]
Fe_3O_4/polyaniline	10 nm	Core-shell NPs	-	Photothermal cancer therapy	[113]
Polyaniline/polyglutamic acid	80 nm	Cysteine-functionalized NPs	-	Photothermal cancer therapy	[123]
Folate/poly(ethylene glycol)-distearoylphosphatidylcholine	100 nm	Polyaniline-loaded NPs	Cisplatin	Photothermal cancer therapy	[114]
Au nanorods/polyaniline	40 nm	Core – shell nanorods	-	Photothermal cancer therapy	[115]
Polyaniline/porous silicon	110 nm	Porous silica particles	Doxorubicin	Photothermal cancer therapy	[116]
lanthanide-based upconversion NPs /Polyaniline	120 nm	Core – shell NPs	-	Bioimaging and photothermal cancer therapy	[117]

6.3.Tissue engineering

6.3.1. Wound healing

The possibility to transplant tissue is limited by several issues, such as immune rejection and donor shortage [124]. Novel research studies are looking for the combination of cells with the active molecules (drugs or biomolecules) to improve the regenerative therapeutic effects [125]. In this framework, in the last decades, a lot of studies were devoted to the development of proper 3D scaffolds that can work as a temporary substrate, helping to the growth of cells in an organized fashion, before transplanting them within patients [126]. This necessity comes from the fact that the cells injected from *in vitro* cultured cells can easily escape, leaving the zone of injection with an uncertain fate through the circulatory torrent. In this regard, not only scientific literature agrees with addressing this issue, but also regulatory supranational directives (*e.g.* EU668/2009 and 47/2007/EC) are now pointing towards the necessity to use cells in combination with suitable support structures. Consequently, great attention has been devoted to the polymers that can be applied for the production of the three-dimensional scaffolds and developing the injectable devices for tissue regeneration. In this field, PANI can improve the scaffold physical properties [62,127]. This improvement in the elasticity and mechanical performances allows the scaffolds to better mimic the native tissue properties [127,128]. For instance, the composites based on PANI could reach a high conductivity range and low tensile strain with the consequent high fibroblast and myoblasts adhesion [129].

Electrical stimulation of the fibroblasts loaded within the PANI composite scaffolds presented low cell death and improved metabolic rate. Sharma et al. [130] developed a composite system based on PANI-carbon nanotubes, the nanofibers of poly(*N*-isopropyl acrylamide-*co*-methacrylic acid) (PNIPAm-*co*-MAA), and PC/PNIPAm-*co*-MAA by electrospinning. The seen excellent growth of cells on the surface of the composite can be due to the higher conductivity and mechanical strength

of polyaniline and carbon nanotubes. PANI-based NPs were also used to improve the performances of the graphene papers [131]. The combination of flexibility, biocompatibility, and electrochemical properties, coming from nanostructured PANI and graphene, makes them to be good candidates for hybrid devices for the biomedical sectors, such as flexible biosensors, batteries, and bioelectrodes along with the ability to culture the electrically excitable cells. Indeed, the conductivity given by PANI in hydrogels is also used in cellulose nanofibers [132], resulting in better degradability and biocompatibility. The amelioration of the composite systems in the applications of tissue engineering was shown in the regeneration of cardiac cells[132].

PANI has also been mixed with gelatin, and the co-electrospun nanofibers were utilized to support the cell growth [133]. The experimental results revealed that all the PANI/gelatin nanofibers support the H9c2 cell attachment and proliferation and can control the tissue culture-treated plastic and smooth glass substrates. The use of PANI nanocomposites in cardiac tissue engineering is very promising [134]. For instance, PANI associated with caprolactone producing patches was able to better guarantee the high viability of human mesenchymal stem cells than the neat polycaprolactone (PCL)[134].

Hsiao et al. [135] developed a mesh (**Fig. 10**) including aligned composite nanofibers of PANI and PLGA, as an electrically conductive platform for coordinating the beatings of the cultured cardiomyocytes synchronously. The PANI/lactide composite was also applied to stimulate the neuromuscular junction [136] and nerve regeneration [137] because of its ability to provide electrical signals. Due to this ability, PANI was used in combination with PCL to prepare the electrically active fibers that can maintain stable electrical features in the simulated cell culture conditions for up to one week with the improved NGF-induced neurite outgrowth of PC12 cells [138].

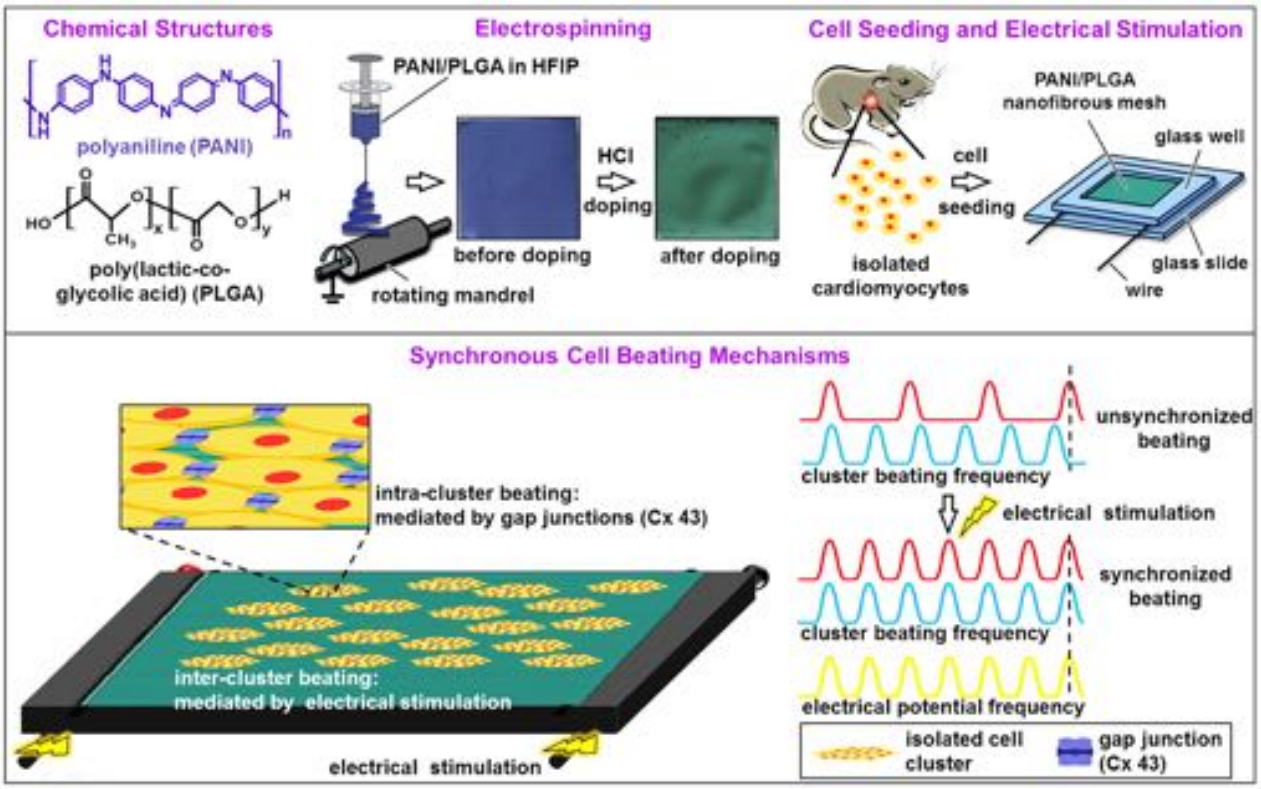

Fig. 10. Schematic diagrams on the preparation procedure of polyaniline/poly(lactic-*co*-glycolic acid) (PANI/PLGA) nanofibrous mesh, cell sowing, electrical excitation, and synchronous cell thrashings mechanisms. Reprinted with permission from ref [135]. Copyright 2013 Elsevier.

PANI nanotubes are one of the most promising nanostructures for cardiac tissue regenerations because of their electroactive characteristics. Their biocompatibility and low hydrophilic characteristics can be enhanced by their functionalization with polyglycerol dendrimers [139].

6.3.2. Bone regeneration

Evidences of clinical requests concerning the bone regeneration date back to ancient Egypt and are very important in the present age. A more rigorous scientific method has been followed since 1889 when "modern" researchers began to focus their efforts on what can be defined as the early bone tissue regeneration [140]. Although nowadays several hundred millions of surgical intervention *per* year are carried out, autograft bone still remains the current clinical gold standard for the

treatment of critical-sized and non-union bone defects. Being advantageous for the immunocompatibility, autografts nevertheless carry a wide spectrum of risks, such as general anesthesia, complex surgical maneuvers, secondary infections, secondary fractures, pain, site morbidity, *etc.*; since they lead to high percentage of failure (more the 10%) followed by important costs increases [141–143]. Furthermore, it is generally accepted that not all the defects can be addressed, particularly the bigger ones, as far as few healthy sites can be harvested without loss of function [143]. The requirement of proper bone replacements for the remodeling of native bone tissues is hence evident and sees a wide spectrum of proposed solutions related to the academia, clinics and industry [144]. In this framework, surgeons can choose from substitutes that can be divided into three main categories apart from autografts:

1) allografts, *i.e.* bone segments taken from cadavers and duly sterilized
2) xenografts, *i.e.* bone segments taken from animal bones (bovine, equine, porcine, *etc*.) duly acellularized and sterilized
3) synthetic scaffolds

Allografts derived from cadavers bone are an acceptable option. However, there are some concerns, such as diseases transmission, toxicity associated with the requirement of sterilization, immunologic rejection risks, and very high sample variability that progressively leads to other available alternatives; the challenge still remains an open scientific and clinical topic but current focus remains on autografting rather than xenografting and synthetic scaffolds [141,142].

There are many different bone grafts available on the market. Bone is the second most transplanted tissue after blood. Today, no products based on PANI are currently certified for routine clinical use. Nevertheless, the use of PANI in new generation of synthetic bone scaffolds is progressively taking its way, particularly for the tissue engineering applications, *i.e.* where the

use of scaffolds and stem cells is meant to provide support to restore tissue anatomy and functionality. Indeed, new highlights point towards the use of moderate content of PANI in the conductive nanofibrous scaffolds made from bioresorbable aliphatic polyesters, such as poly(lactic acid) (PLA), which significantly promotes the osteogenic differentiation of bone marrow-derived stem cells [145]. Similarly, osteoinductivity of polyethersulfone-based electrospun scaffolds increased by using PANI [146], showing the same mechanism of action found on PLA-PANI scaffolds.

Another class of emerging resorbable biomaterials is poly-3-hydroxybutyrate (PHB). This material, doped with conductive PANI, has been tested for the preparation of the scaffolds that increase the proliferation of human mesenchymal stem cells [147]. The use of PANI-enhanced structure is, indeed, gaining interest in drug delivery purposes. For instance, very recently, a thin coating of PANI on lignin was developed to carry aminoglycoside gentamicin sulfate (GS) or magnetite nanoparticles loaded with GS which further deposited by the matrix-assisted pulsed laser evaporation (MAPLE) technique on titanium-based biomedical surfaces. The final purpose is to induce the multi-functional characteristics to the implantable device, e.g. the site-specific controlled delivery of the therapeutically active substance under a magnetic and/or electric field.[148]

6.3.3. Nerve regeneration

A great deal of consideration has been dedicated to the repair and regeneration approaches of the neural tissue because it straightly influences the patient's quality of life. There are several conventional and novel developed therapies to repair the damaged nerves. The development of synthetic scaffolds, which are biocompatible,

biodegradable, conductive, immunologically inert, and infection-resistant, is necessary to support the neurite outgrowth [149].

Polyaniline is applied for the preparation of the bioactive scaffolds to be used in the neural repair owing to its high electrical conductivity, good environmental stability and biocompatibility in contact with the particular cell lines containing cardiac myoblasts and rat pheochromocytoma cells (PC12) [128,137]. These scaffolds can electrically stimulate the cells and regulate some particular cellular activities, and therefore, affect the regeneration process of the tissues that respond to the electrical impulses.

A polyaniline/cellulose conductive composite hydrogel with a hierarchical micro/nanostructure was prepared through the interfacial polymerization technique as a scaffold material of neuron for the sciatic nerve regeneration in rats (**Fig. 11A** to **D**) [149]. Due to the hierarchical micro/nanostructure of PANI and its electrical conductivity, the composite promoted considerably the adhesion and guided the extension of neurons, showing its high potentials for the biomedical applications.

Polyaniline/polyethyleneglycol diacrylate (PANI/PEGDA) hybrid hydrogels with a porous architecture were fabricated through *in-situ* precipitation of PANI in the solution of PEGDA, followed by the crosslinking *via* the UV irradiation. The PANI resulted in the improvement of the biological response of the human mesenchymal

stem cells (HMSC) and PC12. It was also shown that the PANI/PEGDA hybrid materials might be utilized to design innovative devices, which are capable of a more efficient responding to an external electric field for the nerve regeneration [150].

In another study, a PANI/silk fibroin nanocomposite was fabricated through electrospinning and rolling of the electrospun sheet [151]. The *in-vitro* and *in-vivo* biocompatibility of PANI, as well as the positive immune response or graft rejection of PANI-silk fibroin nanocomposite over a period of one year revealed the safety of scaffolds based on PANI nanocomposite. It was also shown that the outstanding electrophysiological parameters achieved after one year of implantation of nerve conduit based on PANI. Cellular recruitment and myelin thick lamellar deposition over regenerating axons inspire more *in vivo* investigations by the conductive polymers for developing the electrically conductive nerve conduits.

The progress of a porous scaffold by incorporating the PANI/graphene nanoparticles into a chitosan/gelatin matrix for the nerve regeneration application has also been reported. Accordingly, the electrical and mechanical properties of the PANI scaffold increased, while its porosity and water retention capacity decreased. Furthermore, the cytotoxicity test showed the largest number of attached *Schwann* cells on the scaffold containing 2.5 wt.% PANI/graphene NPs [152].

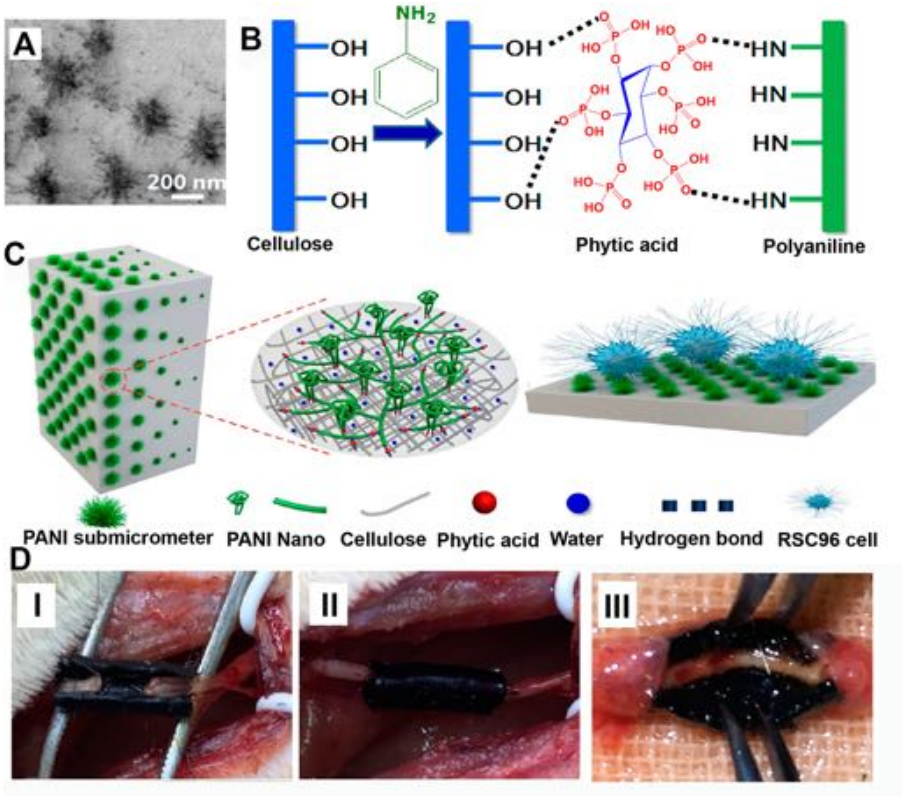

Fig. 11. (A) TEM image of the cross-section of the PANI/cellulose conductive blend. (B) Schematic illustration of the polymerization reaction of polyaniline in the presence of cellulose and phytic acid as the cross-linking agent and dopant. (C) The hierarchical micro-nano-structured polyaniline implanted in the cellulose matrix and the RSC96 cell adhesion. (D) Intraoperative image of the PANI/cellulose composite hydrogels, immediately after cutting (I), after sewing (II), and after 3 months (III). PANI/cellulose obviously speeded the injured nerve regeneration after 3 months. Reprinted from ref [149]. Copyright 2016 American Chemical Society.

6.3.4. Cardiac tissue engineering

Cardiac tissue engineering (CTE) is a developing method designed to repair and regenerate a damaged cardiac tissue by applying cellular transplantation and biomaterial 3D scaffolds[153]. An ideal scaffold for the CTE should be electrically conductive and biocompatible with a similar elasticity to the native myocardium[153]. The electroactive materials including conductive polymers, such as PANI, carbon-based nanoarchitectures, such as CNTs and graphene, and metallic nanostructures, such as Au NPs, have been developed and utilized in CTE[153].

However, chronic inflammation in the implanted tissues was reported for pure PANI. Accordingly, researchers have combined PANI with different safe polymers, e.g. from natural to synthetic ones such as gelatin, PLGA, PCL and, polyurethane, to improve its biocompatibility[134,135,154]. Some researchers have shown cellular interactions with PANI and its blends in CTE. For instance, nanofibrous blends of PANI and gelatin were fabricated by means of co-electrospinning, supported attachment, migration, and proliferation of cardiac myoblasts. In this regard, Hsiao et al. prepared the PANI-PLGA aligned fibers to fabricate a 3D environment for the synchronous beating of cardiomyocytes[135]. The cardiomyocytes formed isolated cell clusters and beat synchronously. The HCl-doped PANI improved the electrical conductivity and cell adhesion along with attracting positively charged proteins of the cell membrane. In order to achieve electrically conductive compounds, a number of studies have been conducted to introduce PANI into various materials. For instance, cardiac patches based on camphorsulfonic acid-doped conductive PANI were fabricated by solvent casting[133]. The patches showed high biocompatibility and led to attachment, elongation, and proliferation of C2C12 myoblasts. Even after 4 days, the scaffolds conductivity was similar to the native myocardium.

Apart from the aforementioned composites and blends of PANI, the PANI containing metal/metal oxides nanostructures and carbon-based nanomaterials can be investigated for future studies. These nanofillers may be sued lonely or in combination with each other. Despite the widespread lab studies of the PANI and its blends, their use in clinical practice is still hampered by safety aspects. In order to get a complete safety profile, it is necessary to conduct clinical trials for the final products before being commercialized.

6.4.Biosensors

Biosensors are analytical devices that connect the biological sensing, such as monosaccharides, cells and nucleic acids, to a detector or transducer. Biomolecules response and then the detector/transducer convert the biochemical reaction as a biological response into a computable signal [155]. Biosensors possess three main components: a bio-recognition element, an immobilization surface such as NPs and conducting polymers, and a detector/transducer unit [156].

Sensors and biosensors have found many clinical applications, such as glucose for diabetic patients, and environmental applications such as monitoring organophosphorus pesticides [157].

The advent and advances in the conducting polymers heralded a novel generation of biosensors. Among all the electrically conducting polymers, PANI is of great interest because of its unique properties, such as easy and reversible doping/dedoping ability, adaptable electrical conductivity, and good stability [158]. Moreover, PANI displays two redox couples which ease the charge transfer between an enzyme and a polymer. Therefore, there is no need to add additional diffusional mediators to the biosensing system for the electron transfer because the PANI performs as a self-contained electron transfer mediator. As a result, the high long-term stability for the biosensor can be achieved because the localization of the mediator to the surface of the sensor avoids the mediator leaching into the media (**Fig. 12A**) [156]. Due to great electrochemical properties and optical detection along with *in vivo* biocompatibility, the PANI based nanocomposites can be used to detect the negligible amount of biomolecules with high sensitivities and fast responses.

Synthesis of different nanoarchitectures of PANI including spherical particles [159], rods [160], wires [161], tubes [162], and fibers [163] leads to performance improvement in sensing. For instance, the PANI nanofibers have higher sensitivity with a faster response as compared to their traditional bulk counterparts, since they contain a larger surface area and have a shorter penetration depths for the target (bio)molecule [86].

6.4.1. Enzyme and cholesterol biosensors

Polyaniline-based nanocomposites have been extensively used for enzymes detections, such as estimating the blood glucose level, which is important in homecare diagnostics [8]. For instance, conducting silica-PANI nanobeads showed a great sensitivity (38.53 $\mu A.mM^{-1}cm^{2}$) with an extensive linear range (from 1 to 16 mM) and a 96.4% glucose response current after 45 days [164]. The TiO_2 NPs/PANI nanocomposites were also employed to achieve a good response with the detection limit of 18 μM and shelf life of 30 days [165]. The NiO NPs/PANI nanowire/graphene oxide nanosheet composites have also been utilized for the glucose detection (376.22 $\mu A\ mM^{-1}\ cm^{-2}$) with a linearity range (2-5.560 mM) in the presence of some interfering compounds, such as dopamine, uric acid and ascorbic acid [166].

A 3D nanostructured hydrogels based on platinum NPs-PANI were also fabricated for the determination of glucose (**Fig. 12B**) [167]. Other types of nanostructures, such as gold NPs [168], carbon nanotubes [169], and copper NPs [170] have been exploited for the detection of the glucose level. Apart from enzyme biosensors, PANI has been applied for the detection of other biomolecules. For instance, the electrodes based on chitosan-grafted polyaniline porous structured cryogel were utilized for the determination of sialic acid as presented in **Fig. 12C** [171].

The development of lipids determinations, such as cholesterol biosensors, is clinically important because of hypertension, arteriosclerosis, and cardiovascular diseases. The detection of the free cholesterol is based on an oxidation reaction catalyzed by the cholesterol oxidase, a water-soluble enzyme [172]. Highly sensitive biosensors based on PANI, such as carbon nanotubes/PANI and PANI fibers, have been utilized for the detection of cholesterol [173,174]. Other biomolecules, such as triglyceride, have also been detected by using PANI-based biosensors [156].

Ascorbic acid (Vitamin C) is an important analyte in the food and beverages industries and medical applications. For instance, it is a vital antioxidant in the brain. Also it is involved in some

diseases such as diabetes mellitus [175,176]. Bartlett *et al.* used microelectrodes coated with PANI-poly(styrene sulfonate) copolymer to catalyze the ascorbate oxidation. They found that the current for the ascorbate oxidation is independent of the thickness of the coated copolymer indicating that the reaction carries out at the outer surface of the copolymer film [177]. However, in many studies, different conducting polymers have shown greater promises (e.g. polypyrrole family for the DNA sensors and poly(3,4-ethylenedioxythiophene) for the detection of small molecular oxidizable analytes such as dopamine, uric acid, and ascorbic acid)[178,179]. Nevertheless, PEDOT showed several restrictions for *in-vivo* applications owing to its low biocompatibility and unfunctionality required to be improved[180].

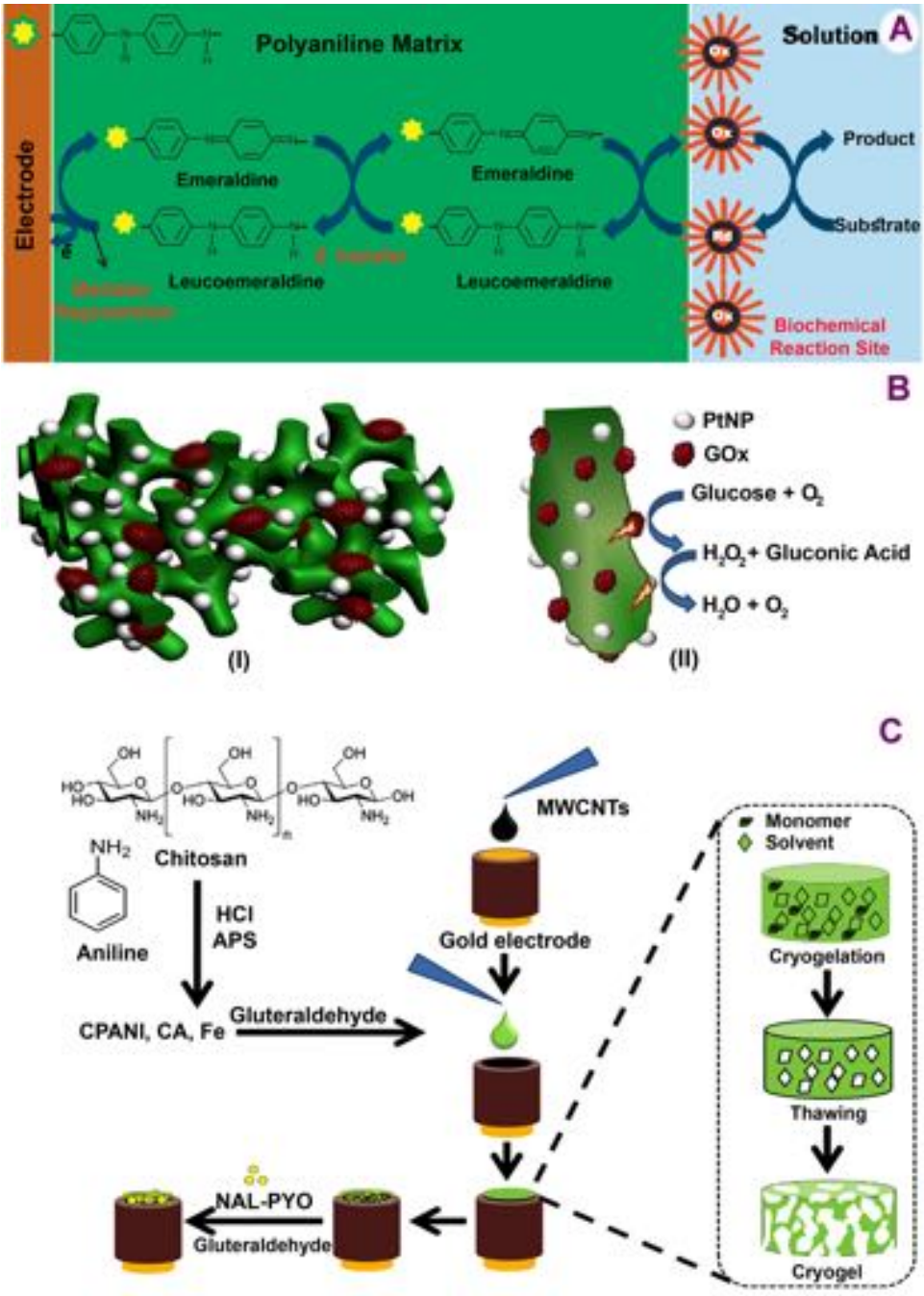

Fig. 12. (A) Schematic image of an amperometric biosensor based on polyaniline network showing electron transfer between the biochemical medium and electrode surface. Reprinted with permission from ref [156]. Copyright Elsevier. (B) Schematic 3D image of the Pt nanoparticles/polyaniline (PtNP/PANI) hydrogel, in which the glucose oxidase (GOx) enzyme and Pt NPs immobilized onto the PANI hydrogel matrix (I) and a 2D scheme of the PtNP/PANI-based glucose biosensor reaction mechanism (II). Reprinted from ref [167]. Copyright American Chemical Society. (C) Preparation of the modified electrode based on the chitosan grafted polyaniline

(CPANI) cryogel for the immobilization of pyruvate oxidase (PYO) and *N*-acetylneuraminic acid aldolase (NAL) enzymes. Reprinted with permission from ref [171]. Copyright Elsevier.

6.4.2. Hydrogen peroxide and phenolic compounds biosensors

The determination of hydrogen peroxide is important in the food industry. PANI, due to its remarkable catalytic activity and selectivity for its substrates, is used to attain the peroxidase-modified electrodes for the preparation of the electrochemical biosensors [8,181]. For example, the glutaraldehyde functionalized-PANI, nanoCu-PANI-Ni foam, and silver–PANI nanotube nanocomposite with good sensitivities have been used for the H_2O_2 detection [182,183].

Phenolic compounds, as toxic materials, are ubiquitous in nature and found in food, environmental and biological samples and, therefore, the detection of such compounds is vital to preserve the quality of the products [8]. Polyphenol oxidase, which contains copper atom(s) in its active center, have been employed for the phenol determination through the catalysis of phenol oxidation [184]. In regards to the types and mechanism of action, the polyphenol oxidases are of three types including tyrosinase, catechol oxidase and laccase [184]. In a study, polyphenol oxidase enzyme was immobilized on the PANI-activated carbon composite for the determination of phenol [185].

6.4.3. Geno- and Immuno-sensors

Genetic material detection has found many applications in medical and forensic science. DNA determination has been used for the disease diagnosis, gene analysis, and fast detection of the biological weapons [156,186]. For instance, the PANI nanotubes-indium tin oxide electrode has been used as the electrochemical genosensor for the ultrasensitive detection of chronic myelogenous leukemia (detection level ~ 1×10^{-16} M) [187]. In another study, the flower-like carbon nanotubes-PANI hybrid has been used for the amperometric detection of DNA with remarkable sensitivity and a wide linear detection in the range from 1 fM to 10 nM [186].

The immunosensors based on PANI are used for the interaction between antigen and antibody, i.e., the lock and key model. The development of nanotechnology has resulted in the precise immobilization of antibodies along with various types and concentration of antigen [8,188]. For instance, the potassium ferricyanide-doped PANI NPs have been used for the preparation of label-free immunosensor to detect the carcinoembryonic antigen with a wide linear range (1.0 pg mL^{-1} to 500.0 ng mL^{-1}) and a low detection limit of 0.1 pg mL^{-1} [189]. In a work conducted by Li et al. [190], a film based on graphene nanosheets-PANI (GNS-PANI) was prepared for the synthesis of thionine/GNS-PANI/Au NPs. This immunosensor was applied for the detection of kanamycin with the detection limit of 8.6×10^{-9} M. Other immunosensors based on graphene/PANI/Au nanocomposites were also used to detect tuberculosis [191]. Table 3 represents a summary of PANI and its nanocomposite based biosensors.

Table 3. Summary of PANI and its nanocomposite-based biosensors.

Nanostructure	Analyte	Detection Limit	Sensitivity ($\mu A\ mM^{-1}\ cm^{-2}$)	Linear range	References
PANI-poly(ethylene oxide)	Glucose	0.82 mM	16.04	1 to 10 mM	[192]
PANI/tinoxide/reduced graphene oxide	Glucose	0.047 ng mL^{-1}	N.R*	0.1 ng mL^{-1} to 5 g mL^{-1}	[193]
Ni-PANI-reduced graphene oxide	Glucose	0.08 µM	6.050	0.1 µM to 1.0 mM	[194]
Graphene-PANI	Glucose	2.769 µM	22.1	10.0 µM to 1.48 mM	[195]
TiO_2/PANI-graphene oxide	Glucose	18 µM	6.31	0.02 mM to 6.0 mM	[165]
Pt NPs/PANI	Glucose	0.7 µM.	96.1	0.01 to 8 mM	[167]
Multi-walled carbon nanotubes–PANI/Pt	Cholesterol	0.8 µM	109.9	2.0–510.0 µM	[172]
PANI/multi-walled carbon nanotubes /starch	Cholesterol	0.01 mM	800	0.032 to 5 mM	[173]
Mesoporous PANI nanofiber decorated graphene	Cholesterol	1.93 mg dl^{-1}	0.101 μA mg^{-1} dl cm^{-2}	1.93 to 464.04 mg dl^{-1}	[174]
PANI/crystalline nanocellulose/ionic liquid modified Screen-Printed Electrode	Cholesterol	0.48 µM	1 to 12 mM	35.19 µA mM/cm^{-2}	[196]
PANI/single-walled carbon nanotubes	Triglyceride	N.R.	4.28×10^{-4} mA mg^{-1} dL	50 to 400 mg dL^{-1}	[197]
PANI/catalase/glutaraldehyde	Hydrogen peroxide	2.18×10^{-6} M	N.R.	5.0×10^{-6} to 1.0×10^{-4} M	[183]
Silver/PANI nanotube	Hydrogen peroxide	0.2 µM	N.R.	0.1 to 90 mM	[182]

PANI nanotubes	Hydrogen peroxide	3.56×10^{-10} mg/mL	N.R.	1.0×10^{-9} to 0.10 mg/mL	[198]
Gold NPs doped poly(8-anilino-1-naphthalene sulphonic acid)	Tyramine (a phenolic compound)	0.71 µM	N.R.	10 to 120 µM	[199]
Carbon nanotubes-PANI nanohybrid	DNA	0.33 fM	N.R.	1 fM to 10 nM	[186]
Gold NPs/PANI	DNA	0.01 fM	N.R.	0.001 to 1000 pM	[200]
Gold electrode modified with Au and PANI NPs	DNA	2.5×10^{-10} M	N.R	$10^{-9}$to 1×10^{-6} M	[201]
PANI nanotubes	Nucleic acid	10^{-16} M	1×10^{-16} M	10^{-6} to 10^{-16} M	[187]
Potassium ferricyanide-doped PANI NPs	Carcinoem-bryonic antigen	0.1 pg mL^{-1}	N.R.	1.0 pg mL^{-1} to 500.0 ng mL^{-1}	[189]
Graphene/PANI-Modified Screen-Printed Au electrode	Tuberculosis	15 ng/mL	N.R.	20 to 100 ng/mL	[191]
PANI/Au NPs	Acrylamide	5.0×10^{-11}M	N.R.	5.0×10-10 M to 2.0×10-7 M	[202]
Polyamidoamine grafted multiwalled carbon nanotube	Urea	0.4 mM	6.6 nA/mM	1 to 20 mM	[203]
PANI-cladding modified fiber	Urea	100 nM	N.R	100 nM to 100 mM	[204]
PANI-encapsulated carbon/Cu composite nanofibers	Polyphenol	0.24 µM	41.65 µA mM^{-1}	500 nM to 110 µM	[205]
Poly(carboxybetaine) functionalized PANI nanowires	Carcinoembryonic antigen	3.05 fg mL^{-1}	N.R.	1.0×10^{-14} to 1.0×10^{-10} g mL^{-1}	[206]

Peptide nanotube-Au nanoparticles-PANI immobilized pencil graphite electrode	Prostate specific antigen	0.68 ng/mL	N.R.	1 to 100 ng/mL	[207]
Glassy carbon electrode/PANI-ZnO NPs	Dopamine	0.153×10^{-7} M	0.089 μA/μM	0.2 to 2.4 μM	[208]
Glassy carbon electrode/PANI-Fe_3O_4 NPs	Dopamine	0.176×10^{-7} M	0.058 μA/μM	0.2 to 2.4 μM	[208]
Glassy carbon electrode/PANI-NiO NPs	Dopamine	0.166×10^{-7} M	0.078 μA/μM	0.2 to 2.4 μM	[208]
Molybdenum disulfide nanosheets-PANI/Au NPs	Dopamine	1×10^{-6} M	0.0274 μA/μM	1 to 500 μM	[209]
Graphene nanosheets/Pt/PANI	Dopamine	3.33×10^{-6} M	1.53 and 0.35 μA/μM	2.0 to 10 and 40 to 400	[210]
Nitrogen-doped functionalized graphene/Ag NPs/PANI	Ascorbic acid (vitamin C)	8 μM	N.R	10 to 11.460 μM	[211]
Indium tin oxide coated glass substrate/manganese phthalocyanine/PANI	Fenitrothion (a pesticide)	0.049 μmol dm^{-3}	4.67 $Acm^{-2}M^{-1}$	0.12 to 15.00 μmol dm^{-3}	[212]

*N.R.: Not reported

7. Conclusion and perspectives

This review presents a comprehensive overview of polyaniline and its nanocomposites, underlining advantages and properties, from structure, synthesis, physicochemical properties, to their potential in a wide spectrum of biomedical applications. Conductive polyaniline-based nanocomposites surely represent a new and promising, but not yet completely explored, area of biomaterial science where promising results and unresolved technology challenges both call for opportunities of deeper studies and developed researches. Polyanilines are, indeed, gaining a continuously increasing interest from the scientific community. However, it should be mentioned from an industrial perspective that some of these challenges have also important drawbacks on regulatory and quality assurance issues: this widely explains the relatively low amount of clinical data related to the use of PANI.

There are some major limitations such as cytotoxicity, processability, significant difference of *in-vivo* and *in-vitro* studies, and physicochemical properties on the applications of PANI and its nanocomposites into clinical practice. However, the low physical properties and biocompatibility of PANI is the main challenge in the tissue engineering applications, especially those that are aimed to be employed inside of the human body, e.g. for the bone regeneration. This issue has been moderately solved with the fabrication of PANI composites containing nanostructures, including Ag and TiO_2, and/or biodegradable synthetic polymers, such as PCL, PLGA and PLA which improves their mechanical properties and integration into the biological tissues. Besides, non-biodegradability of the pure PANI scaffolds still restricts their applications in the tissue regeneration. Thus, a great consideration has been focused on the development of the degradable PANI blends and composites with bio-based polymers.

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Abbreviation used

APS, Ammonium persulfate; CNTs, Carbon nano-tubes; CTE, Cardiac tissue engineering; CS-*g*-AT, Chitosan-*graft*-aniline tetramer; DMF, Dimethyl formamide; DMSO, Dimethyl sulfoxide; DPPH, 1,1-diphenyl-2-picrylhydrazyl; EC50, Half maximal effective concentration; EM, Emeraldine; EM-B, Emeraldine-base; EM-S, Emeraldine-salt; ER, Electrorheological; GNS, Graphene nanosheets; GS, Gentamicin sulfate; HaCaT, Human keratinocyte; HEK, Human embryonic kidney, HMSC, Human mesenchymal stem cells; ICPs, Inherently conducting polymers; KPS, Potassium persulfate; LE, Leucoemeraldine; MAA, Methacrylic acid; MAPLE, Matrix-assisted pulsed laser evaporation; MMP, Mitochondrial membrane potential; MPP, Modified polypropylene; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NIH/3T3, Mouse embryonic fibroblast; NIR, Near-infrared; NMP, *N*-methyl-2-pyrrolidone; ND, Nanodiamond; NPs, Nanoparticles; PANI, Polyaniline; P3ABA, Poly(3-aminobenzoic acid); Pas, Polyacetylene; PC12, Pheochromocytoma cells; PCL, Polycaprolactone; PEGDA, Polyethyleneglycol diacrylate; PEG-DA, Dibenzaldehyde-terminated poly(ethylene glycol); PEO, Poly (ethylene oxide); PHB, Poly-3-hydroxybutyrate; PFu, Polyfuran; PG, Pernigraniline; PLA, Poly(lactic acid); PLGA, Poly(lactic-*co*-glycolic acid); PNIPAm, Poly(*N*-isopropylacrylamide); PPy, Polypyrrole; PSiNPs, Porous silicon nanoparticles; PTh, Polythiophene; *p*TSA, Para-toluene sulfonic acid; PUF, Polyurethane foam; PXT, Polyxanthonetriazole; rGO, Reduced graphene oxide; ROS, Reactive oxygen species; RRS, Reactive radical species; ROS, reactive oxygen species; SDDS, Smart drug delivery systems; STPU, Siloxane terminated polyurethane; THF, Tetrahydrofuran; UA, Usnic acid;

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