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An Overview of Polyaniline in Tissue Engineering

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Abstract

Electrical response in tissue regeneration has been demonstrate, so growing use of conductive polymers as a main component of scaffolds have developed. Advantages of Polyaniline outweigh other conductive polymers, these including, cost-effective, easy to fabrication, more biocompatible than others, etc. On other hand, cell signaling has been proved as dynamic biochemical that could be promoted cell behaviors such as adhesion, proliferation, and differentiation. In addition, oligoaniline has been emerged to solve some limitation of polyaniline such as biodegradability and biocompatibility problems. Recent researches have been shown that all cells such as cardiac, neural, muscle, bone and fibroblast cells respond to electrical stimulation and to enhance their functions. Bio-mimicking scaffolds is a key role in tissue engineering to achieve a target goal. Hence, the use of polyaniline/oligoaniline has increased. In this review, we investigated properties of polyaniline/oligoaniline and its applications in a variety of tissue engineering.

Keyword: Polyaniline, Oligoaniline, Tissue engineering applications, Regenerative medicine

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1. Introduction

Tissue engineering for regeneration requires the three main elements, cell and extracellular matrix and growth factor[1]. The extracellular matrix (ECM) must be chemically, physically, mechanically, and electrically similar to the target tissue.

All cells communicate with each other through electrical signals, but the intensity of these signals varies in different tissue types [2]. Several cells types respond to electrical signals such as cardiomyocytes[3], neurons[4,5], osteoblasts[6], muscle[7,8]. Bassett et al.[9] in the 1960s showed the positive effects of electrical stimuli on tissue regeneration of dog's bone. Another report is about the increase in DNA synthesis of mouse osteoblast cells consequence of electric field stimulation [10]. Other studies have shown that electrical currents affect the migration behavior of keratinocytes, vascular endothelial cells, and corneal epithelial cells [11,12]. Recently, due to the effect of electric current on cellular behavior, the electrical property is used either to mimic the scaffold such as a cardiac, neuron, and skeletal scaffold or treat clinical diseases such as Parkinson's or headaches and arthritis [13].

Some time for reaching conductive scaffold are used from other conductive elements such as carbon nanotube and gold that these make scaffold possible for the transmission electrical signal when external electrical source applied, on other hands these conductive particles are non-biodegradable in implants and other their drawback are inhomogenous in composites, as result current electricity does not spread throughout the scaffold [14]. Finally, to overcome these issues, conductive polymers were known. Conductive polymers (CPs) can conduct electricity in a biological environment without an external electrical source. They can be distributed homogenously in scaffold and be able to dissolve in an organic solvent so be able to copolymer with other polymers before processing and spread efficient electricity throughout composite [14]. There are several types of CPs such as polypyrrole (PPy), polyaniline (PANI), and polyacetylene (PAC). Each of these polymers contains special electrical conduction systems, including aromatic units and/or alternating single and double bonds in the polymer chain.

Among the conductive polymers, interest in polyaniline in industrial and medical applications is increasing today, specifically in tissue engineering and regenerative medicine, biomaterial applications (Fig1). Thus, the growing development of polyaniline in the tissue engineering field has led to this present review article which discusses different aspects of PANI such as its properties that make it one of the attractive biomaterial components, its synthesis methods that make it easy to process, and its applications in tissue engineering that is growing.

2. Polyaniline

Polyaniline is most popular among conductive polymers due to its unique properties, including biocompatibility [14,15], thermal [16] and optical and electrical conductivity [17], antibacterial [18], easy to synthesis, ion-exchangeable [19], low cost, having nitrogen bonds on either side of phenylene ring makes it highly reactive [20], variable monomer oxidation state [17]. The intensity of the electrical properties of polyaniline depends on the monomer oxidation state and the degree of protonation of the polymer during polymerization [17]. So it is categorized as three-state structures with different properties: emeraldine, pernigraniline base, and leucoemeraldine base. Among them, emeraldine is known as a highly electroconductive which half oxidation state and this structure has two forms that are called salt emeraldine and base emeraldine [17](Fig2). Other types of polyaniline are classed a complete oxidation and a complete reduction that are called pernigraniline base and leucoemeraldine base, respectively. Many methods of synthesis exist and electrochemical or chemical methods are generally common methods for synthesizing polyaniline [14]. PANI has poor mechanical, very poor solubility in common solvents, poor cell adhesion, poor cell growth on unmodified polymer, non-biodegradable [21], low processability [22], and lack of flexibility [23]. Although PANI is one of the attractive conductive polymers [24]. Therefore, in most studies polyaniline is found to be composite or/and blend with other polymers, especially with natural polymers.

2.1. Conductivity

As mentioned in the preceding section, all kinds of polyaniline structures don't support electrical properties, due to oxidation state (Fig2). Emeraldine base is not inherently conductive unless it makes conductive via doping and convert to emeraldine salt. This doping could be included either p-doping (oxidation) or n-doping (reduction). According to degree doping and oxidation, crystallizing or amorphous structure, and chain length [25], proton ions can be move-in along and between PANI's branches. Consequently, an electric current is generated. Sometimes Acidic solutions are used as donor protons to structure such as hydrochloric, sulfonic acids [14]. If polyaniline is in a medium containing electrolyte ions, it is possible to switch the polyaniline property. In other words, the structure of polyaniline is involved in the protonation and de-protonation so these properties are interestingly used for artificial muscle tissue [17]. The environment of the body is humid, so it is very important that the polymers used to maintain their electrical properties in this environment, such as polyaniline and oligoaniline [19]. Electrical properties are effects on cells, in an experience polyaniline-co-poly ε-caprolactone nanofibers were aligned by electrospun then it was found that these nanofibers compared to random polycaprolactone could provide to orientate myoblast cells [26]. In addition, PANI and its copolymers can improve cell responding, including adhesion, spreading, and differentiation [27]. All in all, there are many factors to control the degree of conductivity of polyaniline that this unique property has made the polymer highly attractive for scientists in tissue engineering and used in a scaffolding of different tissues.

2.2. Processability

Different applications require the production of special structures such as fibers, films, and so on. In addition to structures, there are various techniques for producing these structures. A thin film of PANI has been produced by applying different methods such as casting, self-assembly, inkjet printing, electrospinning, etc [22]. PANI is able to polymerize in situ. It is noticeable that pure CPs are difficult to electrospinning because of high charge density and rigidity, usually, CPs are blended with natural polymers or/and biodegradable polymers such as PLLA(L.polylactice acid), PLGA(poly lactic-co-glycolic), PCL(polyε-caprolactone), chitosan, and silk. The advancement of blending is an improvement of solubility and ease of electrospinning [28]. With the advancement of tissue engineering and the growing applications of 3D printing[29], it is necessary that polyaniline also can prepare by 3D printing. Thank to technology that polyaniline can also be produced via 3D printing [30]. In addition, some applications of tissue engineering require that the conductive material be deposited on the required surfaces. In 2004, Dong et al. [31] deposited a thin layer of polyaniline on PMMA fibers. But the challenge of preparing polyaniline for the production process is because of its weakness in being unsolvable in most solvents and water so to solve this problem, emeraldine base, for example, dissolves in a common solvent such as chloroform, the advantage of using this solvent is that emeraldine base is led to emeraldine salt with good conductivity, and development of PANI structure to fibers, nanotubes, and nanowires [14]. Zhang et al. [32] in 2017 has prepared an electroactive scaffold based on silk fibroin copolymer with poly(aniline-co-N-(4-Sulfophenyl) aniline via green method without any organic solvent. This is water soluble, conductive, good mechanical, biocompatible, and good cell responding. Similarly, Marjina et al. combined aniline with aminobenzoic acids (ABAs) gives copolymers that are the ability to soluble in polar aqueous and some solvents such as dimethylsulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP) [18]. One challenge of fabrication of PANI has remained that poor solubility of PANI in most common solvents and brittle structure of PANI because of rigid π-conjugated bonds, makes it difficult to process into 3D geometry and complex structure [22].

2.3. Biocompatibility

Biocompatibility is one of the important factors for a biomaterial for ensuring that these can be applied in both in vitro and in vivo without any side effects and undesirable inflammatory response. The first serious

use of polyaniline film in the year 2000 was performed as a subcutaneous biomaterial implant in the male rabbit abdomen. This implant remained successful for up to 90 weeks without any signs of toxicity [33]. It has been shown pure PANI has cytocompatible with H9c2 cardiac myoblast [34], and PC-12 cell [35], cytocompatible of a composite of PANI has shown to be with NIH-3T3 fibroblasts [15], L929 fibroblasts [36], human mesenchymal stromal cell[37], neural stem cell [38], and porcine skeletal muscle cells [39], among others. Although some biocompatible of PANI has been investigated in vitro and in vivo, Wang et al. studied PANI that was observed some inflammation and fibrous tissue encapsulation in vivo [40]. PANI is known as a non-biodegradable polymer and with a small amount of potential inflammation in the long term [14].

Generally, it is increasing to use of oligoaniline or copolymer/functionalized polyaniline with other biocompatible polymers such as PCL, PLA, and gelatin or immobilizing cell adhesive peptides like RGD, RYSGI, and YIGSR. Biodegradable and biocompatible/soluble polymers could be provided increasingly either solubility byproducts of PANI for renal clearance or be taken by macrophages so oligoanilines or aniline monomers will not exist in local, consequence, avoid any inflammation and side effects of long-term use [16]. Cell adhesive peptides improve cell adhesion or/and proliferation even without growth factors, for example, PANI modified by RYSGI and YIGSR were observed high biocompatible and cell adhesion while unmodified PANI did not [14].

In addition, it is noticeable that doped acid in PANI leaches out from the PANI backbone through a local environment that causes acute toxicity around scaffold-based polyaniline. base Applications of PANI are limited by its drawbacks that could be causing chronic inflammation one implanted in a long time [23]. But on the other hand, it is important to note that other factors can also be effective in biocompatibility, such as the concentration of conductive polymers [41,42]. For example, The threshold concentration of polyaniline, which causes the toxicity of a human keratinocyte and a mouse embryonic fibroblast cell line, has been estimated to be about 150 $\mu g/ml$ [28,41]. H9c2 cardiac myoblast was seeded on a surface of PANI film, although all seeded cells attached on a scaffold, they had slowly rate proliferation that this was a possibility of the result of leaky dopant acids. There is still an open question that what amount of dopant acid is used to make conductivity while there is no side effect on both cell response and inhibition of biocompatibility. Cell viability also depends on the structural type of scaffold, Renata et al. , for example, demonstrated that polyglycerol dendrimers grafted PANI nanotubes (PLGD-PANINT) electrospun fibers present to promote extremely cell adhesion, the proliferation of cardiac cell than PLGD-PANINT casting film [43]. All in all, some of the minor cytotoxicity seen in research that can affect their cell viability and growth. However, biocompatibility can be increased by copolymerizing with other natural/biocompatible polymers or using oligoaniline and immobilizing the peptides onto the backbone of polyaniline.

2.4. Biodegradability

Biodegradability of a scaffold in tissue engineering is a principle to aid tissue remodeling. On the other hand, all the oxidation states of polyaniline are not biodegradable and the researchers combine them with biodegradable, biodegradable polymers to overcome this problem. For example, the combination of polyaniline with biocompatible and biodegradable polymers such as polylactic acid, PEGylation, chitosan graft-polyaniline/oxidized Dextran, and others [44,45]. Oligoaniline means a short chain of aniline (trimer, pentamer) significantly increases biodegradation rate and biocompatibility of copolymer. In fact, oligoaniline is an excellent candidate for promoting biological degradation by macrophage or renal clearance by the kidney [46]. Aniline pentamer was cross-linked to chitosan, improving some characters including its water solubility and enzymatic degradation, electroactivity. Zhang et al. [47] grafted polyaniline pentamer and glycine ethyl in polyphosphazene as perform to conductivity and biodegradability, respectively. Liu et al. [48] synthesized a hydrogel-based pentamer aniline grafted onto gelatin backbone showed that it was lost its mass between 45 and 65% within 28 days.

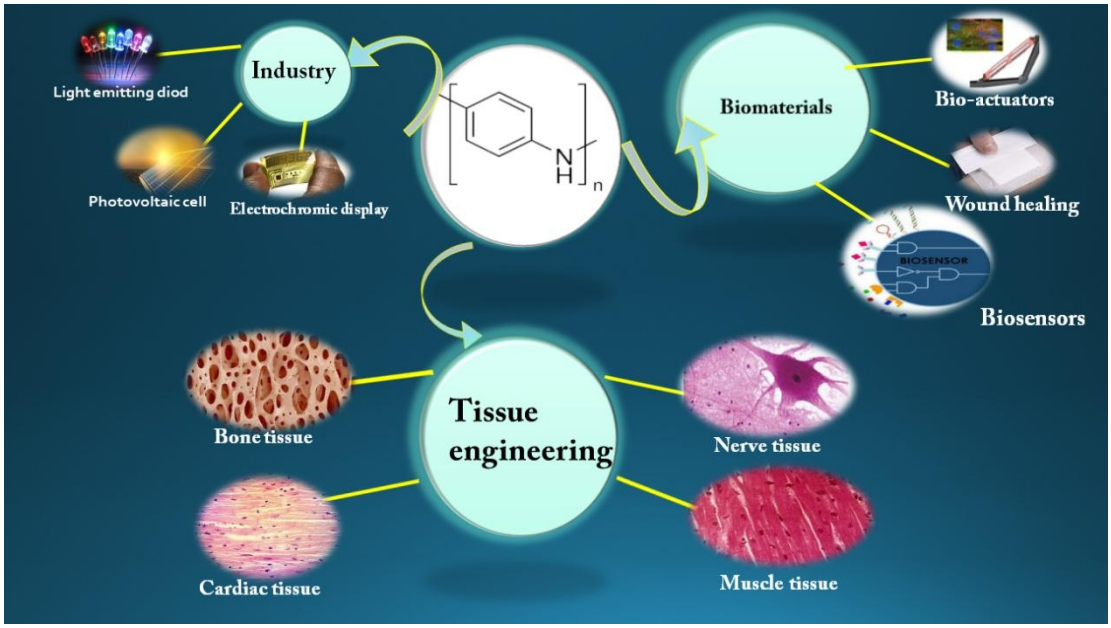

Figure 1: Polyaniline and its applications in different fields

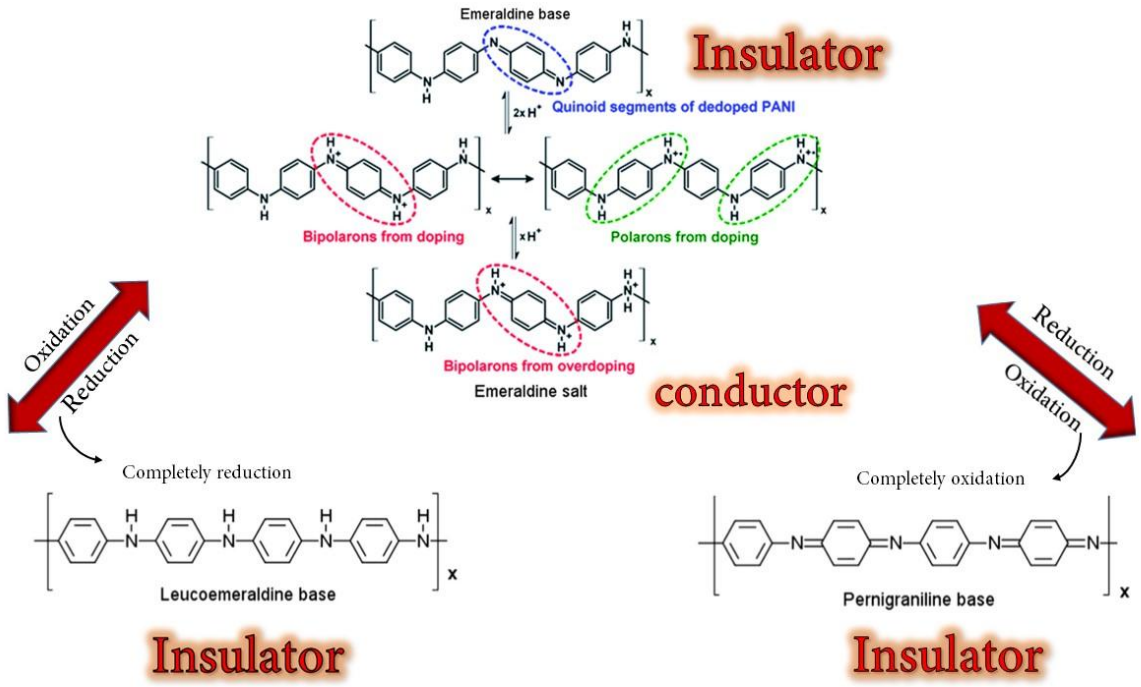

Figure 2: Oxidation states of PANI and various conductivity states of PANI

Cui et al. [49] grafted tetraaniline with polyester amide, put it in Tri-HCl buffer solution with proteinase K, it degraded within 6 days and loss of their mass went down from 42% to 25% with increasing tetraaniline components. In another study, polyaniline pentamer was prepared to block copolymer ABA polymer with polylactic in two ends of it, which encourages to degradate [50]. similarly, to increase the degradation rate for 200 hours, loss of 60% mass, aniline pentamer was combined with polylactic acid and AB block [51]. Baheiraei et al. [52] synthesized novel biodegradable electroactive polyurethane containing aniline pentamer (AP-PU) for cardiac tissue and it was tested in PBS solution with pH 7.4 and pH 5.5 for 4 and 6 months. It was observed that the weight of film was lost in pH 7.4 and pH5.5 for 4 months and 6 months, respectively. Properties of degradable rate and conductivity are controlled by optimizing the right ratio of two/more used polymers.

2.5. Antibacterial efficacy

The main challenge for tissue engineering scaffolds and biomaterials is that cell-scaffold interactions such as adhesion and proliferation and even cell viability are also inhibited by simultaneously bacterial colonization on scaffold then prevents their performance**.** Antibacterial scaffolds have been developed for cardiac, bone, cartilage, ligament, skin, nerve, and vascular tissues. Some articles use silver nanoparticles or some biomaterials such as chitosan to create antibacterial properties in scaffolds (42,50). The presence of polyaniline in the structure of a polymer can have antibacterial properties especially against *E.coli, S.aureus* [14,18,45]. There is a possible way that the mechanism of bacterial killing by polyaniline is that: Doped acidic ions during synthesis, release in the environment via electrostatic interaction protons and bacteria, it breaks down the cell wall and ultimately kills bacteria [45]. The antibacterial property of a film which was made of PANI-polyvinylalcohol (PVA) was tested against E.coli and, S.aureus that has found all bacteria killed, unlike polyvinyl alcohol which is not capable of killing bacteria. On study quaternized chitosan graft-polyaniline/oxidized dextran as an injectable hydrogel that its antibacterial properties are exacerbated by chitosan and polyaniline [45]. Some polyaniline is combined with silver nanoparticles that have a greater effect on the antibacterial properties against E. coli and S.aureus [54,55]. Prepared films based-polyaniline base and salt with Ag deposition were tested. PANI salt with Ag showed a significant effect on E.coli and S.aureus while PANI base-Ag film can be improved antibacterial properties depending on silver concertation to inhibit S.aureus except for E.coli [56]. Functionalized polyaniline with aminobenzoic acid (PANI-ABA) presents bacteria inhibition against bacteria such as E.coli, S.aureus, and P.aeruginosa [57]. In another study, PANI copolymerized with poly3-aminobenzoic acid (P3ABA) provided the best substrate for fibroblasts and wound healing application, and it can be a suitable novel antimicrobial agent against E.coli and S.aureus [58]. As consequence, modified PANI with other antibacterial polymer and Ag shows more effectiveness than pure PANI.

3. Applications of PANI in tissue engineering

3.1. Skin tissue engineering

Cellular activities including cell adhesion, cell proliferation, migration and proliferation can be promoted by cell-cell interaction then cell-cell signaling is facilitated by conductive scaffold base. The electrical stimulation of the skin cells is evaluated from 2.6 mS/cm to 1×10^{-4} mS/cm [59].

A foam was synthesized by Usnic acid-loaded polyaniline/polyurethane to improve the new wound dressing system as antibacterial/antibiofilm against Escherichia coli(E.coli) and Staphylococcus aureus(S.aureus), Using acid and polyaniline perform as antibacterial agents to strengthen the antibacterial properties [60]. similarly, the Composition of PANI /chitosan electrospun nanofibers leads to cytocompatibility of human dermal fibroblast cells and human osteoblast cells with a ratio of 3:5 PANI/CS are known as a potential wound dressing. Another composition is PANI-co-PLA-co-COS(chitosan oligosaccharide)-co-PABSA (poly o-aminobenzenesulfonic acid), which is available in the market and compared to the control sample, it reduces the wound area [55].

Scaffold tissue engineering and wound dressing-based hydrogel are widely used in biomedical applications. Jin Qu et al. [61] synthesized an injectable hydrogel as wound dressing by mixing N-carboxyethyl chitosan (CEC) and oxidized hyaluronic acid-graft-aniline tetramer (OHA-AT). This hydrogel can be injectable, antioxidant, antibacterial, suitable gelation time, and electroactive. Zhao et al. [55] prepared a quaternized chitosan grafted polyaniline and functionalized PEG-co-poly glycerol sebacate hydrogel with benzaldehyde and the result indicated that Hydrogel containing PANI improved closing wound area compared to control sample which available in the market. Hydrogel based PANI is capable to store and release various growth factors such as VEGF (vascular endothelial growth factors), and EGF (epidermal growth factor) which all promote healing.

However, the extent of the use of polyaniline in wound healing and its effect on wound healing has received much attention, the importance of its use has also been of great interest in tissue engineering. In this section of the review article, we have examined samples of scaffolds containing polyaniline in the skin. In one study, electrospun nanofibers of PANI/chitin were created randomly and aligned. It was tested on dermal cells and it was found that cell growth and cell viability support better in aligned structure than randomly [55]. Gh et al. [62] reported PANI and polypyrrole (PPy)-coated silk fibroin which has good mechanical and bioresorbable and conductive characters and skin keratinocyte cells were tested and both polymers were found to enhance cellular growth and proliferation based on their electrical properties. Jeong et al. [63] fabricated camphor sulfonic acid (CPSA) doped PANI composited with poly L lactic acid-co-ε-caprolactone (PLCL), CPSA and PLCL are responsible for elastic/bioresorbable, electroacticity respectively. Overall, researchers believe that future use of these skin scaffolds research will pay more attention.

3.2. Cardiac tissue engineering

The heart muscle is an electrically active tissue that is capable of moving and transmitting an electrical message and allows the heart to beat. Heart disease, the leading cause of death in the world, is often associated with an irregular heartbeat and electrical heart failure. Recently, heart tissue engineering as a treatment for patients with heart failure has gained a lot of attention. Cardiac tissue engineering is a therapeutic approach that aims to mimic heart tissue and build new tissue to repair, replace or improve the function of the damaged tissue. Creating an integrated electric current throughout of heart is essential for maintaining it healthy. Scientists usually use gold particles, and carbon nanotubes in scaffolds to make electrical stimulants, but among the new methods of treating heart failure and improving electrical integrity, tissue engineering using conductive polymers has received much attention.

Fernandes et al. synthesized PANI nanotube modified with dendrimer poly (L lysin) in two ways: electrospun and film casting. Cardiomyocyte rat cells were cultured on them then voltage range (10-40 v), Frequency 5 Hz, and 5 ms were applied. After 70 hours and 40v, the maximum cell viability of cardiac cells on cast film and electrospun nanofibers were 30% and 75%, respectively in the same condition [64]. Similarly, dendronized polyaniline nanotubes were fabricated by electrospun enhanced cell viability and cell attachments of cardia cell than cast film [43]. This could be because of electrospun aligned fibers. In another study, coaxial and uniaxial electrospinning have been used to spin fibers in core-shell and simple fibers, respectively [19]. A uniaxial mixture of PLA-co-PANI 5% fibers and shell/core of PLA/PANI-co-PAL were synthesized. Cytotoxicity assay was tested and found that biocompatibility and cell viability of coaxial fibers are more than uniaxial in initial hours. This fact is due to that PANI was captured in the core by shell and doesn't allow to release in the environment. Both samples contained cardiac cells in the incubator and observed that the heart cells had a beat and contraction over 1 hour to 13 days and both structures could be used in cardiac tissue engineering. Whereas, in another sample of this experience, a shell containing PLA/PEG and a core containing PLA/PANI were created. Due to the presence of PEG in the shell, the structure is porous and the polyaniline is removed from the structure and the biocompatibility is reduced [19]. Hu et al. prepared a

Table 1: Different scaffold of cardiac tissue based PANI

Composite	Cell type	Definition	Ref
Nanofibers of PANI/gelatin	H9c2 rat	Because of the high ratio of surface to volume, there is promising cell attachment and proliferation compared to TCP over 6 days. Modular tensile strength and elastic increase from 5.77 to 10.49MPa and from 499 to 1384MPa respectively, with increasing PANI content.	[16]
Aligned nanofibrous meshes of PANI/PLGA	Neonatal rat cardiomyocytes	Electrostatic interaction between negative proteins and positive polymer lead to promote seeding and attachments, Simultaneous secretion of connexin43 protein.	[65]
PANI nanotube modified dendrimer PEG	Chinese hamester ovary cells	PANI nanotube is hydrophobic and dendrimer of PEG causes it to become hydrophilic, Stimulates cardiac cell differentiation without toxicity and this scaffold has the potential for cardiac cell culture.	[43]
Electrospun nanofibrous of PANI/PLGA	Cardiac cells	Used solvents is acetone and chloroform, range of fiber diameter is 2000-4000nm, biocompatible and biodegradable, conductive, suitable mechanic property, approved by FDA.	[66]
Electrospun fibers PVA/ gelatin grafted to oligoaniline (1:10, PVA:GelOA)	Human mesenchymal stem cells	Fiber diameter (150-300nm), biocompatible, Better growth and proliferation of hMSC in the conductive scaffold than non-conductive one, slow release rate of anti-inflammatory drug of dexamethasone (DX), Increase in DX release rate by 30% in 40min with applying stimulation than passive one.	[67]
Polyurerthane-co-aniline pentamer coated PCL	Neonatal cardiomyocytes	Nontoxicity, Biocompatibility and stability of PCL coated PU-PANI in wet environment than PU-PANI , electrical conductivity 10^{-5} s/cm (in order of electrical conductivity of native heart tissue 10^{-4} s/cm), compression and strength modulus of 4.1 and 1.3Mpa, respectively.	[68]
Electrospun nanofibers Camphorsulfonic acid doped PANI(C-PANI)/gelatin	H9c2 rat	Increasing PANI content causes to reduces fiber diameter under100nm, Biocompatible, proliferation.	[21]

film with properties such as micropatterned surface, electroactivity, and elastic and anisotropy for bio-mimicking native heart tissue [69]. Biocompatible and biodegradable copolymers such as aniline trimer (AT) and polyglycerol sebacate (PGS) were provided. H9c2 rat heart cells were used, and all concertation of AT (5 wt%, 10 wt%) have been shown good viability and proliferation but 10 wt% of concertation AT enhanced cell to cell signaling, maturation, and synchronous Ca^{+2} transition of neonatal rat cardiac cells. The presence of micropattern on film surface leads to promote cell alignment of primary cardiomyocyte of rat and amount of Ca^{+2} intercellular [69]. So, in addition to the type and concentration of biomaterials used, the type of structure and production technique must also be considered.

Another study reported that copolymerized PANI short fibers and PCL to form foam for cardiac tissue regeneration. Scientists asserted that the presence of PANI short fibers throughout composite scaffold causes electrical conductivity in the structure. Human mesenchymal stem cells (hMSC) were cultured on two samples and the observed viability of composite is more than PCL. The cells were differentiated over the period of 3 days and the cell growth on these patches was 40% in the first days but increased to 100% in 5 days [37]. Other studies on heart cells based on polyaniline scaffolds are reported in (Table1).

3.3. Nerve tissue engineering

Due to the lack of replacement of lost neurons, so the repair of the nervous system is complex. According to the report of the World Health Organization (WHO), the number of neurological disorders will increase 6.77% by 2030. Researchers have been persuaded by extensive studies in the field, such as cell therapy and tissue engineering, to new approaches to nerve regeneration. Most other biomaterials are implanted in the form of scaffolds to improve nerve regeneration and to compensate for damage to both the central nervous system (CNS) and the peripheral nervous system (PNS). With the emersion of conductive polymers such as polyaniline and polypyrrole, the process of healing and regeneration of damaged nerve tissue even without growth factor delivery is accelerated.

In a recent study, Shrestha et al. [70] coated PANI on titanium nanotube (TNT) via the electrochemical method for implant device for regeneration in cell nerve growth. PANI-titanium nanotube showed antibacterial activity and corrosion resistivity because of the presence of PANI. PC12 and S42 cells were cultured on PANI-TNT scaffold, then found that cell activity improved such as proliferation and differentiation to approach neuronal cells functions means axonal growth and migrate to the peripheral nervous system (PNS). It has been also observed that scaffold-based PANI-TNT accelerated regeneration and differentiation of PC12 cells to neuronal.

In another study, Haghbin et al. [71] synthesized a conductive scaffold containing polycaprolactone (PCL) and polyaniline (PANI), and a urethane group for neural tissue engineering. PC12 cells were tested as assay biocompatible and interaction cell-scaffold. To achieve the essential properties for the nerve scaffold, the optimal value is suggested as follows: UPCL/PCL/PANI45:20:35, PANI, and Urethane are responsive to carry conductive activity and controlled degradable rate, respectively.

Farkhondehnia et al. [72] made of an aligned electrospun nanofibrous scaffold containing PCL/PLGA (25/75) and PANI (1%, 10%, 18% w/v) for treatment of spinal cord injuries. PANI is one of the attractive conductive polymers that be enhanced the electrical conductivity of nerve cells in vitro and in vivo. PLGA is a biocompatible copolymer that its biodegradable and mechanical properties are controlled by choosing the required ratio of its components. PCL is usually used as a stable polymer in a wet environment with a slow degradable rate. A-172 cell lines have been cultured on a scaffold with different concertation of PANI, they found that increase in concertation of PANI from 0% to 18% w/v, consequence, conductivity increases from 0.17 to 0.32 $S/cm \times 10^{-4}$, but cell viability increased because of leaching of PANI from the scaffold. Cell proliferation in MTT assay showed that it improved by 56% in 10% PANI in the scaffold. In addition, morphology cells on all formulations of aligned

Table 2: Different scaffold-based PANI for regeneration of skeletal muscle

Components	Cell type	Definition	Ref
Electrospun oriented nanofibers of PCL/PANI3%	mouse C2C12 myoblasts	Highly aligned nanofibers could lead myoblasts to orientate along fibers, in addition aligned nanofibers conduct electrical directly and causes to promote formation myoblasts cells.	[26,73]
poly(caprolactone), silk fibroin,and polyaniline (PC/SF/PANI) nanofiber yarn	C2C12 myoblasts	C2C12 arranged along of nanofiber yarn, they express MHC over 7 days	[74]
Nanofibrous (polyacrylonitrile)PAN-PANI	Satellite cells	Present of PANI guide to high cell proliferation and high degree of differentiation	[75]
Electrospun fibers of (PANI)/polyacrylonitrile (PAN) modified by O_2 plasma	mouse fibroblast cells mesenchymal stem cells	mesenchymal stem cells differentiated into muscle-like cells, good adhesion and proliferation, M-cadherin, troponin, α-ACTININ, MYOSIN, and MYOGENIN were expressed after21 days	[76]

nanofiber under electrical stimulation showed a long shape like neurite length. Scaffold containing 18%w/v PANI presents high elongation cells along the nanofibers whereas 18%w/v causes low cell proliferation and biocompatibility so 10% PANI was known as optimized content.

Injectable scaffold-based hydrogel has been paid more attention as minimally invasive. A scaffold-based hydrogel made of in situ precipitation of polyaniline in polyethyleneglycol diacrylate (PEGDA) and hydrogel microporous are formed by the removal of sodium chloride particles and structure was cross-linked by applying UV and this substrate was so far favorite of PC12 and hMSCs for providing 3D structure and electrical activity.[77] Conduits are known as especial form hydrogel with cylindrical tubes used for peripheral nerve regeneration applications. In one study, PANI blended poly-L-lactic acid (PLLA) conduits then were tested on rat nerve cells and found that neurite elongation was measured $24\pm4\mu m$. Similarly, another study synthesized PANI-based conduits, hMSCs were cultured on this scaffold then this scaffold provided electrical fields in the range of 10 mV/cm to 2 V/cm so caused promoted cell proliferation and aligning cells along with filopodial extensions and conducting to the formation of nerve-like cells[78].

In summary, scaffolds for repairing damaged nerve tissues are made of film, electrospun nanofibers, and hydrogel. These neural scaffolds, with three-dimensional structure, suitable micro-porosities, provide electrical guidance for the nerve cells to repair. In this section, recent research in this field has been attempted.

3.4. Bone tissue engineering

Bone is a vital component of the human skeleton, and because of its stiffness, it acts as a framework around which the soft tissues surrounding it allows it to move [79]. Bones heal spontaneously after breakage, injury,

or disease, so bones are one of the few organs capable of self-healing after injury but severely affected by the degree of bone healing if the injury is intense enough to cause some loss of bone volume, damage to the vascular system, or localized wound infection, the bone will no longer be able to recover fully and the defects will remain in the damaged position [80]. In such cases, a discontinuity is formed that requires a major repair to restore bone function and mechanical function. This is where the concept of (bone tissue engineering) becomes important and the issue of selecting the right material as bone replacement is suggested so that it can perform its functions as best as it can while still having the least side effects for the patient. Present polyaniline as components of bone scaffolds lead to promote cell bone proliferation rate and cell signaling. Often PANI composite with hydroxyapatite (HA), bioactive glass silicone, PCL, and PLA for target bone tissue regenerative.

One study tetraaniline grafted on poly (ester amide) (PEA-g-TA) as biocompatible and biodegradable copolymer and put it into Tris-HCl buffer containing proteinase K then degraded over 144 h and losing its mass up to 43% [49]. Mouse preosteoblastic MC3T3-E1 cells were cultured on this substrate with different concertation of TA and observed that cell viability decreases with increases in TA concertation. The PEA-*g*-TA stimulated by pulsed electrical signal could promote significantly the differentiation of MC3T3-E1 cells compared with the control sample.

Sarvari et al. [81] created biocompatible and biodegradable and porous scaffolds made of poly (2-hydroxy ethyl methacrylate)-co-poly(N-isopropylacrylamide)-co-poly(ε-caprolactone) (P(HEMA-b-NIPAAm-b-CL))/polyaniline (PANI) for bone applications. PCL, PANI, PHEMA, and PNIPAAm provide mechanical properties, electrical activity, hydrophilicity, and biocompatibility, respectively. These properties are required for a desirable bone scaffold for the adhesion, differentiation, and proliferation of MG63 cells. In vitro cytocompatibility was evaluated over 168h and found no signs of cytotoxicity, the electrical conductivity induced by polyaniline was about 0.03 S/cm, conditions of the scaffold provide bio-mimicking substrate for cell attachment, proliferation, and differentiation of MG63 to form artificial nanostructured osteoblastic tissue.

Ghorbani et al. [82] prepared electrospun nanofiber polyurethane-polyaniline coated with poly(vinyl alcohol)- 3-Glycidoxypropyl-trimethoxysilane (GPTMS) by using oxygen plasma treatment technique. After oxygen plasma treatment, the degree of roughness and mean height were measured, and found that these properties increased from 96.59 nm to 144.4 and 267–429 nm, respectively. The contact angle of modified PU-PANI by PVA- GPTMS with oxygen plasma was 62.50°. Moreover, the addition of 3-glycidoxypropyl-trimethoxysilane caused that hydroxyapatite layers to form on this scaffold so the cell attachment and the viability of osteoblast cells improved and it can encourage the potential for healing of damaged bone tissue.

Bhattarai et al [83] implant-based titanium nanotubes coated PANI(TNTs-PANI) have been used to enhance the corrosion resistance properties, mechanical properties, thermal properties, biocompatibility, electrical conductivity, antibacterial properties, surface biomineralization, and hydrophilicity, and promoting enhanced proliferation and differentiation of preosteoblast MC3T3-E1 cells to form regenerative bone tissue. In vitro biomineralization assay was tested on TNTs, Ti, TNTs-PANI substrate. Amine groups present in the TNTs-PANI structure can do ionic interaction with calcium, which adsorbs phosphate groups on their own to form hydroxyapatite layers on this scaffold. Following the formation of the mineral phase on the nanotube, a smooth, homogeneous, and high surface-volume ratio surface is provided for the adhesion and proliferation of MC3T3-E1cells. MC3T3-E1 cells were seeded on Ti, TNTs, TNTs-PANI substrate, due to the presence of the amine group and its derivatives, the rate of confluence was more than 85% higher than the other two. There was a porous structure to support ion exchanges and protein carriers through the substrate and make a uniform layer of MC3T3-E1 cells attached to the TNTs-PANI to differentiate to high mass production of cytoskeleton density. In addition to investigating the activity of alkaline phosphatase to prove bone cell differentiation and formation, they are also investigating the synthesis of

type I collagen. Within 1–2 weeks, each MC3T3-E1 cell in all three scaffolds synthesized type I collagen but present cells on TNTs-PANI express a high level of this protein, one of these reasons is that the matured cells on this substrate are stimulated by polyaniline to grow.

Hardy et al. [84] prepared the composition of 3-D silk foam doped pyrrole and 2-hydroxy-5-sulfonic aniline to improve differentiation of hMSCs to osteoblast cells. HMSCs were tested on three substrate of pure silk only, silk-based conductive polymer with applying electrical stimulation and without applying it. Although calcium phosphatase enzyme activity and calcium deposition and collagen production have been observed in the composite substrates, the composite substrate with applying external electrical stimulation made ECM more biomimicking and led to significantly increased differentiation and form bone tissue.

3.5. Skeletal muscle tissue engineering

Around 40% of adult human body volume is composed of skeletal muscle. Musculoskeletal diseases range from muscle weakness to paralysis and even death. Muscle cells are not capable of reproducing in adults as tissues such as hematopoietic tissue, skin, and other tissues regularly proliferate. The skeletal muscle of the body responds to electrical activity through neuromuscular junctions (NMJs) by expansion and contraction to generate force and power. Research has shown that myoblast cells increase the rate of proliferation and production of muscle contraction by electrical stimulation. Artificial muscles must have the characteristics of a native muscle, that is, the proper mechanical properties, and after the force is lifted, the muscle will be recovered to its original shape. Therefore, biomaterials that respond to temperature, pH, and electrical stimulation have been used and have been found to use shape memory alloys and electroactive ceramics and polymers in this field.

Beregoi et al. [17] spun electrospun nanofiber PMMA and for preventing any unwanted reaction and improving electrical activity, gold was sprayed on nanofiber. On other hand, polyaniline was deposited electrochemically on these fibers to improve both the electrical properties and the polymer in the presence of electrolyte ions in aqueous (sulfuric acid) or solid medium (electrolyte polymers or poly methacrylate-based gels) to be protonated/deprotonated. That is, the exchange of protons and the exchange of ions are necessary for the contraction of the muscle. To prove ion exchange, they inserted the prepared fibers into the electrochromic cell according to its especial protocol, they observed that in the presence of organic sulfuric acid solution in the cell, fiber coated polyaniline type emeraldine base (EB) with blue color was converted to polyaniline type emeraldine salt (ES) by protonation. Amniotic fluid-derived stem cells (AFSC) were applied for MTT-assay, after 5days result showed no signs of cytotoxicity and no effect on cellular phenotype. In addition, fibers coated PANI-250 had a high degree of cell adhesion.

Zhang et al. [32] produced 3-D scaffold-based silk fibroin(SF) and water-soluble conductive poly(aniline-co-N-(4-sulfophenyl)aniline) with biodegradability and biocompatibility properties. The modulus of the muscle scaffold should be above 200kPa, which increases with the increase in the percentage of polyaniline in the range of 200-450kPa. One of the requirements of scaffolds is that porosity that in all samples of this experiment porosity was 90% as a result change in percentage of PASA did not have any effect on porosity. Cell viability of SF/PASA scaffold was tested on cell line L929 fibroblast and C2C12 myoblast cells. Toxicity testing on SF/PASA0, SF/PASA1%, and SF/PASA2% scaffolds showed that these scaffolds are capable of adhesion and proliferation on the L929 fibroblast cell and did not differ significantly between their different concentrations on adhesion, toxicity, and proliferation. Myoblast cells (C2C12) were used to show their ability to repair muscle tissue, and these cells had good adhesion to the scaffold but were sensitive to electrical stimulation as the percentage of polyaniline scaffolds increased as the degree of cell spreading increased. So, due to the presence of PASA and increase in the amount of it in a scaffold, the electrical property of the scaffold increased, interestingly the rate of cell growth, cell proliferation,

and spreading as well as the differentiation of the C2C12 myoblast cells also increases.

Given that muscle tissue is important for generating force. Different polyaniline scaffolds with different structures have been developed to repair skeletal muscle tissue (Table2).

4. Conclusion

In recent years, attention has been attracted toward conductive polymers such PANI for stimulating electrical activity of scaffold of tissue engineering and promoting its cell-cell signaling and also the functionality of tissue cells like a muscle, bone, fibroblast, and especially cardiac and neural cells. In this review paper, we have attempted to highlight the essential properties of polyaniline as a biomaterial used in tissue engineering and these essential properties include biocompatibility, biodegradability, electrical conductivity, and its antibacterial. Since it has been demonstrated that the behavior of different tissue cells is affected by electrical stimulation, it is expected that the use of polyaniline or oligoaniline in the structure of tissue engineering and regenerative applications will be welcomed. Therefore, this article briefly reviews its use in various applications such as skin, heart, nerve, bone, and muscle and future researches. But due to the limitation of polyaniline in its non-biodegradability and consequently the development of cytotoxicity, it has led to ongoing research into the production of a novel biomaterial-based on polyaniline or oligoaniline compositions to resolve its biodegradability problem. We hope that this review provides enough knowledge about the polymer and also was useful for the reader and it has been able to generate interest and creativity in development and research in this field.

Conflict of Interests

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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