Recent advances of triboelectric nanogenerator based applications in biomedical systems

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Abstract
Triboelectric nanogenerators (TENGs) are a promising power and sensing solution for biomedical applications attributed to the high electrical output and sensitivity with low-cost and widely available materials. Here, the recent developments in TENG-based biomedical applications with various structures and functionalities are discussed and summarized. Wearable TENGs perform well in motion and respiratory monitoring with excellent flexibility and low bio-risks. Implantable TENGs enable interactions with the cardio-cerebral vascular system and nervous system to monitor and treat different diseases with good biodegradability. Furthermore, explorations of TENGs in in vitro systems, including drug delivery, cellular proliferation and differentiation, are reviewed. Perspectives on the biomedical applications of TENGs are proposed based on investigation in this area in the past two decades. With continuous efforts in miniaturization and optimization of robustness, the TENG-based self-powered biomedical systems will definitely play an important role in the healthcare market in the future.

KEYWORDS
biomedical systems, in vitro systems, in vivo applications, triboelectric nanogenerators

1 | INTRODUCTION

Disease prevention, diagnosis, and therapy are attractive research topics since they are essential to human health. Accordingly, precise signal monitoring of health-related physiological parameters, which can reflect the health conditions of patients in real time, is of paramount importance.1-4 Current instruments for clinical diagnosis, such as electrocardiograph (ECG) monitor, electroencephalograph (EEG), gastroscope, and enteroscope, are usually bulky, and it is hard to upgrade them into wearable devices to realize in vivo real-time monitoring.5 Additionally, clinical instruments for therapeutic purposes such as using the pulse generator to stimulate brain are usually expensive, which hinders their wider applications and more frequent use on patients. Low-cost portable, wearable, and implantable devices are urgently required to meet the demands of in vivo health monitoring and disease treatment.6,7

Rapid development in flexible materials and technologies has given rise to the emergence of wearable

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electronics in recent years. Products such as smart watches, sports bracelets, and wearable micro devices with characteristics of miniaturization and flexibility have been produced. However, these traditional products are hampered by short battery life-span, and thus frequent charging or battery replacement is required. A possible solution is to convert the energy extracted from the surrounding environment into electricity, especially the mechanical energy generated by human motions in daily activities that is dissipated into the environment via heat, which can be realized through nanogenerators. The triboelectric nanogenerator (TENG), a promising new energy harvesting technology proposed in 2012, presents a huge potential for applications in biomedical systems attributed to its high electrical output and sensitivity. Zhang et al developed a multifunctional TENG based on textile, which was used as a water energy collector and self-powered body motion sensor. And their group also reported a wearable self-charging power system (SPS) consisted of a H-TENG and several supercapacitors, which could transfer the energy stored in the raindrop into stable output. Compared with piezoelectric nanogenerator for biomedical systems, which shows narrow material selections, TENG has been proven to be a reliable and sustainable energy harvester with a wide selection of materials for fabrication and low manufacturing cost. It can convert various forms of mechanical energy around us into electrical energy on the basis of the coupling effects of triboelectric effect and electrostatic induction for further applications as a power source. Moreover, TENG on its own can serve as a highly sensitive sensor for detection of physical signals, providing a method for achieving self-powered biomedical systems for disease diagnosis and treatment.

Previous review articles have summarized some wearable and implantable nanogenerators with applications as sensors and power sources for biomedical systems. For example, Li et al discussed implantable nanogenerators as energy harvesters from the aspect of materials in 2017 and Prof. Lang's group reviewed biomedical systems with the nanogenerator as the power source in 2018. In 2019, Zhao et al summarized different TENG-based medical sensors. In 2019, Liu et al summarized different wearable and implantable TENGs (iTENGs) serving as power sources or self-powered sensors, where the iTENGs were reviewed in terms of biodegradability. In 2019, Zhang et al described recent research on TENG-based green hybrid power system. However, these review articles only focused on a certain type or a certain aspect of TENG-based biomedical systems, and some state-of-art applications of TENG in biomedical systems are not yet well discussed, such as drug delivery. Therefore, a systematic review for TENG applied in biomedical systems comprehensively covering recent developments is still required.

This review summarizes the recent development of various types of TENG-based biomedical applications. TENG can either serve as a sensor for detecting biological signals or act as a power source for powering commercial medical sensors, implying a huge potential in self-powered biomedical systems for monitoring health and regulating physiological functions, such as sensors for heart rate, blood pressure, respiratory rhythm, motion, power sources for drug delivery, tissue repairing, nerve stimulation, and so on. In this article, recent advances in TENG-based biomedical systems are divided into three main parts. The first part focuses on the in vivo applications of TENGs that are implantable via the encapsulation by biocompatible materials for both health monitoring and disease treatment. The second part mainly discusses wearable TENGs that collect physical signals from the human body. The last part summarizes other TENG-based explorations such as cell proliferation and differentiation, and drug delivery. Wearable TENGs exhibit huge advantages on its flexibility and biosafety, while in vivo and in vitro systems provide more direct ways to treat different diseases and monitor human health status in real time. Challenges and perspectives of employing TENG in biomedical systems based on its current development are discussed at the end of this review.

2 TENG-BASED APPLICATIONS IN IN-VIVO BIOMEDICAL SYSTEMS

TENG, based on Maxwell’s displacement current, presents high sensitivity for detecting mechanical stimuli with outstanding electrical output, and the pulse output can be easily recorded and recognized. Thus it can be actuated by weak mechanical motions such as inspiratory movement, systole of the heart and blood flow, a feature that is desirable for in-vivo biomedical monitoring.

2.1 TENG for cardiac monitoring and treatment

iTENGs, which are encapsulated with bio-compatible or bio-degradable materials, are usually employed for two functions, serving as self-powered biosensors for endocardial pressure heart rate monitoring or electrical power source for stimulation applications such as cardiac pacemaker, for interactions with the nervous system, and for administration of regenerative medicines such as wound healings. Liu et al reported a miniaturized TENG-based self-powered endocardial
pressure sensor (SEPS) with excellent flexibility and sensitivity that can also detect cardiac arrhythmias such as ventricular fibrillation and ventricular premature contraction (Figure 1A). The TENG presented a multilayer structure, where a spacer was sandwiched by an inductively coupled plasma-treated Polytetrafluoroethylene (PTFE) film with gold electrode deposited on the back surface and an aluminum (Al) layer, and the total structure was encapsulated by a Polydimethylsiloxane (PDMS) layer with a size of 1 cm × 1.5 cm × 0.1 cm. Integrated with a heparin-coated polyvinyl chloride (PVC) stretchable catheter, minimally invasive implantation of the SEPS was achieved in a male adult Yorkshire pig, where working signals of ECG, femoral arterial pressure (FAP), and SEPS were documented and a sensitivity of 1.195 mV mmHg⁻¹ was obtained.

Figure 1B shows an implantable wireless cardiac sensor based on TENG that was proposed by Zheng et al. The iTENG had a similar multilayer structure, with a PTFE film and a gold layer working as the triboelectric surface pair, while its deformation-recovery ability was realized through a highly resilient titanium strip that worked as the keel structure. In vivo evaluations for 72 hours of this iTENG were successfully demonstrated,

![Image of TENG structure](image-url)

and the $V_{OC}$ of ~10 V and $I_{SC}$ of ~5 μA were obtained as driven by the heartbeat of the adult swine, which are consistent with the signal waves recorded by ECG. Additionally, the authors proposed a self-powered wireless transmission system for real-time wireless cardiac monitoring, with the electrical output successfully recorded.

Besides cardiac monitoring, TENG was also implanted in vivo for powering cardiac pacemaker (Figure 1C). In 2014, Prof. Li’s group proposed an iTENG with the Al-Kapton pair with a spacer enclosed in the structure to power a prototype pacemaker driven by the heartbeat of a living rat, a power density of up to 8.44 mWm$^{-2}$ was achieved by normal breathing of the rat and the pacemaker was successfully powered in vivo with the assistance of an external capacitor for energy storage. In a subsequent study, they demonstrated the use of an iTENG-based symbiotic cardiac pacemaker in a large animal model for regulating and preventing the deterioration of sinus arrhythmia. The performance of the iTENG was improved by introducing a memory alloy keel, where energy of 0.496 μJ was obtained from each cardiac motion cycle, which exceeded the required endocardial pacing threshold energy of 0.377 μJ.

### 2.2 TENG interacted with nervous systems

As an invasive therapeutic method, neuromodulation has been widely used to regulate body functions via introducing artificial neurophysiological signals to the nerve system. Recently, TENG has been demonstrated to realize variable therapeutic purposes by generating electrical stimulation for neuromodulation (Figure 2).

In 2018, Yao et al reported a battery-free vagus nerve stimulation (VNS) system based on TENG for effective weight control, whose flexibility and compatibility were ensured by encapsulating the entire device with a polyimide, PDMS and ecoflex composite. (Figure 2A) The device was attached on the surface of the stomach of rat models, and it generated biphasic voltage signals when contact and separation processes were continuously driven by the peristalsis of the stomach at a frequency of 0.05 Hz as recorded. A bilateral VNS, for both the anterior vagus nerves (AVNs) and posterior vagus nerves (PVNs) that could be observed by staining images, was employed by wrapping the two gold leads nearby the gastro-esophageal junction. As directly connected to the vagus nerve, the voltage output generated by the TENG successfully suppressed food intake and thus reduced fat mass; an average body weight reduction of 350 g was achieved within 100 days (38% less than the control groups).

A series of studies in direct muscle stimulation for rehabilitative treatment toward muscle function loss were conducted by Prof. Lee’s group in 2019. Figure 2B shows a stacked-layer TENG proposed to successfully power muscle stimulation at a short-circuit current of 35 μA. The current pulse generated by the TENG was introduced to the skeletal muscle tissue via the multiple-channel intramuscular electrodes, which were implanted and sutured in the tibias anterior (TA) muscle tissue with fixation by a knot. The 6-electrode sites on each side of the intramuscular electrodes were separated by insulating the substrate of polyimide to prevent current flow between two sides, and thus multiple channels were formed to transfer current output, allowing motor-neuron mapping of stimulation efficiency optimization with the assistance of the stimulation efficiency matrix. The diode-amplified TENG was also developed by them to overcome the current threshold for direct muscle stimulation, which significantly enhanced the stimulation efficiency. Furthermore, Prof. Lee’s group investigated the factors of electrode configurations and stimulation stability that hindered the TENG muscle stimulation, and provided a guidance to achieve stable stimulations as well, validating the possibility of TENG powering muscle stimulation. A water/air-hybrid TENG for peripheral nerve stimulation was reported by Lee et al in 2018 (Figure 2C). A sponge and a suspended dielectric thin film were applied to enhance the output of the device as well as its robustness regarding multiple phases of water droplet. Connected with the neural electrode, the water/air-hybrid TENG performed efficient nerve stimulation and in vivo monitoring of rats.

Figure 2D shows a self-powered control system that was composed of a TENG as the sensor and a bistable micro-actuator for control purpose. It was proposed by Hassani et al in 2018 for the therapeutic purpose of underactive bladder control. The TENG sensor was structured by a wet sponge enclosed between the PDMS and copper surfaces to allow charge transfer by the motion of water through the sponge. The sensor was placed between the bladder surface and the flexible bottom PVC sheet and the voltage output was connected to a spring-based actuator, which was fabricated by the shape memory alloy NiTi with an external voltage of 4 V applied for the restoration phase. When enough water was squeezed out of the sponge due to the force by the liquid filling the bladder, the actuator started to compress the bladder to void as the voltage output of the TENG was larger than 4 V, which in turn weakened the voltage output of TENG, then the actuator turned to the restoration phase again. This self-powered control system was reported to realize a voiding percentage of up to 78% of the bladder volume in a rat-model in vivo experiment, a
performance that was comparable to that of the common catheterization method.

2.3 TENG for regenerative medicine

When external energy strategies, such as voltage output stimulation, laser therapy, near-infrared treatment, are applied on fibroblast cells, cell migration across the scratch wound is accelerated, which is beneficial to the scratch-wound healing process. Thus, TENGs are also employed in the field of regenerative medicine in short-term treatment in combination with biodegradable materials, especially for in vivo self-powered cure system for wounds. In 2015 Tang et al reported an in vivo low-level laser cure system powered by TENG for osteogenesis of a mouse model. A vertical contact-separation (CS) mode TENG with pyramid-array patterned PDMS and TiO$_2$ pair was applied to power a capacitor for driving the infrared laser through a rectifier. It was demonstrated that a larger obvious mineralized area in the TENG-based infrared irradiation groups of murine calvarial preosteoblasts was obtained compared with the reference group without laser treatment, a result that was similar to the results of the battery-lasered irradiation group. In order to meet the demands for biodegradable implantable electronics after realizing the therapeutic purpose, Zheng et al in 2016 proposed a biodegradable TENG (BD-TENG) to harvest biomechanical energy for short-term...
applications. The BD-TENG had a multi-layer structure with a space enclosed inside and was entirely encapsulated by bio-degradable polymers with excellent biodegradability and biocompatibility. Two sterilized BD-TENGs coated with poly(l-lactide-co-glycolide; PLGA) and PVA were implanted in the sub-
dermal region of Sprague Dawley (SD) rats in vivo, and the wounds were cured well after 9 weeks without any obvious infection or significant inflammatory reactions. Besides, the output voltage of BD-TENGs driven by the respiratory motion decayed a lot with time, which could be attributed to the fibrous encapsulations by the foreign body response. Additionally, the growth of neuron cells was demonstrated to be orientated successfully by the DC-pulse electric field generated between two electrodes with comb structures by the powering of the BD-TENG. An iTENG with tunable biodegradation was proposed by Li et al in 2018; the contact-separation process of the device was ensured by the hemisphere array structure of Au. The Au nanorods were doped in a PLGA film (the bottom biodegradable dielectric layer) to respond to NIR treatment. The encapsulation layer and the triboelectric surface (the top dielectric layer) employed biodegradable materials as well. To evaluate the in vivo controllable degradation against time, the PLGA-iTENG was implanted into the subdermal region of SD rats after sterilization. (Figure 3C) Computed-tomography (CT) images showed that faster degradation could be obtained when Au-Nano-Rods (AuNRs) doping and NIR treatment were used in combination, compared with other groups that had undergone only one or no treatment at all, demonstrating the feasibility of using tunable biodegradation in healthcare applications. Further experiments on tissue repair were conducted by the authors, and the results showed the migration process of fibroblast cells was significantly accelerated by the output of the TENG. In 2018, Long et al reported an electrical bandage on the basis of TENG for skin wound healing. The TENG, with a polyethylene terephthalate (PET)-Cu foil-PTFE multilayer structure, generated electricity from the skin movement to induce an alternative electric field between the two dressing electrodes that were located near the wound. Rapid closure of rectangular skin wound along the electric field was demonstrated within 3 days by applying the electrical bandage with skin wounds, as shown in Figure 3D, while 12 days were required for normal healing process with multiple closure directions.

3 WEARABLE TENGS FOR HEALTH MONITORING

Compared with iTENGs, wearable TENGs enable more flexible applications with less concern on biosafety and biocompatibility. In this section, wearable TENGs that work as self-powered monitor are reviewed in three categories according to different functionalities.

3.1 Wearable self-powered heart rate sensors

More and more people are living in a sedentary lifestyle, which has obvious health risks such as the increased risk of heart diseases. This has made the development of latent disease monitoring devices an increasingly interesting research topic for scientists. It has been reported that 90% of cardiovascular diseases are preventable. Heart rate has been widely used to evaluate the health status of individuals; it is also an important index to reflect the stability of the cardiovascular system. A series of technologies have been extensively applied to measure heart-beating pulses, such as photoplethysmography (PPG) and piezoelectric pulse transducer (PPT). However, these technologies have disadvantages, such as difficulty in data recognition and analysis, low density of devices and high cost that limit their development. To address these issues, TENG is employed as a promising and user-friendly self-powered active sensor to monitor these medical signals.

In 2014, Peng et al demonstrated the use of a membrane-based triboelectric sensor (M-TES) as a self-powered method to monitor air pressure variation for personal healthcare and security surveillance. A piece of acrylic sheet served as the substrate of M-TES, and two copper films were deposited at both sides of substrate as electrode. Fluorinated ethylene propylene (FEP) film was pasted over the electrode and packaged by a latex membrane. There was an air conducting aisle in the middle of the equipment, which formed an air cavity when air pressure changed. M-TES could detect changes in chest pressure caused by heartbeat rhythm, and generate voltage signals accordingly. The voltage output was able to trigger the security alarm through the processing unit (Figure 4A). Therefore, the periodical air pressure change resulted in output voltage signals to reflect the heart rate in real time. The simple and low-cost M-TES was demonstrated to be able to respond effectively to changes in air pressure caused by footsteps, heartbeats and respirations without the help of any external energy supplies.

In 2019, Chen et al proposed a TENG-based flexible self-powered detector installed on the thumbnail for calculating oxyhemoglobin saturation and pulse rate by detecting stable photoplethysmography (PPG) signals. Driven by a stretchable TENG that was fabricated with a crumpled gold (Au) electrode and a PDMS triboelectric layer, the LED was able to emit light that contained hemoglobin information. Then, the reflected light was detected by the photodetector (PD) to acquire blood oxygen information. (Figure 4B). The output performance of TENG could be significantly improved by the rough nanostructures on the electrode and PDMS.
The advanced technologies in personal disease diagnosis and health monitoring system highly depend on the development of body sensor network (BSN). Conventional devices are powered by traditional batteries that have the shortcomings of limited lifespan and harmful to the environment. TENG has been recently developed as a promising method to detect indication of body functions and give data on the health status of individuals in the form of wearable self-powered sensors. In 2017, Lin et al reported a wireless BSN system driven by downy-structure-based TENG (D-TENG) for noninvasive real-time human heart-rate monitoring (Figure 4C). The system was composed of a power management circuit, a heart-rate sensor, a bluetooth module for wireless data transmission and a signal processing part. The D-TENG consisted of two basic functional units, the polytetrafluoroethylene (PTFE) thin films and an acrylic sheet. The highly integrated BSN system was motivated by the energy collected from human walking through the D-TENG. In order to make the BSN work as a real-time heart monitor, heart rate signals were first obtained by a signal process circuit, then transmitted by Bluetooth wireless technology for display in a smartphone.

In 2017, Ouyang et al demonstrated a self-powered ultrasensitive pulse sensor (SUPS) to convert human pulse biomechanical signal into electric signal. The SUPS exhibited perfect performance when it was pressed on the radial artery. An output voltage of 1.52 V, response time of 50 μs and signal-noise ratio of 45 dB were realized to obtain pulse signals that could be easily processed. Besides, the performance of the SUPS was tested by an implanted intraaortic balloon pump (IABP).
where the cardiovascular system was regulated through systole and diastole of the balloon pump (Figure 4D). Additionally, the SUPS was integrated with a Bluetooth chip to support real-time monitoring of the cardiovascular system on a smartphone.

Motion sensors that work by monitoring body/muscle motions from eye-balls, body gestures, and finger poses have been widely used in e-skin and health-care systems. 50–54 Chiu et al proposed a self-powered gesture sensor to be installed on the back of hand to discern finger motions (Figure 5A). 50 Two hands could form 64 gesture combinations, a number that was sufficient to represent 26 English letters. Chitosan/glycerol films were applied to make the triboelectric surfaces to ensure its performance in harsh conditions such as high humidity. This system was also integrated into gloves to boost its availability and practicability. In 2019, Partha et al established a TENG-based pressure sensor (TEPS) for usage in self-powered human gesture detection. 52 It performed well with high sensitivity even under tiny pressure changes with fast response time (<9.9 ms). Different signal profiles were created by utilizing the TEPS sensor to differentiate multiple gestures from the human elbows, knees, and fingers.

In 2018, Wang et al proposed an extendible and self-powered TENG motion sensor based on kinesio tapes (KT-TENG) (Figure 5B). 51 The KT-TENG comprised two triboelectric layers (PET and Kapton films), with two kinesio tapes and electrode layers on the back side, and electric signals output produced by tiny motions. The bending angles and slight movements showed linear relationship with the $Q_{SC}$ as well as $V_{OC}$, enabling its good performance on real-time human motion monitor. Fang et al reported a new type of sensor system that was made by assembling stretchable-rubber-based (SR-based) TENG devices to detect moving directions, and thus could overcome the limitations of rigid substrates. 53 This system consisted of an elastic rubber layer and an Al film. The SR-based TENG exploited the length expansion through introducing an in-plane charge separation, resulting in the potential difference between the Al electrode and the ground, and an alternating output current was generated by periodically released. Serving as a multifunctional sensor, the SR-based TENG was also able to detect breathing and joint motion.

For body motion detection, TENG can distinguish different gesture types produced by different electric signals, demonstrating the possibility of using TENG to detect abrupt motions such as people falling and other hazard signals. In 2019, Ahmed et al developed a multifunctional self-powered alerting sensor enabled by the smart ferrofluid-based triboelectric nanogenerator (FO-TENG) as an efficient platform for real-time hazard monitoring. 54 As shown in Figure 5C, the output voltage amplitude of the sensor increased with increasing swimming speed, and different swimming techniques produced distinct signal profiles. The FO-TENG signal was higher than normal when the swimmer was drowning, due to the struggling and random motions with giant amplitude from the swimmer. The waterproof FO-TENG was composed of a silicone rubber tube, a patterned copper wire electrode with ferrofluid as the triboelectric layer. It was also integrated with the human body in different arrangements and worked as a multifunctional self-powered sensor with extraordinary confirnability. Guo et al presented an all-fiber hybrid piezoelectric-enhanced TENG (TPNG) on conductive fabrics manufactured by electrospinning silk fibroin and polyvinylidene fluoride (PVDF) nanofibers. 55 Compared with other textile-based nanogenerators, TPNGs showed higher power levels of voltage (500 V), short-circuit current (12 μA) and power density (0.51 mWcm$^{-2}$). It could be customized to be embedded in clothes in any sizes and shapes to identify multiple types of body motions, a feature that made it very promising in real-time health monitoring.

Gait monitoring is critical in clinical biomotion analysis, sports training and medical diagnosis. Monitoring human motion enables identity recognition since each person has his/her own gait characteristics. Han et al reported a TENG-based band for detecting muscle activity and recognizing identity through identifying gait patterns (Figure 5D). 56 The soft, stretchable and low-cost band was fabricated with a rubber tube wrapper with physiological saline as the electrode. The band could detect walking information, including six types of human motions (swallowing, jumping, squatting, breathing, calf raising, and bicep curling). In 2018, Lin et al proposed a smart insole for real-time gait monitoring based on TENG. 57 The TENG-based sensors, which were fabricated by rubbers and copper layers, were distributed at the front and rear sides of the insole. The TENGs relied on contact-separation motions of two triboelectric layers to generate electrical output, with excellent stability and mechanical durability. Furthermore, the various gait patterns such as jump, and run was exactly presented by the time difference between two feet contact with ground. Jao et al developed a chitosan-based TENG (C-TENG) to harvest biomechanical energy through human motions for self-power healthcare sensing such as sweat and gait detection. 58 Compared with traditional TENGs, the output features of the C-TENG remained unchanged as the relative humidity inside shoes varies from 20% to 80%. A biocompatible chitosan-glycerol film was combined with a textile to exert its multifunctional capability in this work.
Wearable electronics that can function well underwater is attracting increasing attentions. Such devices need to be waterproof and contain a sustainable power source. Zou et al., inspired by the electric eel (Electrophorus electricus) that could generate thousands of volts of electricity under water, proposed a bionic stretchable nanogenerator (BSNG) combined with TENG for energy harvesting and underwater sensing (Figure 5E).69 Through utilizing the unmatched stress effect caused by polydimethylsiloxane (PDMS) and silicone, a mechanically controlled tunnel was produced by imitating ion channels in the electrolyte membrane. The BSNG is a promising power source for wearable electronics in mute-position motion monitoring and underwater rescuing.

Sensors for detecting specific sleep postures and conducting physiological analysis in real time have been reported recently to diagnose sleep deprivation through detecting the airflow from breathing and body movements of patients. Song et al. reported an APLE (Al-plastic laminated film)-based TENG device to monitor sleep behavior and body movements (Figure 5F).60 A fold APLE and a 2 mm cantilever spring leaf inside the fold APLE constituted the sandwiched structure of TENG, thus electrostatic charges were created on both parts. The TENG sensitivity was highly enhanced due to the high open-circuit voltage of 55 V. Changes in pressure attributed to body motions during sleeping were sensitively detected by TENG in real time. Lin et al developed a textile TENG array as a bedsheet for real-time sleep behavior and body movements (Figure 5F).61 The textile TENG was a sandwiched structure with conductive fibers laminated onto the top and bottom fabrics, and wavy-structured polyethylene terephthalate (PET) films in the middle. The smart textile exhibited short response time of less than 80 ms and excellent sensitivity of 0.77 V Pa⁻¹. The electrical signals obtained through the textile TENG-based smart mattress would provide real-time information on the sleep quality and health status of the sleeper. This represented a smooth and noninvasive method to monitor sleep behavior with excellent washability and sensitivity, which fits well to the integrated signal processing system.

The e-skin is becoming popular in both commercial and academic communities due to its unique properties and excellent performance. In 2018, Dong et al exhibited a skin-inspired triboelectric nanogenerator (SI-TENG) as a multifunctional e-skin.62 SI-TENG demonstrated favorable stretchability, excellent sensitivity, and accuracy attributed to the three-ply-twisted silver-coated nylon yarn. A VOC of 160 V and an instantaneous average power density of 230 mW m⁻² were generated by this SI-TENG. Its high sensitivity to pressure and fast response can lead to potential applications in wrist pulse detection, voice recognition, and biomedical prostheses.

In 2018, a whirligig-inspired portable TENG (Wi-TENG) equipped with high-frequency rotations and sustainable power was reported by Tang et al.63 The Wi-TENG worked in noncontract freestanding mode with radial-array electrodes to minimize resistance for achieving high-speed rotation. A rotor speed of 11 250 rpm, the maximum ISC, VOC, and instantaneous output power of ~317 μA, ~153 V, and ~40.18 mW was achieved by the Wi-TENG. Being portable and sustainable, the Wi-TENG has been successfully applied in blood glucose test and worked as temperature-humidity detector.

Respiration rate is one of the most vital and reliable indices that directly reflects human physiological health status, and provides pivotal information for diagnosis of potential respiratory diseases and personal health management. In 2018, Cao et al reported a nanofiber-based triboelectric sensor (SNTS) to monitor health conditions through the respiratory rate (Figure 6A).64 A screen-printed Ag nanoparticle (AgNP) electrode and an electrosprun PVDF nanomembrane constituted the SNTS with an arch structure. The air permeability of A4 paper was 1.4 mm/s, while that of this SNTS was up to 6.16 mm/s, which was much higher than traditional cast films. It also exhibited remarkable softness when it was folded, bent, or even twisted, and thus the skin-friendly characteristics ensured its splendid electronic performance. Moreover, SNTS was regarded as a finger motion tracer and activity trailer due to its outstanding performance. In 2018, Wang et al showed a self-powered TENG-based respiratory monitoring driven by air flow, which transformed human respiratory mechanical energy into electric signals to realize real-time monitoring.65 The TENG comprised a flexible PTEE thin film, which generated vibrations under laminar flow. When the PTFE film was installed in a mask, it responded effectively and provided a real-time display of breathing patterns through different air flow rates, as reflected by the charge transfer. Thus, the TENG-based system provided a direct way to measure human breath patterns. In 2019, Zhang et al developed an integrated wireless respiratory monitoring system that was located in the waist through detecting breathing signals by a smart strap (Figure 6B). The cyclical variations perceived by TENG were used to collect respiratory information. The sensor could be activated even by a minimum amplitude of the slide shift (2.5 mm) with efficient wireless transmission as demonstrated by a mechanical test. Xia et al designed an easy-to-fold and portable hybrid triboelectric-electromagnetic generator (TEMG) with high sensitivity to detect airflow. It was used to harvest mechanical energy and had practical application for respiratory rate calculation as well.66
sensing and energy harvesting. In 2016, Zhao et al demonstrated a machine-washable and fabrication-scalable t-TENGs as a wearable respiratory monitor to record human respiratory depth and rate. The new t-TENG consisted of Cu-coated polyethylene terephthalate (Cu-PET) warp yarns and polyamide (PI)-coated Cu-PET (PI-Cu-PET) yarns. The triboelectric charges were effectively generated by very subtle deformation such as tapping or bending, and a maximum short-circuit current density of 15.50 mA m$^{-2}$ was achieved. Thus, the new t-TENG was able to respond quickly to subtle changes in human motions and work as a wearable respiratory detector to monitor human health.

In 2017, Qian et al reported a stretchable electromagnetic shielding hybrid nanogenerator (ES-HNG), which scavenged mechanical and thermal energy as well as monitored human health by attachment to the on human abdomen (Figure 6C). The ES-HNG was composed of a stretchable TENG and some PPENGs forming an island structure, and was able to transform mechanical and thermal energy into electricity. As a computer keyboard cover, ES-HNG could generate energy through charging.

a capacitor to 3 V by typing, which was sufficient to drive the portable devices. Moreover, more than 99% of radiation from the computer or other facilities was shielded by ES-HNG.

4 | TENG-BASED APPLICATIONS IN IN-VITRO BIOMEDICAL SYSTEMS

Applications of TENG in biomedical systems are not limited within in vivo or wearable functionalities. With the advantages of novel materials and design, the use of TENGs with micro-structured patterns and high sensitivity has been explored in several in-vitro applications such as drug delivery,\textsuperscript{69-71} cell proliferation,\textsuperscript{72} sterilization, and functional sensors.\textsuperscript{73}

4.1 | TENG for drug delivery

To treat various diseases with little harm to the body, precise therapeutic drug delivery at the targeted location and controlled drug release is required, and thus a number of noninvasive technologies for drug delivery are established. Among those technologies, TENG is a promising method for drug delivery with no external power source assisted. Zhao et al reported a drug delivery system (DDS) that was controlled by TENG for cancer therapy.\textsuperscript{74} The triboelectric surfaces of the TENG were Ti and PTFE with Cu deposited, and a small magnet was attached on the back of each friction layer to maintain the output performance of the device for long-term applications. The entire device was encapsulated with PTFE and PDMS layers to prevent damages in harsh environment. When red blood cells (RBCs) were successfully loaded with doxorubicin (DOX, an anti-tumor drug) by the hypotonic dialysis method in a suspension and were placed on a simulation device with an electrode-deposited substrate, the electric field of 4 kV cm\textsuperscript{-1} generated by the TENG was applied to the device to release DOX. (Figure 7A) After withdrawing the EF, the DOX drug was loaded in RBCs again for the next release process. Sixty HeLa-tumor-bearing BALB/c-nu mice were treated with phosphate buffer saline (PBS) (the control group), electric field (EF), DOX, DOX + EF, DOX loaded RBCs (D@RBCs), and D@RBC + EF with a dosage of DOX equal to 5 mg kg\textsuperscript{-1} to investigate the antitumor efficacy of the DDS in vivo. D@RBC + EF DDS performed the best therapeutic effect in inhibiting tumor growth, with mice in this group showing the minimum tumor cell proliferation and only 2 of the 5 mice died on the 54th day, while all the mice in the other five groups died within 46 days.

In 2017, Song et al reported an implantable pumping drug delivery system that was driven by a TENG for ocular diseases therapy.\textsuperscript{70} The rotating TENG was fabricated with a PTFE film sandwiched between two Cu electrodes with radial grating structures on the electrode surfaces. The pump system, which was comprised a PDMS ocular drug reservoir, a PDMS microtube and a pair of Au electrodes on the silicon substrate, was driven by the TENG.
through a transformer with pumping flow rates from 5.3 to 40 \( \mu L \text{ min}^{-1} \). (Figure 7B) This system was applied into the anterior chamber of porcine eyes through incision and successfully delivered ocular drugs driven by the biokinetic energies of human hands. TENG integrated with microneedle patterns was also preferred for noninvasive drug delivery. In 2018, Bok et al proposed a drug delivery system composed of deoxyribonucleic acid (SDNA)-based dissolving microneedles device for drug insertion and a CS mode TENG for electric field induction. Here, with a density of 80 microneedles per array (Figure 7C), this system was successfully employed in porcine cadaver skin for drug intercalation, demonstrating its potential for in-vivo drug delivery. A similar electrode structure with silicon nanoneedles to realize noninvasive drug delivery was reported by Liu et al in 2019, in both in vitro and in vivo conditions. Driven by the TENG through simple finger friction or hand slapping, significant enhancement in efficiency of the transdermal biomolecule delivery was realized by the sufficient high local electrical field located at the nanoneedle-cell interface.

### 4.2 Other applications of TENG in in-vitro biomedical systems

Apart from drug delivery system, TENG was also demonstrated in cell differentiation, proliferation and migration with high efficiency. Figure 8A shows a system reported by Jin et al in 2016 for the nonviral direct conversion of primary mouse embryonic fibroblasts (PMEFs) to induced neuronal (iN) cells, with TENG serving as the triboelectric stimulator (TES). Here, the CS mode TENG was structured with an Al film as the top electrode, a PDMS-pillar patterned Kapton film, and a Cu film on the backside of the Kapton as the bottom electrode, where an electric output of \( V_{OC} \approx 30 \text{ V} \) and \( I_{SC} \approx 270 \text{ nA} \) was obtained. The output was connected to the cell culture substrate fabricated with highly conductive Ti-deposited Si, which successfully enhanced the PMEF differentiation, as demonstrated both in the cell culture template and skin tissues of mice. Additionally, in 2019 Tian reported a stimulator that was composed of a spring-CS mode TENG with the triboelectric pair of Al/PTFE and a flexible interdigitated electrode for bone formation. (Figure 8B) They demonstrated that the electric field generated by TENG was effective for promoting the attachment, differentiation and proliferation of the murine calvarial preosteoblasts, MC3T3-EI, where 72.76% in adhesion, 23.82% in proliferation rate, and 28.2% in differentiation rate were enhanced by continuous stimulation, respectively. Similar functionalities of cell proliferation and migration based on a disc-shaped rotating TENG were reported by Hu et al in 2019.

In 2019, Yao et al proposed an omnidirectional TENG to promote hair regeneration in SD rats by using the generated alternating electric field. This system comprised a TENG connected with a pair of comb-shaped electrodes, and the device was placed on the back of rats with the top layer of the electrodes in contact with the skin. (Figure 8C) When the TENG was driven by random motions, spatially distributed electric field was applied on the skin of the SD rats by the comb electrodes, where hair regeneration with higher density of hair follicles and longer hair shaft was successfully manifested. Furthermore, the secretion of vascular endothelial growth factor and keratinocyte growth factor were also enhanced by the system and finally hair regeneration of the defective nude mice was achieved. The TENG-based sterilization system, which was reported by Tian et al in 2017, was another example of the successful application of TENG in biomedical system. Here, the wave-driven TENG was enclosed in a PS shell, and the electrical output of TENG was connected with two Ag/ZnO nano-brush electrodes, where two cambered Al layers were deposited on the inner surface of the shell separately and a rubber ball was employed to slide on the inner surface. This sterilization system was employed to treat Escherichia coli (E coli), Staphylococcus aureus (S aureus) and natural river water, with significant reduction in colony forming units (CFUs) in both instant and sustainable sterilization, as a result of the synergetic work of the electroporation generated during electric field treatment by TENG and sterilization by the sustained intracellular reactive oxygen species (ROS) while withdrawing electric field. (Figure 8D).

The use of biosensors based on TENG for special signal monitoring was realized as well. Zhao et al reported a TENG for detecting neurotransmitters and neural electric signals between neuron synapses, (Figure 8E) as the Schottky barrier height could be tuned by the TENG output. The multifunctional detection of the Schottky to Ohmic reversible (SOR) biosensor was attributed to the reversible conversion between Schottky and Ohmic contacts by the treatment of the high-voltage pulse from TENG, where the Schottky-contact SOR biosensor was highly sensitive to low concentration of neurotransmitters, and the Ohmic-contact SOR biosensor was able to detect bioelectrical signals. In-vitro detection of dopamine monitoring for neural electric signals of the bullfrog sciatic nerve trunk before and after conversion was both realized by the SOR biosensor, demonstrating its ability in multifunctional detection.
SUMMARY AND PERSPECTIVE

In summary, this review presents various types of TENG-based biomedical applications during their rapid development in recent years with different structures and functions. The self-powered TENG can collect biological information and act as power sources for commercial medical sensors, enabling the applications in health monitoring and the regulation of physiological functions, such as sensors for heart rate, blood pressure, respiratory rhythm, motion, power source for drug delivery, nerve stimulation, and others. This review discusses the in vivo applications of TENGs that are implantable via the encapsulation with biocompatible materials for both health monitoring and disease treatment, and the applications of wearable TENGs with various structures for collecting information of physical characteristics. Other explorations based on TENGs such as cell proliferation and differentiation, and drug delivery are also reviewed. The output performance of reviewed TENGs as reflected by the $V_{OC}$ and the output power are summarized in Table 1, where the function and size of each TENG are listed as well.

TENG can be implanted into the body, mounted onto the skin or clothes, or woven into fabrics as smart...
<table>
<thead>
<tr>
<th>Type</th>
<th>NO.</th>
<th>Functions</th>
<th>$V_{OC}$</th>
<th>Power</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Vivo</td>
<td>10</td>
<td>Endocardial pressure sensor</td>
<td>Up to 6.2 V</td>
<td>N/A</td>
<td>1 cm × 0.5 cm × 0.1 cm</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>Power cardiac pacemaker</td>
<td>~12 V</td>
<td>107 mW m$^{-2}$</td>
<td>1.2 cm × 1.2 cm</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>Power cardiac pacemaker</td>
<td>Up to 65.2 V</td>
<td>8.44 mW m$^{-2}$</td>
<td>39 mm × 61 mm × 0.99 mm</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>Peripheral nerve stimulation</td>
<td>~30 V</td>
<td>0.496 μW/cycle</td>
<td>2 cm × 2 cm</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>Skin wound healing</td>
<td>0.2-2.2 V</td>
<td>40 μW</td>
<td>10 cm × 1.2 cm</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>TENG with tunable biodegradation</td>
<td>~2 V</td>
<td>95 μW</td>
<td>1.2 cm × 1.2 cm × 0.65 mm</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Wireless cardiac sensor</td>
<td>~14 V</td>
<td>0.9 μW</td>
<td>25 mm × 10 mm × 1.5 mm</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>Weight control</td>
<td>50-120 mV</td>
<td>N/A</td>
<td>16 mm × 12 mm × 2.5 mm</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>Muscle stimulation</td>
<td>~47 V</td>
<td>N/A</td>
<td>10 cm × 10 cm</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>Sensor for underactive bladder control</td>
<td>35.6 ~ 114 mV</td>
<td>32.6 mW m$^{-2}$</td>
<td>1.4 cm × 2.2 cm</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>Power the infrared laser</td>
<td>~0.2 V</td>
<td>N/A</td>
<td>1.5 cm × 1.0 cm</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>Harvest biomechanical energy</td>
<td>~40 V</td>
<td>N/A</td>
<td>2.0 × 3.0 cm</td>
</tr>
<tr>
<td>Wearable</td>
<td>47</td>
<td>Pressure sensor</td>
<td>0.2-20.4 V</td>
<td>N/A</td>
<td>3.7 cm × 3.7 cm × 0.2 cm</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>Blood oxygen monitor system</td>
<td>~75.3 V</td>
<td>0.2 mW cm$^{-2}$</td>
<td>1 cm × 1 cm</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>Ultrasensitive pulse sensor</td>
<td>~1.52 V</td>
<td>N/A</td>
<td>20 mm × 10 mm × 0.1 mm</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Gesture-sensing system</td>
<td>Up to 250 mV</td>
<td>N/A</td>
<td>2 cm × 3 cm</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>Human motion sensor</td>
<td>Up to 24.1 V</td>
<td>N/A</td>
<td>1.5 cm × 4 cm</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>Human gesture detector</td>
<td>Average 50 nA</td>
<td>N/A</td>
<td>3 cm × 3 cm</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>Movement sensor in different directions.</td>
<td>~65 V</td>
<td>76.27 μW m$^{-2}$</td>
<td>30 mm × 88 mm</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>Hazard stimulus sensing</td>
<td>Up to 14 V</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>Falling-down detection and timely remote alarm</td>
<td>~500 V</td>
<td>3.1 W m$^{-2}$</td>
<td>2 cm × 4 cm</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>Identity recognition through gait pattern</td>
<td>Up to 89.4 V</td>
<td>0.33 mW m$^{-2}$</td>
<td>15 cm × 200 μm (thick), $d = 1$ cm</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>Insole for real-time gait monitor</td>
<td>Up to 35 V</td>
<td>N/A</td>
<td>Diameter = 20 mm</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>Healthcare sensor</td>
<td>Up to 130 V</td>
<td>N/A</td>
<td>5 cm × 3 cm</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>Underwater applications</td>
<td>Up to 600 V</td>
<td>N/A</td>
<td>10 cm × 6 cm × 8 mm</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>Sleep monitor</td>
<td>~55 V</td>
<td>N/A</td>
<td>Diameter = 2 cm</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>Sleeping monitor</td>
<td>Up to 3 V</td>
<td>N/A</td>
<td>2 m × 1.5 m</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>Biomechanical energy harvest and versatile pressure sensing</td>
<td>~160 V</td>
<td>230 mW m$^{-2}$</td>
<td>80 mm × 40 mm</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>Personal health monitor</td>
<td>Up to 153 V</td>
<td>40.18 mW</td>
<td>70 mm × 100 mm</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>Respiratory monitor</td>
<td>10-25 V</td>
<td>N/A</td>
<td>1 cm × 2 cm</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>Real-time respiratory monitor</td>
<td>~2.4 V</td>
<td>1.3 mW</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>Breath detector</td>
<td>~500 V</td>
<td>2 mW for the TEG and 15.8 μW for the EMG</td>
<td>5 cm × 5 cm × 2 mm</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>Respiratory monitor</td>
<td>~5 V</td>
<td>23.86 mW m$^{-2}$</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>Health monitor</td>
<td>~3 V</td>
<td>N/A</td>
<td>12 cm × 3 cm</td>
</tr>
</tbody>
</table>
textiles. It shows great potential in the healthcare market, but there are still challenges to be addressed before its industrialization and commercialization, which are summarized as follows:

1. To enhance the robustness, durability, compatibility, etc. of TENGs in various biomedical situations, further optimizations in the size, biocompatibility, and flexibility of TENG-based systems toward being implanted in specific parts of human body such as muscles are still required.

2. Current applications are limited by the critical clinical challenges toward wider applications and industrialization, especially the issue of foreign body response effect by the immune system. Such a foreign body response will encapsulate the implanted devices with fibroblasts, inhibiting TENG from receiving bio-mechanical motion stimuli toward long-term applications.

3. For wearable TENG, improving its sensitivity and stability are two important factors apart from optimizing the device structure and enhancing anti-interference ability.

4. The output performance of TENG and power management units need to be optimized, such as packaging and miniaturizing of the whole system.

5. TENG is applied as an external power source to provide an electric field assisted by other electrodes management circuits to regulate cell development and drug delivery in vitro, and thus, the interaction between TENG and cells is weak. Future work should simplify biomedical systems with functional TENG structures to directly realize the strong interaction between TENG and cells. Additionally, further studies on the TENG-based devices to regulate cell adhesions and apoptosis are greatly helpful for the development of anti-cancer strategies.

Despite these challenges, considering the following advantages of TENG, various available materials with low-cost for fabrication, simple fabrication process, extraordinary high sensitivity and output in response to slight stimuli, as the current trend of electronic equipment toward wearable and portable electronics, the prospect of TENG-based wearable health monitor systems will surely have an brilliant future in the healthcare market.

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