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Carbon Nanomaterials for Tailored Biomedical Applications

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Abstract **- Carbon Fibre (CF) and Carbon Nanotube (CNT) are typical Carbon nanomaterials that possess unique features which make them particularly attractive for biomedical applications. This paper is a review of the Carbon Fibre (CF) and Carbon Nanotube (CNT) for biomedical applications. In this paper, we describe their properties and tailored biomedical applications. The most recent state of the art in biomedical applications of CFs and CNTs were reviewed.**
Keywords: **Biomedical, Carbon Fibre, Carbon Nanotube, Sensors, Tissue Regeneration**

I. INTRODUCTION

Research activities on Carbon nanomaterials became visible in the mid-1980s. There are three major types of Carbon nanomaterials: Carbon Fibres, Carbon Nanotubes and Carbon Spheres. They have a high specific surface area and good fusion properties. This special attribute has endeared these materials to electrochemical research where they are widely applied as biosensors. Carbon nanomaterials were reported to enhance the biological activities of enzymes in small molecules. This property has been utilized in biomedicine and drug release [1]-[3].

Carbon fibre (CF) is a long thin strand of fibre, composed mostly of carbon atoms, with a diameter of 0.005-0.10mm. It has good physical, chemical, and biological characteristics which make it suitable for diverse applications. Carbon fibres are lightweight, have high strength, and are chemically stable. Carbon fibres are popular for their biocompatibility which has been clinically proven for use as biomaterials for biomedical applications [4]-[11]. Carbon fibres are pliable and can be easily moulded with adaptation into complex human-like structures. It has a density of 1.6-2.2 g/cm^3 compared to the density of compact bone which is 2.0 g/cm^3 [12].

The application of carbon fibre to biomaterials has started over 30 years ago. Since then various products have been developed including foot prostheses, polyester for abdominal wall repairs, limb support structures and human kneel reconstruction structures and others [13], [14].

The term carbon fibre is a generic term referring to fibres manufactured by pyrolysis of organic precursor fibres (polyacrylonitrile (PAN), rayon, or pitch) in an inert environment [15]. The product, carbon fibre possesses a graphitic structure with strong crystalline covalent bonds. It is highly anisotropic along the axis direction but has weak van der Waals forces between its layers.

In determining the biocompatibility of carbon fibre, Richard Peterson carried out research using a bis-phenol-epoxy/carbon-fibre-reinforced composite rod and titanium-6-4 alloy screw. The bisphenol-epoxy/carbon-fibre-reinforced composite is measured in 1.5 mm diameter and compared with also 1.5 mm diameter size of the titanium 6-4 alloy screw which was manufactured to retain bone implants. It was observed that carbon fibre reinforced composite stimulated osseointegration inside the tibia bone marrow to a great extent when compared with the titanium 6-4 alloy.

The osseointegration inside the bone marrow is measured as per cent bone area (PBA). At an implant surface of 0.8 mm, the per cent bone area (PBA) was 41.6% for carbon fibre and 19.5% for titanium 6-4 alloy and for an implant surface of 0.1 mm, the per cent bone area was 77.7% for carbon fibre and 19.3% for titanium 6-4 alloy. This shows that the per cent bone area increased significantly with the carbon fibre composite over the titanium 6-4 alloy [10].

Carbon fibre composites particularly, at the nanoscale have been employed in the biomedical industry to develop new biomedical materials in meeting the most challenging human biomedical needs. It has also been employed in regenerative medicine and cancer treatment. It has been realized that these materials can be used for effective scaffolding for bone tissue regeneration and repairs of tendon and ligaments, suture materials, and the repair of hernia rings [10], [13], [14], [16], [17]. It is worth noting that the high proportion of living organism tissues is composed of carbon compounds. This is also one of the main reasons for carbon being compatible with living tissue. Research showed that carbon fibre does not inhibit tissue growth. This is why it can serve as a scaffold for tissue proliferation [13].

A breakthrough in nano-scale carbon fibre came through with the discovery of carbon nanotube (CNT). CNTs possess some remarkable structural, electrical, chemical, and mechanical properties making them significantly relevant in the biomedical industry and hence a subject of research. It can display metallic, semiconducting, superconducting and electron transport properties. It possesses a hollow core suitable for storing guest molecules. CNTs also have the largest elastic modulus of any known materials [18]. It has been proven that CNT drug delivery can be applied for cancer ablation [19]. In the pharmaceutical industry, nanotechnology is employed to formulate therapeutically active agents in biocompatible nano-forms. This can be either as nano-capsules or conjugates. It helps to improve the safety and efficiency of drugs in drug delivery[20]. The application of CNT and its compatibility with other materials improve with time by functionalization. CNTs, if properly functionalized, can be soluble in many solvents. Functionalized CNTs found applications in medicinal chemistry as substrates for vaccines and drug delivery scaffolds. They are less toxic and are also readily driven to cross cell membranes [21].

Carbon Spheres (CS) have unique chemical and physical properties such as good adsorption, low surface energy, manageable size and morphology. They are widely applied in drug delivery, lithium batteries.

In this paper, the Carbon nanomaterials reported are Carbon Fibres and Carbon Nanotubes. The properties of Carbon Fibres and Carbon nanotubes were highlighted in Section 2. The tailored applications of CF and CNT are discussed in Section 3 as relates to their use in Orthotics and Prosthetics, tissue repair and engineering, heart valve repair, pharmacokinetics and drug delivery, regenerative medicine, bone repair, and biosensing. The state of art in the use of CFs and CNTs are briefly presented in Section 4. Finally, a summary of the work is provided in Section 5.

II. PROPERTIES OF CARBON FIBRE (CF) AND CARBON NANOTUBES (CNT)

The Carbon fibre has a graphitic structure with carbon atoms within a layer bonded by covalent and metallic bonds. The bonding between the layers isthe Vander Waals bonding, which makes the carbon layers easily slide over one another. Graphite possesses a difference in the in-plane and out-of-plane bonding and hence has a high modulus of elasticity parallel to the plane and a low modulus of elasticity perpendicular to the plane. Therefore, due to these variations in property across the planes, graphite is highly anisotropic. Hence, to attain a high modulus of carbon fibre, the graphitic crystal orientation is improved by various types of thermal and stretching treatments [22]-[25].

Carbon Fibre has high stiffness, high tensile strength, low weight, high chemical resistance, high temperature tolerance and low thermal expansion. Hence, it is applied in areas of demanding lightweight combined with high mechanical properties [26].

The electrical and thermal conductivity of CFs increases with their purity [15]. The electrical resistivity of CF ranges from 9.5×10^{-6} Ωm to 18×10^{-6}Ωm. CF reinforced composites has an in-plane resistivity of about 5 Ωm. This is closer to bone longitudinal resistivity which is about 45 Ωm when compared with titanium or titanium alloys which are $4.2\text{-}19.9 \times 10^{-7}$Ωm [13].

Furthermore, CF has excellent moisture and chemical resistance at room temperature. However, it oxidizes at high temperatures from 350 - 450^0C and this oxidation may increase with fibre impurity [15], [22], [24]. CF also has excellent fatigue resistance; it shows a complete elastic recovery after unloading.

Carbon Fibres are grouped based on the following.

A. Carbon Fibres based on Modulus Properties

1. Ultra-high-modulus Carbon Fibre (UHM) (modulus >450Gpa)
2. High-modulus Carbon Fibre (HM) (modulus between 350-450Gpa)
3. Intermediate-modulus Carbon Fibre (IM) (modulus between 200-350Gpa)
4. Low modulus and high-tensile Carbon Fibre (HT) (modulus < 100GPa, tensile strength > 3.0Gpa)
5. Super high-tensile Carbon Fibre (SHT) (tensile strength > 4.5GPa)

B. Carbon Fibres based on Precursor Materials

The raw material used in the production of carbon fibre is called the precursor. About 90% of the carbon fibres produced is made from polyacrylonitrile (PAN) while the remaining 10% are made from rayon or petroleum pitch.

1. PAN-based carbon fibre
2. Pitch-based carbon fibre
3. Mesophase pitch-based carbon fibre
4. Isotropic pitch-based carbon fibre
5. Rayon-based carbon fibre
6. Gas-phase-grown carbon fibre.

C. Carbon Fibres based on the Final Heat Treatment Temperature

1. *Type-I, High Heat Treatment Carbon Fibres (HTT):* In this type, the final heat treatment temperature should be above 2000°C and can be associated with high-modulus type fibre.

2. *Type-II, Intermediate Heat Treatment Carbon Fibres (IHT):* The final heat treatment temperature should be around or above 1500°C and can be associated with high-strength type fibre.

3. *Type-III, Low Heat Treatment Carbon Fibres (LHT):* In this type, the final heat treatment temperatures are not greater than 1000°C. These are low modulus and low strength materials.

CF is very unique and highly sought after due to the following under-listed properties.

1. Rigidity or Stiffness: This is measured by its Young Modulus and depicts how much a material deflects under stress.
2. Corrosion Resistant and Chemically Stable: CFs do not deteriorate and are chemically stable and resist corrosion.
3. Electrically and thermally conductive.
4. Excellent Fatigue resistance.
5. Good Tensile strength.
6. Low Coefficient of Thermal Expansion.
7. Non-flammable and Fire resistance.
8. Non-toxic and biologically inert.

Similarly, CNTs are lightweight with high electrical conductivity and tensile strength. The tensile strength of multi-walled CNTs is about 0.15TPa [27]-[29]. Figure 1 is a schematic representation in a log scale of Carbon fibre and Carbon nanotubes. Some key qualities of CF and CNT that are required for biomedical applications are

a. Biocompatibility: Biocompatibility of a material is defined as the ability of the material to perform with an appropriate biological host response in a specific application without causing damage to the host. The material must not induce an un-welcoming response from the host, but rather promote harmony and good tissue-implant integration. It should also not be toxic to the body. For a biomaterial, an initial burst of the inflammatory response is expected and is sometimes considered essential in the healing process. While this initial inflammatory response may be accepted, prolonged inflammation is not desirable as it may lead to tissue necrosis and hence incompatibility.

b. Sterilizability: Sterilization involves treating the material to kill microorganisms without losing its property. Sterilization techniques include gamma, gas (ethylene oxide (ETO) and steam autoclaving.

c. Manufacturability: The success of a material to be used as a biomaterial for medical application does not only depend on biocompatibility. It is often related to the ability and ease of the material to be formed into complicated shapes (that is its manufacturability). Many candidate materials may be biocompatible but may not be easily machined to the desired shape which is a critical factor for medical devices.

It is noteworthy that it may be easy to make a one-off laboratory biomaterial prototype but can be challenging to produce a thousand units of identical devices with the same good quality control and having to be packed and ‘stored’ in a sterile manner before application. This poses a major challenge in the biomedical industry [30]. However, it is believed that with the emergence of additive manufacturing, this need shall be met.

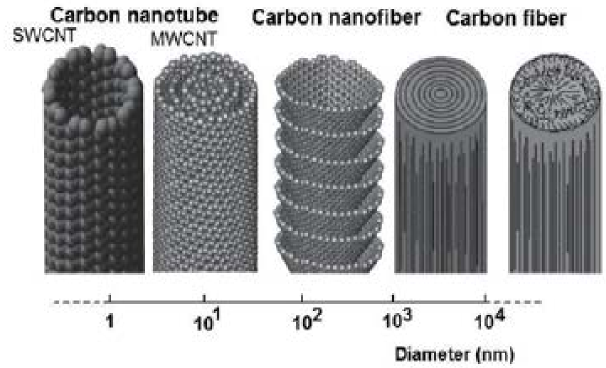

Fig. 1 Log Scale comparisons of the diameter dimensions for the various types of fibrous carbons [31]

III. TAILORED BIOMEDICAL APPLICATIONS OF CFS AND CNTS

Carbon Fibres and Carbon Nanotubes have several applications in the biomedical industry. They are used clinically as a scaffold to induce tissue proliferation for ligament or tendon repairs applied for wound healing processes for soft and hard tissues [28], [29], [32]-[34]. Carbon fibre has as well been proven biocompatible for ligament replacement in human knee reconstruction [12], [35]-[38].

As highlighted earlier, carbon fibre also possesses good electrical conductivity. CF electrodes have been used for neural recording [39]. They are used in applications for voltammetry recognition of biological molecules [40]. Carbon nano-fibre was independently applied to improve the proliferation of cardiomyocytes and it can provide electrical conduction for the stimulation of cardiomyocytes [32], [41]-[43].

Carbon fibre reinforced composite plates stimulated better healing than metal plates when used for bone fracture repairs by internal fixation. This is because carbon fibre allows stress to be applied more uniformly as a lower modulus material [44], [45]. It was reported that an improvement in tensile strength, impact toughness, shear strength, flexural strength, and fatigue strength was shown when discontinuous chopped carbon fibre was added to acrylic bone cement [44].

A. Carbon Fibre used in Orthotics and Prosthetics

Carbon fibre has been employed widely in the manufacturing of orthotics and prosthetics devices. They are used in foot prosthetics due to their ability to provide good energy storage and dynamic response return than any other biocompatible material. The loss of limb from accident, disease, war or fight has increased the demand for fleet feet material giving rise to high demand for carbon fibre. The prosthetics and related orthotics together make up $2.8 billion of the global market [46]. Figures 2-4 are some of the products from the use of CF in prosthetics and orthotics.

Fig. 2 A Bionic Carbon Fibre mechanical hand [47]

Fig. 3 A 3D printed Carbon Fibre Prosthetic Leg [48]

Fig. 4 Carbon Fibre orthotics feet [49]

B. Carbon Fibre and Carbon Nanotube for the Treatment of Bone Fractures

CFs and CNTs are being employed in the treatment of bone and cartilage injuries to facilitate tissue regeneration. The CF is a good scaffold material for bone regeneration and tissue repairs [17], [50], [51]. The nanofibers for the scaffolding in bone regeneration are produced by electrospinning [17]. Figure 5 is a depiction of the electrospinning system. Figure 6 shows a macroscopic and microscopic view of a CF implant in an animal.

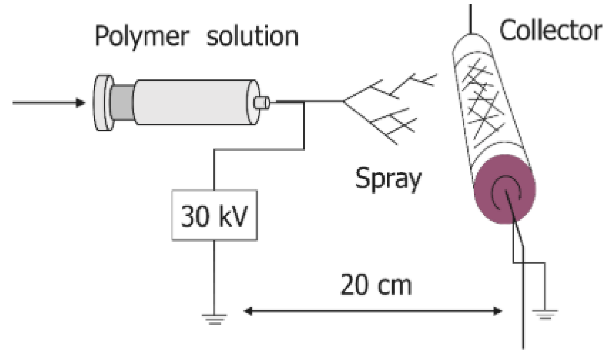

Fig. 5 A schematic diagram of the electrospinning system for producing a thin carbon nanofiber web. The polyacrylonitrile solution was ejected from the needle tip under a high electric field and subsequently deposited in a form of the web on the collector [17]

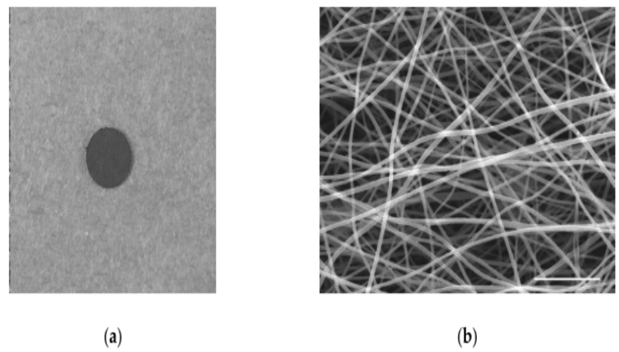

Fig. 6 250 nm type thin carbon nanofiber web (TCFW).
(a) Macroscopic view of an implant for animal testing (diameter: 5 mm);
(b) Scanning electron microscopy image. Nanofibers are presented as web structures. Scale bar, 5 µm [17]

C. Carbon Fibre and Carbon Nanotube for Repairs of Abdominal Wall and Tissue Defect

CFs and CNTs were employed clinically for the repairs of abdominal wall defects. They are available as a prosthetic sheet for bridging abdominal wall defects. Successful repair of abdominal wall defect requires closure of defect without undue tension on the suture line. Abdominal wall defects are repaired to reduce or avoid recurrence rates. Surgeons have used prosthetic materials of different structures and compositions to bridge the tissue defects of large hernias that cannot be approximated primarily without placing excess tension on the suture line [52]-[59]. Figure 7 shows the repairs of a large umbilical hernia in a male calf using carbon fibres.

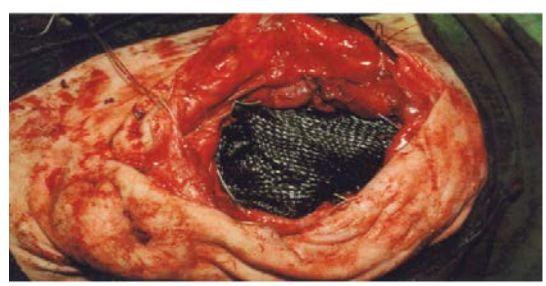

Fig. 7 Repairs of large umbilical hernia in a crossbreed male calf with carbon mesh showing the opening of the hernia sac and placing of carbon mesh for repair of hernia ring as inlay graft [13].

D. Carbon Fibre for the Construction of Heart Valve

Carbon fibres have also found significant application in the construction of human heart valves due to their biocompatibility and ability to lower the incidence of blood clotting. The human heart valve consists of tri-cuspid flaps of flexible living tissue. Due to some health reasons mostly from rheumatic fever, the tissue hardens making the valve to be less efficient. It is therefore medically advisable to replace it with an artificial heart valve or membrane cut from other parts of the same body. Though some materials including chrome-cobalt, polypropylene, and silicon rubber have been used for the construction of human heart valves, recently carbon materials have been mostly employed owing to their biocompatibility advantages as stated initially (Jenkins *et al.,* 1977). Carbon nanofibres embedded PLGA polymer was employed in heart valve tissue engineering application [62]. A biosynthetic collagen-carbon nano fibre scaffold was used for regenerating damaged heart tissue [63].

E. Carbon Fibre in Regenerative Medicine

Effective scaffold materials must be able to hold cytokines or cells at the local application sites and hence facilitate the construction of new tissue. CF was found to be a suitable candidate for this feature. CF is a distinct material that has two strong conflicting and benefiting properties in interaction with biological systems. These two conflicting characteristics include *Bioactivity* and *Bio-inertness*. Also, it has high strength, and because it is bio-inert, it does not corrode in the body. This is expressed relative to the site of application *in vivo*.

In vivo studies on bones showed that bone tissues are easily generated in areas surrounding carbon fibres [64]-[66]. Also in vitro studies showed that osteoblasts cultured on carbon fibres improved cell adhesion and were activated [67]-[69].
The bioactivity of carbon fibre is a critical property that can be exploited for more benefits if truly understood. An investigation is also in progress to ascertain the reason(s) for this bioactivity; why is possible at certain sites? If it was caused by its surface properties, a specific shape, reaction with the sites or because of the latent characteristics of carbon itself. In conclusion, more studies ought to be carried out to ensure an effective application of these wonderful properties of carbon and hence making them applicable as scaffold materials in regenerative medicines.

F. Carbon Nanotubes (CNTs) for Pharmacokinetics and Drug Delivery

Nano-sized systems are the key interest of scientists involved in the design of novel drug delivery systems [70]-[77]. CNTs possess metallic, semiconducting, and superconducting electron transport properties. They have a hollow core suitable for storing guest molecules [78], [79]. CNT is also known to possess the largest elastic modulus of any known materials [18]. Studies on the biomaterial applications of carbon nanotubes have progressed. With regards to their diagnostic applications, CNT based systems possess great potential in improving the existing diagnostic techniques. Though CNTs are promised to have a great impact on biomedical materials, it is worth noting that CNTs are different from conventional carbon fibre and therefore may possess some differences in functionality.

Functionalised CNTs have some beneficial properties in biomedicine and hence CNTs based systems are developed to explore their usefulness in the therapeutic, diagnostic, and analytical applications. Carbon nanotube-based systems have been rigorously investigated in cancer therapy to carry and deliver drugs and to evaluate them for potential lymphatic targeted therapy, gene therapy, thermal therapy and photodynamic therapy [76], [80]-[83]. In addition to their importance in cancer therapy, CNT based systems have been employed for the treatment of genetic disease, fungal infections, neurodegenerative disorders like Alzheimer’s disease, and most often as scaffolds for tissue engineering [84]-[86].

According to some reports, the functionalization of CNT significantly enhances its therapeutic effects and minimizes toxicity. This strengthens the argument that modification of CNTs can have intriguing results and may bring breakthroughs in the therapy of infectious diseases, cancer and neurodegenerative diseases [77], [87], [88].

Now, studies conducted on the pharmacokinetics of CNTs are preliminary. The principle about their cellular uptake and metabolism is yet not very clear and hence cannot be categorically stated to be the safe in-vivo application for now. The data available regarding the pharmacokinetics and immune reactivity of functionalized carbon nanotubes is yet not sufficient. Although it is hypothesized that the safety factor of nanotubes in nano-medicines can be ameliorated [75], [76], [89]. Furthermore, the length and type of tubes have been somewhat implicated in their toxicity. These observations necessitate further research for the synthesis techniques able to produce pure carbon nanotubes with consistent composition at comparable economic costs. Therefore, if the concerns about their toxicity are cleared through comparative and investigative research, the use of CNTs based systems in nanomedicine shall become a reality. Other issues related to the biomedical applications of carbon nanotubes are the inevitable presence of impurities during their processing, the lack of proper predictability of their interaction with the environment, variability in composition and most importantly cost of manufacture [89].This is why it is of ultimate importance that exhaustive research ought to be done in this field and are being carried out. Hence it is expected that this will create a great impact on the pharmaceutical industry.

It is noteworthy that CNTs do not only have therapeutic applications. They have also been investigated for their diagnostic applications. Functionalization of CNTs with various biomarkers can be exploited for the tailoring of handheld devices having ultrasensitive detection limits and huge specificity [89]. This could mean that functionalised CNT can stand at a highly competitive level with conventional diagnostic techniques. Figure 8 shows a schematic for drug delivery and cancer therapy using CNT.

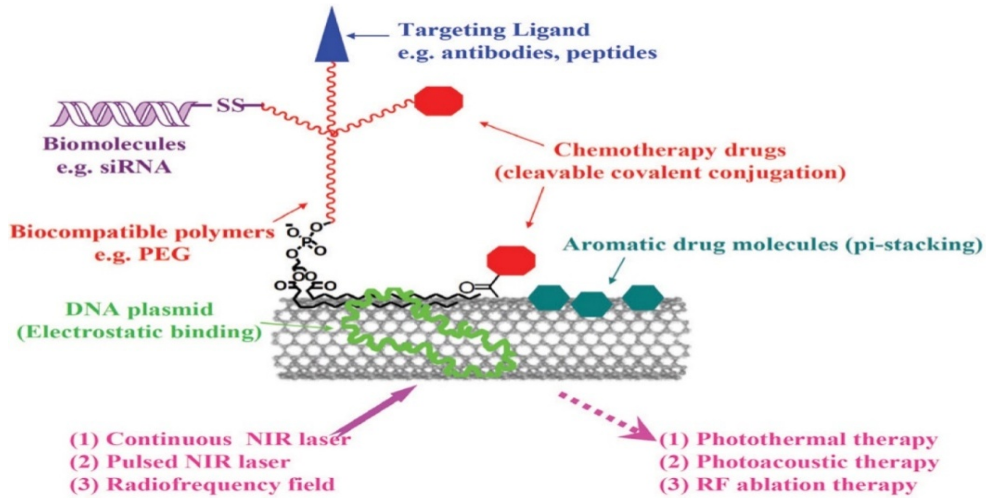

Fig. 8 A schematic drawing showing various approaches for CNT-based drug delivery and cancer therapies [90]

G. Carbon Nanotubes (CNTs) as Biosensors

A biosensor is an analytic device that consists of a receptor that interacts with the targeted analyte to be measured and a transducer (or detector) that transforms the signal from the interaction into a form that can be easily measured [91]. The one-dimensional structure of CNTs permits signals to be conveyed in a restricted space. This makes the CNTs to be very responsive to electrical and chemical changes in their environment [91], [92].

There are generally two main groups of CNT-based biosensors: CNT field-effect transistors (CNT-FETs) and CNT electrochemical sensors (CNT-ECS).

The CNT-FETs were first demonstrated in 1998. They are referred to as the field-effect transistor which uses a single CNT or an array of CNTs as the channel material instead of bulk silicon in the traditional metal-oxide-semiconductor field-effect transistor (MOSFET) structure [93], [94]. The CNT-ECS is also known as Chemiresistors. They are known for their low detection capacity, high sensitivity, and quick response. This is due to their high surface area, low overvoltage and rapid electrode kinetics [95]. CNT based detection systems and biosensors possess excellent specificity, and efficiency and maybe cost-effective [78], [84], [96]. As stated earlier, much work needed to be done in this field to authenticate these features. Figure 9 shows the schematic for Electrochemical and Electronic CNT biosensors.

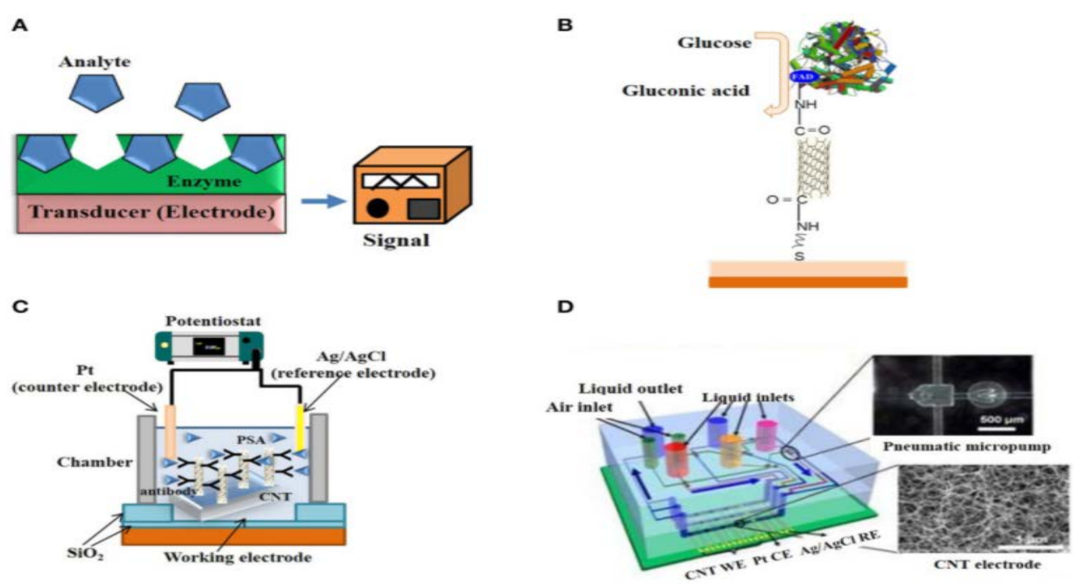

Fig. 9 Electrochemical and Electronic CNT biosensors (A) Typical design of an enzyme-based electrochemical biosensor.
(B) SWNT electrically-contacted glucose oxidase electrode. (C) Schematic illustration of a label-free amperometric biosensor for PSA detection.
(D) Schematic illustration of a microfluidic chip based on CNT electrodes [3]

IV. THE STATE OF ART IN THE APPLICATION OF CARBON FIBRE AND CARBON NANOTUBES AS BIOMEDICAL MATERIALS

CNTs and CFs have been investigated and reported in many areas of medicine for the past 25 years [13]. The biomedical test has proven that a high proportion of living organisms are composed of carbon compounds. This shows that carbon fibre can be tolerated by tissues. In the early period of the application of CF in medicine, one of the appreciated uses was the replacement or repair of ligaments and tendons with carbon fibre [4], [7], [37], [60], [97] and in orthopaedics, as implant when reinforced with PEEK [98]. The physical and chemical properties of carbon fibres are determined by their microstructure, and this is important in biomedicals. Most studies on carbon fibre implants show that carbon fibres do not inhibit tissue growth rather disintegrate into lymph nodes hence can be used as a scaffold for tissue proliferation [8], [54], [99]-[102].

Though there were various views on the mechanism of the disintegration of carbon fibre with details on how the implanted carbon fibres could be removed or disintegrated. Becker *et al.,* [97] proved that the implanted carbon fibres broke and migrated gradually into the nearest lymph nodes without causing any detrimental health effects. On the other hand, it was reported that fragmentation of fibres did not occur, and implant debris was not found in the regional nodes. They claimed that carbon fibres significantly induced more tissue in growth than polypropylene mesh within 6 -12 months [103].

It has been established from several studies that CF and CNT acted as a scaffold for the regeneration of tendons and ligaments (Lekshmi *et al.,* 2020; Lewandowska-Szumieł *et al.,* 1999; Zhengni Liu *et al.,* 2014; Ma, 2008; Rajzer *et al.,* 2010; Shen *et al.,* 2021; Suri & Schmidt, 2009). CFs was considered a good biomaterial in the form of composites for total hip replacement and internal fixation. Recent research on the biomedical properties of carbon fibre at the nano-level in form of CNT has proven that carbon fibre possesses great biomedical applications that are yet to be exploited. CNTs' ability to be hybridized with other organic and inorganic materials makes them excellent candidates for many biomedical applications such as biosensing [3], [29], [91], [92], [109], [110] tissue engineering [72], [84]-[86], [111] and drug delivery [2], [72], [74], [75], [112]-[114].

V. CONCLUSION

Carbon Fibres (CFs) and Carbon nanotubes (CNTs) are very propitious candidates for the development of new biomedical devices. The discovery of new Carbon-based nanomaterials for health care is thriving, particularly in the development of advanced composites for biomedical applications. Carbon fibre, are cognised carbon nanomaterial is significant for its applications in prosthesis and orthopaedics. It has been used for the repair of bones and cartilage, repairs of abdominal wall defects, replacement of tissues and as an effective scaffold material. In addition to their importance in prosthesis and orthotics, carbon fibre in the form of functionalised carbon nanotubes have been employed for the treatment of genetic disease, fungal infections, neurodegenerative disorder and for cancer therapy. Carbon fibres in the form of carbon nanotubes have also proven potential importance for medical diagnostic applications. The current challenge in the application of carbon fibres for biomedical applications isthe issues regarding regulation to enable the authorised applications of most of the discovered features and most importantly, exhaustive research activities to conclude the present potential application. In conclusion, carbon fibres have continued to gain recognition as the healthy choice in prosthetics and implant surgery and it also possesses potential astonishing uses through nano-fibres and functionalised systems (Carbon nanotubes). CNTs have been applied as biosensors in nanofluidic applications and are used in drug delivery. Therefore, it is recommended that more research is required to explore these potential uses.

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