Vietnam Journal of Science and Technology ***62*** *(4) (2024) 615-634*

doi:10.15625/2525-2518/19824

Bio-based nanomaterials and their biomedical applications: a short review

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Received: 1 January 2024; Accepted for publication: 2 July 2024

Abstract. Recent advancements in biomedical technologies have led to the exploration of bio-based nanomaterials, which offer exceptional properties such as high surface area, biocompatibility, and environmental friendliness. Additionally, the bio-based nanomaterials are widely available and provide a sustainable architecture for various applications. This review highlights three distinct nanomaterials synthesized from and/or with bio-sources: nanocellulose, silver nanoparticles, and carbon dots/carbon quantum dots, representing natural polymers, metallic nanoparticles, and organic nanoparticles, respectively. This review discusses their synthesis methods and their potential applications in tissue engineering, wound healing, and biosensing. The review also includes an outlook on the utilization and challenges of these nanomaterials in biomedical applications.

Keywords: nanomaterials, medical application, nanocellulose, biosensors, carbon quantum dots.

Classification numbers: 2.7.1, 2.7.2.

1. INTRODUCTION

The term ‘biomaterials’ is defined as “materials intended to interface with biological systems to evaluate, treat, or replace any tissue, organ or function of the body” or “any synthetic material which is used to replace part of a living system or to function in intimate contact with

the living tissue" [1]. Nanomaterials, on the other hand, are useful functional materials that are between 1 and 100 nm in size and larger than a single atom or smaller groups of atoms [2]. Depending on their dimensions, bionanomaterials can take on many forms. Three-dimensional (3D), two-dimensional (2D), one-dimensional (1D), and zero-dimensional (0D) can all be classified. While 1D nanomaterials take the form of nanofibers, nanowires, and nanotubes, 0D nanomaterials are often quantum dots or metal nanoparticles like silver and gold nanoparticles. Thin films, multi-layered thin films, nanosheets, and nano-walls are larger-scale 2D nanomaterials, whereas 3D nanomaterials are bulk materials made up of discrete macroscale-sized particles [3]. The development of biomedical applications, particularly for tissue engineering, wound healing, and biosensors, has been facilitated by the intriguing features of bio-based nanomaterials. This review comprises three different nanomaterials produced from natural or bio-sources, will explore the potential of these nanomaterials in tissue engineering, wound healing, and biosensors. Nanocellulose, including cellulose nanofibers (CNFs), cellulose nanocrystals (CNCs), and bacterial cellulose are a type of biopolymer that can be produced from natural sources, mainly plants and bacteria while the other two nanomaterials included in this review are metallic and organic nanoparticles, which are silver nanoparticles (AgNPs) and carbon quantum dots (CQDs), respectively.

2. BIO-BASED NANOMATERIALS

Recent innovations in nanotechnology for biomedical engineering have led to the exploration of various types of nanomaterials. For use in biomedical applications, nanomaterials must be non-toxic, biocompatible, hydrophilic, and non-immunogenic to avoid adverse effects on humans [4]. With a focus on the sustainable architecture of nanomaterials, natural sources have been increasingly utilized in their production. For example, agricultural wastes have been used to synthesize CO_2 adsorbents for environmental applications and supercapacitors for energy applications [5, 6]. The nanomaterials synthesized from natural materials, particularly from plants and microorganisms, are attracting the interest of researchers due to their comparable physical and chemical properties. This section emphasizes the potential of three different categories of nanomaterials: biopolymers, metallic nanoparticles, and organic nanoparticles, represented by nanocellulose, AgNPs, and CQDs, respectively.

2.1. Nanocellulose

Nature's most abundant polymer, nanocellulose, has been considered as biopolymer with a wide range of applications due to its physicochemical properties. The nanocellulose is an appealing material for biomedical applications, particularly for producing scaffolds, due to its lightweight nature and high mechanical strength [7]. Additionally, it is non-toxic, hydrophilic, biodegradable, and biocompatible [7]. As a derivative of cellulose which is constructed by a linear polymer of anhydro-D-glucose units linked together via β-1,4-glycosidic linkage, nanocellulose can be divided into three types, which are CNFs, CNCs, and bacterial cellulose (BC) [8, 9]. To promote sustainability and environmental safety, agricultural wastes and plant-based biomass, such as rice straw, rice husk, pineapple leaves, sugarcane bagasse, and oil palm waste, are being used for nanocellulose production [10].

In most cases, the CNFs and CNCs are produced by mechanical and chemical treatments from plant sources, whereas BC is produced through the extracellular excretion of bacteria [8, 9]. Typically, a stable nitroxyl radical, 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO), is used

for the selective oxidation of the cellulose C6 hydroxyl group (-OH) into a carboxyl group (-COOH) to produce CNFs [11]. Under the oxidation system of TEMPO/$NaClO_2$/NaClO or TEMPO/NaBr/NaClO at pH 10-11, the negative charges of the carboxyl groups weaken the intermolecular hydrogen bonds [11]. This results in nanosized cellulose or nanofibers with widths of 25-40 nm and crystallinity of 50 - 70 % [12, 13]. Another method involves mechanical treatment, which includes crushing, grinding, and the impact and attrition produced by the tumbling and rolling of balls in a ball mill [14]. This method produces cellulose fibrils or nanofibers with a rope-like shape, measuring 50 nm in diameter and up to 2 µm in length [14]. Additionally, cellulosic materials can be processed through a high-pressure homogenizer. The rapid pressure changes in the homogenizer rupture amorphous cellulose, producing CNFs between 10 and 20 nm in diameter [15]. Although mechanical treatments are straightforward and avoid the use of harsh and hazardous chemicals, they require high energy consumption, leading to increased operational costs. Therefore, the TEMPO oxidation method is preferred, as it offers flexibility in reaction conditions and rapid processing. Different from CNFs, CNCs which are highly crystalline with rigid rod-like structures, is commonly produced by acid hydrolysis using sulfuric acid having an average diameter of 5 - 60 nm and a length of 100 - 300 nm [16]. The use of strong acids in CNC production results in consistent end products with a whiter color after drying due to the low content of lignin and hemicellulose [7]. Additionally, the CNCs are purer compared to CNFs, despite being produced from different plant sources [7].

In addition to plant sources, nanocellulose can be naturally produced through the extracellular excretion of certain bacteria, most commonly from the genera *Gluconacetobacter*, *Acetobacter*, *Rhizobium*, *Agrobacterium*, *Achromobacter* [17]. This type of nanocellulose is known as BC. These bacteria are typically cultured on standard Henstrin and Schramm (HS) medium under optimal temperature and pH conditions [17]. The BC forms 3D networks of ribbon-like fibers with diameters ranging from 25 to 115 nm [18, 19]. The BC has excellent properties, including high crystallinity (48 – 89%) and thermal stability (220 - 360 °C) [20]. Compared to other methods, biologically produced nanocellulose is purer, as it is free from contaminants such as extractives, lignin, and hemicellulose. This purity makes BC particularly suitable for biomedical applications.

2.2. Silver nanoparticles

Metallic nanoparticles have become one of the nanomaterials used for the advancement of biomedical applications as they offer unprecedented capabilities due to their physical, chemical, and biological properties. In medical field, silver nanoparticles (AgNPs) are one of the widely discovered metallic nanoparticles due to the remarkable versatility as they exhibit high surface area-to-volume ratio and antibacterial, antioxidant, and anti-inflammatory activities [4]. Research has established different synthesis methods in terms of physical, chemical, and biological pathways such as laser ablation, chemical vapor deposition, reduction reaction, and microbiological reactions [21]. These synthesis methods each comes with several advantages and disadvantages. The physical synthesis methods would give rapid reaction and requires no involvement of harmful chemicals and radiation but the issues such as solvent contamination, high energy consumption would cause the AgNPs produced to be distributed non-uniformly and gives out low yield [22]. Meanwhile, the chemical synthesis method practically requires the use of silver nitrate ($AgNO_3$) as a precursor and trisodium silicate and sodium borohydride as the reducing and stabilizing agents [23]. The chemical synthesis of AgNPs can give high yield but the process is costly and involves the use of hazardous chemicals as well as producing poorly defined size of AgNPs and particle aggregation [22]. Therefore, researchers have been working

on the green method, which is more environmentally friendly, cost effective, time-efficient, and sustainable using plant extract from various natural sources that produces stable, clinically adaptable, and biocompatible AgNPs [24].

In general, the green synthesis of AgNPs is done using the oxidation reaction of Ag^{+} to Ag^{0} by different biomolecules such as flavonoids, ketones, aldehydes, tannins, and carboxylic acids obtained from plant extracts to act as a reducing agent and a stabilizing agent [23]. Different parts of plants of interest including the seeds, petals, barks, stems, and leaves will be cleaned before being extracted for the synthesis process. The different morphology of AgNPs synthesized from different plant sources is presented in Table 1.

Table 1. Different sources of plant extracts for the green synthesis of AgNPs.

Plant	Part used	Particle size (nm)	Shape/ Morphology	Ref.
Syzygium cumini	Fruit extract	47 - 52	Spherical	[25]
Tagetes erecta	Flower petal extract	24 - 49	Spherical	[26]
Araucaria angustifolia	Pine nut extract	~90	Spherical	[27]
Calendula officinalis	Flower petal extract	<100	Truncated prisms	[28]
Ocimum sanctum	Leaf extract	20 - 35	Spherical	[29]
Cucumis prophetarum	Leaf extract	30 - 50	Spherical	[24]
Curcuma longa L.	Plant extract	10 - 40	Spherical	[30]
Achillea wilhelmsii	Plant extract	20 - 80	Cubic	[30]
Matricaria chamomilla L.	Plant extract	10 - 30	Spherical	[30]

In the synthesis of AgNPs, there are a series of parameters to be considered for the synthesis process which are the concentration of plant extracts, concentration of $AgNO_3$ precursor, reaction temperature, pH of the system, and reaction time [31]. The formation of AgNPs can be characterized by UV-vis spectroscopy, Fourier transform infrared (FTIR) spectroscopy, scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffraction (XRD), zeta potential measurement, and dynamic light scattering (DLS) measurement [31]. Using UV-vis spectroscopy, the successful formation of AgNPs can be determined by the surface plasmon resonance (SPR) phenomenon where a broad absorption peak appears around 400 - 450 nm due to the oscillating free electrons in the AgNPs simultaneously with the light wave resonance [23]. This will be accompanied by the color change in the solution from colorless to dark brown as the reduction process happens when the $AgNO_3$ is added into the plant extracts [32]. The FTIR spectroscopy could help to determine the functional groups from the plant extract biomolecules that involved in the stabilization and reduction of the AgNPs such as alkanes, ketones, and amines; while XRD would help to determine the crystal size and lattice parameters of the AgNPs [31, 33]. Furthermore, the morphology of the synthesized AgNPs can be investigated from SEM and TEM images. On the other hand, the stability of the AgNPs can be investigated from their surface charge by Zeta potential measurement; while the particle size and the size distribution would be determined from dynamic light scattering [31].

2.3. Carbon dots/carbon quantum dots

A carbon-based nanomaterial called carbon quantum dots (CQDs), commonly referred to as CDs, has been employed in a variety of biomedical applications. The CQDs are sp^2 or sp^3 hybridized carbon atoms that are composed of 0D nanomaterials with a particle size of less than 10 nm and quasi-spherical [34]. Beginning with the discovery of fluorescent nanoparticles by Xu *et al*. in 2004 [35] who purified single-walled carbon nanotubes made from arc-discharge soot and the use of the term "carbon quantum dots" by Sun *et al*. in 2006 [36], the CQDs have been used for their distinctive properties such as low toxicity, biocompatible, hydrophilic, high conductivity, chemically stable, and having fluorescence emission effect [35 - 37]. The CQDs can be produced with either a top-down or bottom-up strategy. To transform bulk-sized carbon sources into nano-sized quantum dots, the top-down approach uses techniques like laser ablation, electrochemical carbonization, chemical ablation, and mechanical milling [38, 39]. The latter approach involves techniques such as pyrolysis, thermolysis, hydrothermal or solvothermal, and microwave irradiation.

Table 2. Properties of CDs/CQDs synthesized from different natural sources by hydrothermal and solvothermal reactions.

Source	Reaction conditions	Purification	Morphology	Fluorescence color	Ref.
Purple Perilla	260 °C, 5 h	Filtration, dialysis	Spherical, < 5.0 nm	Blue	[40]
Cabbage	140 °C, 5 h	Centrifugation, dialysis	Quasi-spherical, 2.0 - 4.0 nm	Blue	[41]
Catharanthus roseus	200 °C, 4 h	Filtration	Spherical, 5.0 nm	Blue	[42]
Corn cob-derived graphite powder	220 °C, 12 h	Filtration	Quasi-spherical, 4.0 - 6.0 nm	Blue	[43]
Red lentils	200 °C, 5 h	Centrifugation, filtration	Spherical, 4.0 - 10.0 nm	Blue	[44]
Source	Reaction conditions	Purification	Morphology	Fluorescence color	Ref.
Phyllanthus acidus	200 °C, 12 h	Filtration	Spherical, 5.0 nm	Blue	[45]
Dwarf banana peel	200 °C, 24 h	Filtration	Spherical, 4.0 - 6.0 nm	Blue	[46]
Banana juice	150 °C, 4 h	Filtration, centrifugation	Spherical, 0.5 - 2.5 nm	Blue	[47]
Chia seeds	180 °C, 4 h	Centrifugation, filtration	Spherical, < 10.0 nm	Bright green	[48]
Curcuma zedoaria	220 °C, 12 h	Centrifugation, filtration, dialysis	Spherical, 2.5 - 7.2 nm	Blue	[49]
Gingko leaves	220 °C, 10 h	Centrifugation, filtration	Spherical, 3.8 - 5.8 nm	Blue	[50]
Lemon juice	280 °C, 12 h	Filtration	Spherical, 3.0 - 5.0 nm	Green	[51]

Recent innovations consider the sustainability aspect in the synthesis process, hence making the researchers work with green synthesis. To produce CDs and CQDs, the green synthesis route incorporates the use of natural sources such as plant extracts as a carbon

precursor using hydrothermal or solvothermal carbonization process. This method is highly recommended due to its rapidity, safety, lack of use of hazardous chemicals, and ability to produce quantum dots with a high fluorescence quantum yield [37]. Different sources such as perilla leaves, cabbage, corn cob, and banana have been utilized to produce CQDs with spherical shape with a particle size of less than 10 nm (Table 2).

Other than the morphology, particle size, and particle size distribution of CQDs that can be characterized from TEM, it is also important to investigate the optical properties using UV-vis spectroscopy and fluorescence spectroscopy (PL). Malavika *et al*. mentioned that most CQDs produced from biomass sources exhibited blue fluorescence in which the fluorescence may be related to surface functional groups such as C=O and C=N [52]. Additionally, the characterization of CQDs includes FTIR spectroscopy and X-ray photon spectroscopy to further investigate the surface functional groups and qualification of surface states [46]. A series of processes such as centrifugation, dialysis, and filtration are usually performed to purify the CQDs from carbon by-products [53].

3. BIO-BASED NANOMATERIALS IN BIOMEDICAL APPLICATIONS

3.1. Tissue engineering

Tissue engineering, a multidisciplinary subject that first emerged in the 1980s, focuses on restoring living tissues and organs by employing natural or synthetic materials as scaffolds to replace or regenerate damaged tissues and organs [54]. Extracellular matrix (ECM) is a vast network of proteins and other chemicals found in a living human body that surrounds, supports, and gives structure to the body's cells and tissues [55]. In addition to its role in the repair of damaged tissues, the ECM also performs several crucial roles in healthy tissues, including acting as growth factor reservoirs, offering structural support for residing cells, influencing the mechanical properties of the tissues, and providing bioactive signals for cell response [55, 56].

However, depending on the scaffold material's characteristics, implanting it in the human body may result in foreign body reactions. The response begins with proteins from blood and tissue fluids being absorbed onto the scaffold surface. The target organ's tissues and cells or inflammatory cells will then approach the scaffold. Following the attachment of cells, certain proteins will bind to selected matrix proteins that have been released from the scaffolds [57]. Cellular processes like proliferation, differentiation, and phagocytosis will then begin. The functions of native ECM in the tissue of interest must therefore be able to be mimicked by tissue-engineered scaffolds. The porosity, pore size, adhesion, surface chemistry, roughness, biocompatibility, biodegradability, hydrophilicity or hydrophobicity, and mechanical properties of the materials are some of the factors that must be taken into account when constructing the scaffolds [58, 59]. Tissue-engineered scaffolds have been created using a variety of processes, including simple solvent casting, freeze drying, gas foaming, compression molding, injection molding, electrospinning, and 3-D printing [58, 60].

Finding the best material to use as scaffolds to encourage the regeneration of damaged tissues or organs is difficult because other considerations including production costs, processing ease, toxicity, and sustainability must also be considered. Nanocellulose-based scaffolds, particularly those made of plant-derived cellulose, provide high biocompatibility, flexibility, and a 3D hierarchical porous structure that would be useful for use in tissue engineering [7]. Amaral *et al*. produced CNF-poly(globalide) bilayer films made from babassu coconut (Attalea speciosa) derived CNFs as an epidermal scaffold by making use of the strong inter- and

intramolecular interactions of hydrogen bonds in the structure of CNFs [61]. The CNF-poly(globalide) bilayer films were able to accumulate exudates and keep the area around the damaged area wet owing to the large specific surface area of the CNFs. This effectively encouraged the proliferation of keratinocyte cells. Additionally, a hydrogel scaffold made of highly porous wheat bagasse-derived CNFs, sodium alginate, and hydroxyapatite (CNF/SA/HA) has a compressive stress of 419 MPa and a compressive modulus of 1233 MPa at 50% compressive strain, resulting in an exceptional mechanical strength [62]. Moreover, the presence of CNFs aided in boosting the bioactivity of the scaffolds, as demonstrated in the study by Mohammadalipour *et al*., where a scaffold made of polyhydroxybutyrate (PHB) and CNFs derived from wheat straw displayed higher levels of bioactivity than a neat PHB scaffold [63].

The high aspect ratio, large surface area, and exceptional mechanical strength (Young's modulus of 167.5 GPa) of CNCs are a result of their high crystallinity and needle-like structure, which makes them appropriate for use as tissue-engineered scaffolds [64]. After 24 to 72 hours, a scaffold made of cotton-derived CNCs, chitosan, sodium alginate, and hydroxyapatite not only demonstrated great compressive strength but also successfully supported osteoblast MG63 cell proliferation [64]. Furthermore, an electrospun scaffold of rice husk-derived CNCs and poly(lactic acid) (CNC/PLA) composite sized 5 x 5 cm was transplanted on calvarial defect model rats to result in a significant reduction in defect size without any inflammation during the 3 weeks of transplantation [65]. Generally, the CNCs are produced by acid hydrolysis of cellulose with sulfuric acids which causes sulfonate groups to attach and replace the hydroxyl groups on the cellulose structure [66]. The sulfonate groups connected to CNCs' structure aid in promoting cell adhesion and proliferation, therefore their use as a nanofiller is not restricted to enhancing the scaffold's mechanical strength. Additionally, it has been shown that sulfonated CNCs mimicked the sulfonate ECM glycosaminoglycans (GAG) that are involved in enhancing cellular functions [67].

Scaffolds with antimicrobial properties are highly promising for preventing microbial infections in real-world applications, alongside their good mechanical strength. Nanoparticles such as AgNPs and CQDs possess beneficial attributes including antibacterial and anti-inflammatory effects, high chemical stability, and biocompatibility [23, 37]. However, they are not suitable as standalone materials for tissue engineering. Instead, these nanomaterials are often incorporated into scaffolds or hydrogels to enhance their properties. The goal of scaffolds and hydrogels is to mimic the function of the ECM, providing support and facilitating the repair of damaged tissues [57]. The incorporation of nano-sized AgNPs and CQDs helps prevent bacterial infections at the targeted areas, improving the effectiveness of the scaffolds and hydrogels. Hasan *et al*. demonstrated that incorporating AgNPs into a composite of chitosan and carboxylated CNCs resulted in nearly 100 % antimicrobial activity against both *Escherichia coli* (*E. coli*, gram negative) and *Enterococcus hirae* (*E. hirae*, gram positive) bacteria [68]. Similarly, Geng *et al*. developed a hydrogel scaffold containing both positively and negatively charged CQDs, which exhibited excellent antimicrobial activity against *E. coli* and *Staphylococcus aureus* (*S. aureus*) [69]. This scaffold showed impressive results in repairing infected bone defect in mice, with 97 % new bone area regenerated after 60 days [69].

3.2. Wound healing

Being the biggest organ of the human body, skin serves as the first line of defense against injuries and microbial invasion in addition to regulating and secreting bodily fluids. When a part of the skin is wounded, the wound-healing process begins right away when the immunological and biological systems interact and this process continues until the wound is fully healed [70].

Four stages make up the healing process: coagulation and homeostasis, inflammation, proliferation, and remodeling. Vasoconstriction, coagulation, and the development of a fibrin clot start happening as soon as the skin is injured, mostly to stop excessive blood loss. The inflammatory stage then follows to create a protective barrier against invasive infections or other foreign materials and to isolate the damaged section [70]. The proliferation of the epithelial cells surrounding the wound site and the development of granulation tissues start about three days after the wound starts. After the proliferation stage, which lasts for two to three weeks, the wound moves on to the remodeling stage, which can last weeks or more [71, 72]. During this stage, new epithelium is formed, and the collagen type is restored.

A chronic wound is defined as a wound that does not progress through an orderly and timely healing process, leading to subpar anatomical and functional outcomes. An acute wound is defined as a wound that progresses through the healing process in an orderly and timely manner to result in the restoration of anatomy and functions [73, 74]. The purpose of the inflammatory stage in the normal wound healing process is to prepare the wound bed for healing by forming a barrier against pathogens such as bacteria and foreign objects. Although inflammation is a self-limiting process under normal circumstances, in the case of a chronic wound, it promotes further injury and allows for unrestricted inflammation [73]. Commercially available wound dressings come in both passive and interactive or bioactive varieties. The passive type, such as gauze dressings, is by nature non-occlusive, absorbs wound exudates, and covers the wound to allow restoration of skin functions [75]. However, because of the adhesion to the skin, this type of wound dressing can cause additional damage when replaced and is poor at preventing bacterial infection [76, 77]. Another type of wound dressing has been developed by recent research, and it consists of interactive or bioactive materials that come in a variety of forms, including films, hydrogels, nanofibers, and hydrocolloids. These materials serve as a barrier against bacterial infection at the wound site [75, 76].

The porous structure of hydrogels and aerogels is highly advantageous to: (1) absorb wound exudates and provide a moist or tissue-like environment surrounding the wound sites, (2) effectively facilitate the release of bioactive moieties to the wound sites, (3) provide oxygen permeability, and (4) maintain tissue temperature and blood flow in the wound site, is what led to the development of these materials for use as wound dressings [75, 78, 79]. Moreover, hydrogels are simple to remove without affecting the wound site. Due to its special properties, including purity, biocompatibility, the ability to maintain a fine and continuous fibrillar network in either dry or wet state, high mechanical strength (individual Young's modulus of 138 GPa and tensile strength of > 2 GPa), flexibility, high water holding capacity, shape moldability, and biodegradability, bacterial cellulose has significant potential as a material for wound dressing [80 - 82].

Composite hydrogels made of bacterial cellulose and various materials have been produced because bacterial cellulose-based hydrogels must have an antimicrobial action to function effectively as a wound-healing material. Deng *et. al*. developed an injectable self-healing hydrogel with excellent properties against *E. coli* and *S. aureus* with a killing rate of 90.9 % and 96.0 %, respectively [83]. This hydrogel was made of hydroxypropyl trimethylammonium chloride chitosan and dialdehyde-modified bacterial cellulose. Moreover, a nanocomposite hydrogel made of bacterial cellulose, gelatine, and selenium nanoparticles (BC/Gel/SeNP) was developed and demonstrated approximately 100 % antimicrobial efficiency against the bacterial strains of *E.coli* and *S. aureus* [84]. The BC/Gel/SeNP hydrogel exhibited approximately 96 % wound healing efficiency with the greatest production of granulation tissues after 14 days of treatment from a full-thickness skin defect model on rats, attributed to its outstanding

antimicrobial effect. In addition, the observation revealed that the connective tissues and epithelium were more regularly arranged, new blood vessels, fibroblasts, and hair follicles had formed, and no inflammation had developed during the hematoxylin and eosin staining test, all of which suggested a superior wound healing process. Another composite hydrogel made of bacterial cellulose and $Ti_3C_2T_x$ MXene (BC/MXene) was reported to have low toxicity because inactive lactate dehydrogenase activity was seen after 3 days, though there was no information on its antimicrobial activity [85]. This hydrogel has great properties such as high mechanical strength, flexibility, the ability to recover its shape after compression, and high electrical conductivity of 7.04×10^{-4} Scm^{-1}. In a full-thickness skin defect model on Sprague-Dawley rats, the BC/MXene hydrogel's potential in wound healing was demonstrated by a substantial reduction in wound area after 7-14 days. Interestingly, the BC/MXene hydrogel's ability to heal faster with the introduction of electrical stimulation was demonstrated by the fact that 93.8% of the wounds closed [85].

Utilizing nanoparticles such as AgNPs and CQDs as an antimicrobial agent in film- or sheet-based wound dressing materials is another method of producing bioactive wound dressing. A hydrogel made of chitosan and AgNPs produced from *Calendula officinal* was effectively tested on two diabetic patients as the wound dressing on their ulcers, demonstrating the efficacy of plant-based AgNPs in wound healing [28]. Regular replacement of the hydrogel dressing following the state of the wounds produced good results because the wounds healed while experiencing less pain and inflammation during treatment. A cotton fabric was coated with AgNPs synthesized from *Curcuma longa L.* leaves, which showed no toxicity when tested on fibroblast (L929) cells [32]. The wound healing activity of the cotton fabric loaded with the AgNPs was tested on wounded fibroblast (L929) cells, revealing a noticeable increase in cell migration [32]. This suggests active proliferation and growth of the fibroblast cells [32]. Furthermore, Cui *et al*. developed a hydrogel consisting of cationic CQDs, pectin, and acrylic acid to test its *in-vivo* antimicrobial activity and efficacy in wound healing [86]. When this hydrogel, injected with 1 mL of *S. aureus* (10^5 CFU/mL), was implanted on a rabbit's back wound in a subcutaneous model and observed for 7 days, the result was a nearly healed wound with no infection on the surrounding tissues [86]. Another notable invention by Huang *et al*. combined AgNPs and ZnO decorated with N-doped CDs (N-CD@ZnO) into a xerogel to accelerate the wound healing process [87]. In a test where the AgNP/N-CD@ZnO xerogel was applied to a 12 mm circular wound on the back of mice, complete healing was achieved after 10 days [87]. The combination of these nanoparticles contributed to the release of reactive oxygen species (ROS), enhancing sterilization and wound healing [87]. The use of these nanoparticles is highly efficient in wound healing. However, several drawbacks, such as issues with morphological uniformity, potential toxicity to living organisms after prolonged exposure, and environment release, must be further investigated, as these issues could have negative consequences [4, 88].

3.3. Biosensing

The International Union of Pure and Applied Chemistry (IUPAC) defines a biosensor as "a self-contained integrated device, which is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element (biochemical receptor) which is retained in direct spatial contact with an electrochemical transduction element" [89]. The foundation of biosensors started from the studies conducted by Clark and Lyons in 1962 while the first commercialization of a biosensor was done by Springs Instruments in 1975, in which the biosensor was used to detect blood glucose levels in diabetes patients [90, 91]. In

general, biosensors are made up of several components, including a baroreceptor or bio-recognition element that recognizes the target analyses, a transducer that converts bio-recognition events into measurable signals, and electronic components such as an amplifier and processor that create the output signal [90]. The categorization of biosensors can be either based on the type of transducer (electrochemical, calorimetric, thermoelectric, piezoelectric, and optical biosensors) or based on the biorecognition element (enzymatic, microbial, antibody, cell, and tissue, and nucleic acid biosensors) (Figure 1) [92, 93]. Most operations of biosensors involve electrochemical detection such as aerometric, potentiometric, impedimetric, and capacitive, and conduct metrics [94]. For the development of biosensors, it is important to continuously keep focus on the following parameters: (1) sensitivity, which is the relationship between intensity of the transducer's signal and changes in the concentration of the bio-analyte; (2) selectivity, which is the response to the presence of foreign or interfering substances; (3) range, which is the maximum output signal that can be detected by a sensor; (4) reproducibility, which is the capacity to obtain consistent results when measuring the same sample more than once; and (5) stability, which is the biosensor's maximal response over some time [90, 93].

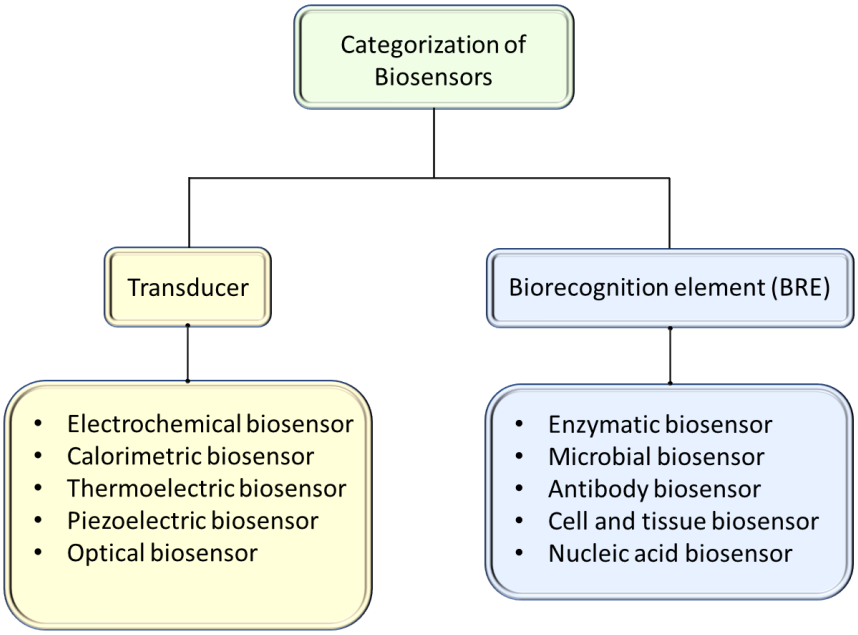

Figure 1. Biosensor classifications based on the type of transducers and bio-recognition elements.

Recent developments in biosensors emphasize the need for environmentally friendly materials that maintain their functional properties. Nanocellulose, a natural polymer derived from various sources, stands out as a promising material for advanced biosensors due to its high surface area, strong mechanical strength, availability, and biocompatibility [95]. For instance, an electrochemical biosensor made from AgNP-decorated nanocellulose paper has shown great potential for glucose detection [96]. Additionally, nanocellulose has been used as a supporting base on a cellulose paper substrate to develop a colorimetric biosensor for glucose detection [97]. Another innovative example is a colorimetric biosensor composed of Fe-doped CDs and nanocellulose composite paper, designed hydrogen peroxide and glucose detection, which utilizes a smartphone monitoring system [98]. Beyond its functional benefits, nanocellulose is also cost-effective. Bacterial cellulose (BC) was employed as a substrate in an immunosensor,

which included a BC substrate coated with chitosan and chondroitin sulfate, to detect the cancer biomarker p53 antigen in MCF7 lysates [99]. This system achieved a limit of detection (LOD) of 0.16 UmL^{-1} [99]. These innovations highlight a new paradigm in the use of biodegradable nanomaterials, showcasing nanocellulose-based biosensors as environmentally friendly and sustainable solutions with advanced technological capabilities.

AgNPs possess unique optical properties, particularly localized SPR, which occurs due to the excitation of their freely moving electrons by visible light [21]. The SPR of AgNPs is notable because it is highly sensitive to surface-adsorbed molecules and can be tuned by varying the concentration of these molecules [21]. An SPR-based biosensor consisting of AgNPs coated with a graphene film on a glass substrate demonstrated excellent selectivity, with an increase as high as 304.6 % [100]. This suggests an improved plasmonic response for biosensing applications due to the interaction between the AgNPs and graphene [100]. Another biosensor, a colorimetric sensor made from lignin-stabilized AgNPs derived from *Dimocarpus longan*, was tested for selective hydrogen peroxide detection in blood serum of hypertension patients [101]. In another study by Hou *et al*., AgNPs were utilized to create networks that amplified the electrochemical signal in an amperometric biosensor designed to detect the wild-type p53 protein [102]. The amperometric biosensor, incorporating the AgNPs, demonstrated high selectivity and impressive detection performance when tested on wild-type p53 protein in various cell lysates, including MCF-7 cancer cells and normal nerve PC12 cells [102].

Fluorescent detection offers several benefits, including high sensitivity, rapid response, reproducibility, and stability [103]. CDs and CQDs are particularly suitable materials for this purpose due to their remarkable optical properties [103]. The fluorescence intensity of CQDs was utilized in a biosensor developed with single-stranded DNA (ssDNA) and CQDs for the detection of acrylamide in food products [104]. The ssDNA acted as a biological recognition element, causing the fluorescence intensity of the CQDs to decrease upon detecting the acrylamide. This biosensor achieved over 90 % recovery when tested on real samples [104]. Additionally, Zhang *et al*. produced pH-sensitive nitrogen-doped CQDs (N-CQDs) as a fluorescent probe for acetylcholine detection in an optical fiber biosensor [103]. This biosensor demonstrated a simple operation and a linear relationship between the fluorescence intensity and the concentration of acetylcholine, with high selectivity and a recovery rate of more than 93 % [103]. Afsharipour *et al*. designed a fluorescence resonance energy transfer (FRET) biosensor using aptamer-modified CQDs and oxidized nanocellulose to detect the tumor marker alpha-fetoprotein (AFP) in human serum samples [105]. With optimized parameters for AFP measurement, the fluorescence intensity increased linearly with the concentration of AFP. This biosensor demonstrated high selectivity and a high recovery rate for detecting trace levels of AFP in human blood serum and urine samples [105].

4. CONCLUSIONS AND FUTURE OUTLOOK

Nanomaterials can take on various forms based on their size, and numerous bio-sources, particularly plants, can be utilized to produce these materials for biomedical applications. Nanocellulose, which can exist as cellulose nanofibrils, cellulose nanocrystals, or bacterial cellulose, have been extensively exploited in developing tissue-engineered scaffolds and bioactive wound dressing materials. Recently, the environmentally friendly process of producing AgNPs from plant extracts has gained attention due to AgNPs' outstanding antimicrobial activity, making them suitable for tissue engineering and wound healing. Similarly, carbon dots, also known as carbon quantum dots, are now being produced through hydrothermal and/or

solvothermal reactions using various natural sources as precursors. These methods yield products with comparable antimicrobial and optical properties, making them suitable for biomedical applications.

However, when using natural or raw materials to produce nanomaterials for biomedical applications, the purity of the end-products is a crucial factor. For instance, producing nanocellulose from plant-based sources requires several treatments to remove unwanted components before cellulose extraction. Similarly, achieving size uniformity and optimizing the morphology of nanoparticles such as AgNPs and CQDs can be challenging, as different precursors or raw materials yield different results. Although reproducibility of these nanomaterials is possible, it requires more time, impacting the scale-up process and increasing operating costs.

Utilizing bio-based nanomaterials for biosensing devices is also challenging, as these materials must be non-toxic and biocompatible. Moreover, several factors must be considered to ensure the biosensors function well, including selectivity, sensitivity, linearity, detection range, and stability. While bio-based nanomaterials may perform as well as or better than commercially available materials, aspects such as processing, pricing, scalability, and sustainability must be fully considered before their complete utilization in biomedical applications. Prioritizing the impact of bio-based nanomaterials on humans, animals, and the environment is vital before advancing nanotechnology development.

Acknowledgements. The authors would like to acknowledge the support given by the Ministry of Higher Education, Malaysia through the Fundamental Research Grant Scheme (FRGS) under Grant No. FRGS/1/2023/TK09/UNIMAP/02/3, and German Academic Exchange Service No. 57315854.

CRediT authorship contribution statement. Nur Atirah Afifah Sezali: Literature search, Writing. Hui Lin Ong: Funding acquisition, Supervision. Al Rey Villagracia: Literature search. Tuan-Dung Hoang: Formatting, Revision.

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

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