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Recent achievement of graphene in biomedicine: Advancements by integrated microfluidics system and conventional techniques

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ABSTRACT

Graphene and its derivatives have become essential materials in modern biomedical research due to their positive impact on various applications. Moreover, the integration of graphene-based materials with microfluidics technology has opened up new possibilities. The novelty of the current review is considering comprehensive analysis of the transformative impact of graphene and its derivatives in biomedical applications, particularly highlighting the integration with microfluidics technology. While many studies have focused on individual applications of graphene, this review uniquely present a holistic view of its potential across various biomedical fields, including drug delivery, gene delivery, tissue engineering, and photothermal treatment, detection, sensor with respect to conventional and microfluidics techniques. In this review, we analysed published research to unveil the increasing interest in graphene's potential applications in healthcare and medicine, as well as its prospects for further exploration. We explore the fundamental concepts of graphene, its properties, and its latest applications in medical implants and biological fields within the context of microfluidics and conventional prospects. The review also addresses the challenges and limitations of these materials and their promising future, recognizing that graphene research is still in its early stages compared to commercial applications.

1. Introduction

Graphene has been widely applied materials with vast application in field of materials science and engineering specially biomedical industry due to their extraordinary physicochemical and mechanical properties including large surface area [1]. It is recognized as the strongest material from a mechanical standpoint, in addition chemical stability shows mechanical compatibility, cell adhesion and low toxicity properties for applications in scaffold production, sensing and drug delivery [2–4]. Drugs can be made more stable, soluble, and bioavailable with the help of graphene-based drug delivery systems, which can improve therapeutic results [5–7]. Since graphene has unique qualities that make it a great contender to replace existing devices focused on medical applications [8–10]. The recent advance of novel research in graphene-based composition materials used in biomedical applications due to rising demand for the production of artificial hard tissue for organ implants where the biomaterials sector needs $2.3 billion a year [11].

Besides, microfluidics is a branch of science and technology that deals with manipulating and controlling small volumes of fluids, typically in the microliter to picoliter range, within microchannels and microscale devices [12]. When graphene is incorporated into microfluidics, it introduces several advantages and applications due to its unique properties. Graphene-based microfluidics is an emerging interdisciplinary field that combines the unique properties of graphene with the precision and control of microfluidic systems [13]. This integration offers numerous opportunities for various applications in science, engineering, and biotechnology (see Scheme 1). Graphene-based microfluidics is an exciting and evolving field with applications ranging from healthcare to energy and beyond [14]. Several current works demonstrate the versatility and promise of graphene in microfluidic systems for a wide array of scientific and technological advancements.

In recent years, the field of graphene research has experienced a

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substantial and rapid expansion. This rising interest is proved by Fig. 1, which presents empirical data sourced from Scopus publications pertaining to graphene and graphene nanomaterials of scientific research. Fig. 1 not only clarifies the extensive research activities within this domain but also explains the applicability of graphene in diverse applications. In the following sections of this review article, we attempt to provide an up-to-date and scientifically grounded overview of graphene materials, with a specific focus on their engineering applications.

Here, our objective is to consolidate the existing body of knowledge and gather insights into potential future applications by synthesizing information from past research and incorporating the latest advancements in technology. Specifically, the focus of this review is to systematically organize a diverse array of research findings encompassing prior work related to graphene-based materials and their modern integration with microfluidic technology. It is noteworthy that a substantial portion of previously published research articles has predominantly concentrated on various methodologies for the synthesis of graphene and its conventional applications. Hence, this review serves as an educational resource, for not only experts in the field but also to newcomers seeking to learn the graphene research, which encompasses both microfluidics and traditional technology.

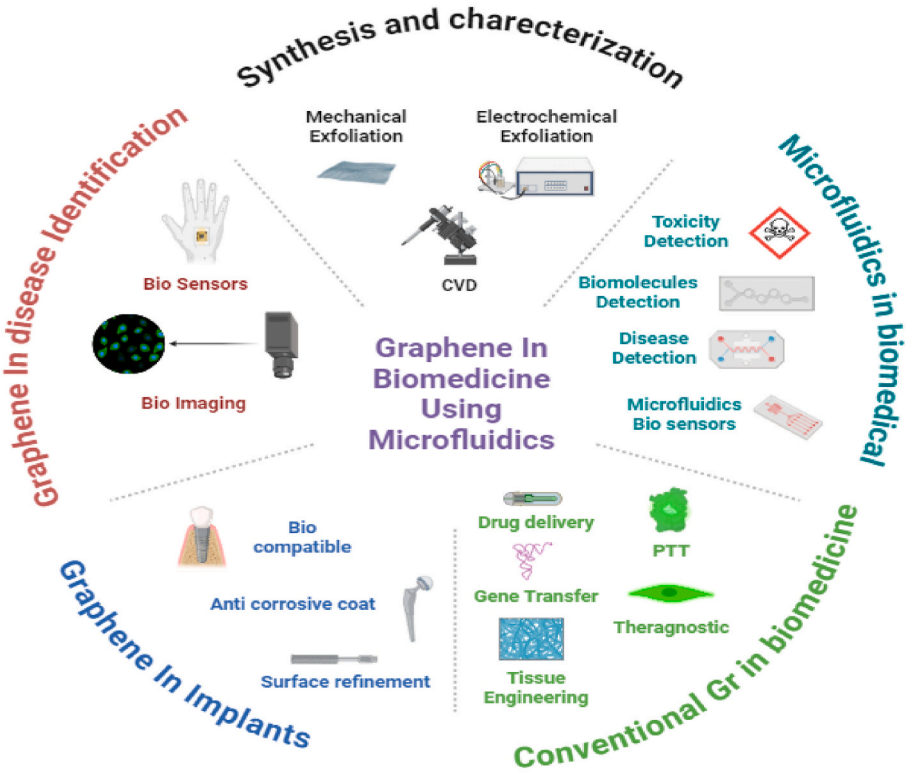
Over the past two decades, numerous reviews and progress reports have extensively covered topics related to graphene-based materials for biomedical applications. However, there remains a lack of a comprehensive review that integrates both conventional and microfluidics techniques. This review article addresses this gap by offering several novel contributions compared to previously published reviews along wish comprehensive analysis of graphene-based materials that can be applied across various biomedical fields. Unlike many existing reviews that focus exclusively on either conventional biomedical applications or microfluidics, this review integrates both aspects. It goes beyond discussing the potential of graphene-based materials and provides deeper insights into the current challenges and limitations in their application. Strategies for overcoming these challenges are discussed, such as enhancing biocompatibility, improving scalability, and ensuring stability within microfluidic environments. Additionally, it discusses areas where further investigation is needed, such as understanding long-term biocompatibility, optimizing fabrication techniques, and improving the specificity of biosensors. Furthermore, the review outlines future research directions that could potentially advance the field, including the development of novel graphene composites and the integration of advanced sensing technologies with microfluidics.

2. Synthesis of graphene

Graphene is a two-dimensional allotrope of carbon consisting of planar sheets with carbon atoms arranged in sp2 hybridized configuration. The unique properties exhibited by graphene arise from the different arrangements of carbon atoms, leading to the development of various modern approaches for its synthesis, commonly referred to as graphene extraction [15]. In 2004, graphene was discovered through the Scotch tape method, and subsequent breakthroughs enabled its production in different forms using innovative approaches [16]. Two primary methods, top-down and bottom-up synthesis, are widely employed to grow graphene according to specific requirements such as layer number, thickness, nature, and size. Based on these two fundamental mechanisms, various techniques have been introduced for graphene synthesis are describe below.

2.1. Mechanical exfoliation

The exfoliation of graphite into graphene represents a cost-effective method for graphene production [17]. The growth of graphene in flake form and the subsequent recognition with the Nobel Prize in Physics in 2010 can be attributed to the micromechanical cleavage of highly ordered pyrolytic graphite [18]. Generally, the graphene layers are sequentially peeled away from the bulk graphite, overcoming the resistance from van der Waals interactions between adjacent layers. A schematic representation of this technique is depicted in Fig. 2a [19], where graphene layers are cleaved from the surface of the bulk highly



Scheme 1. Schematic presentation of the use of graphene-based materials for biomedical applications considering the conventional and microfluidics technology.

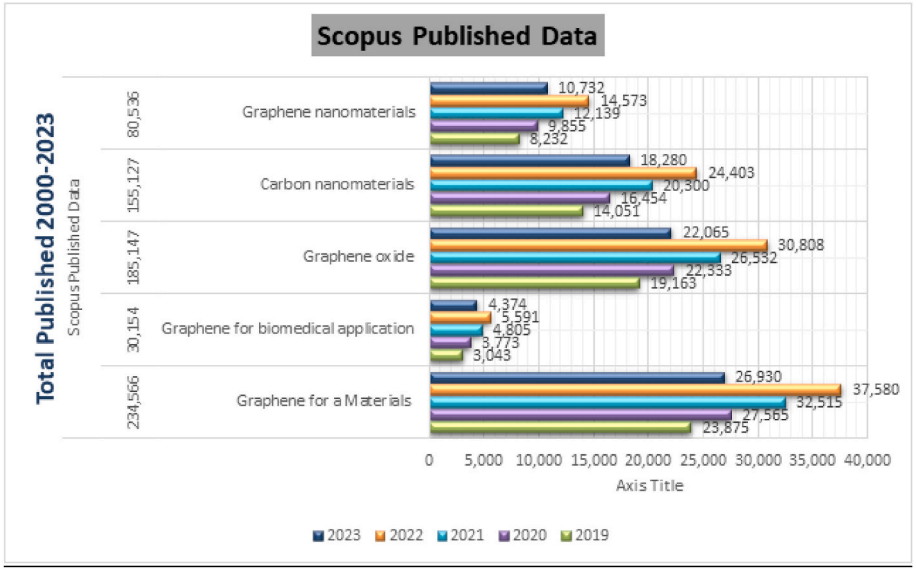


Fig. 1. Scopus Published data analysis of graphene and graphene based biomedical sector.

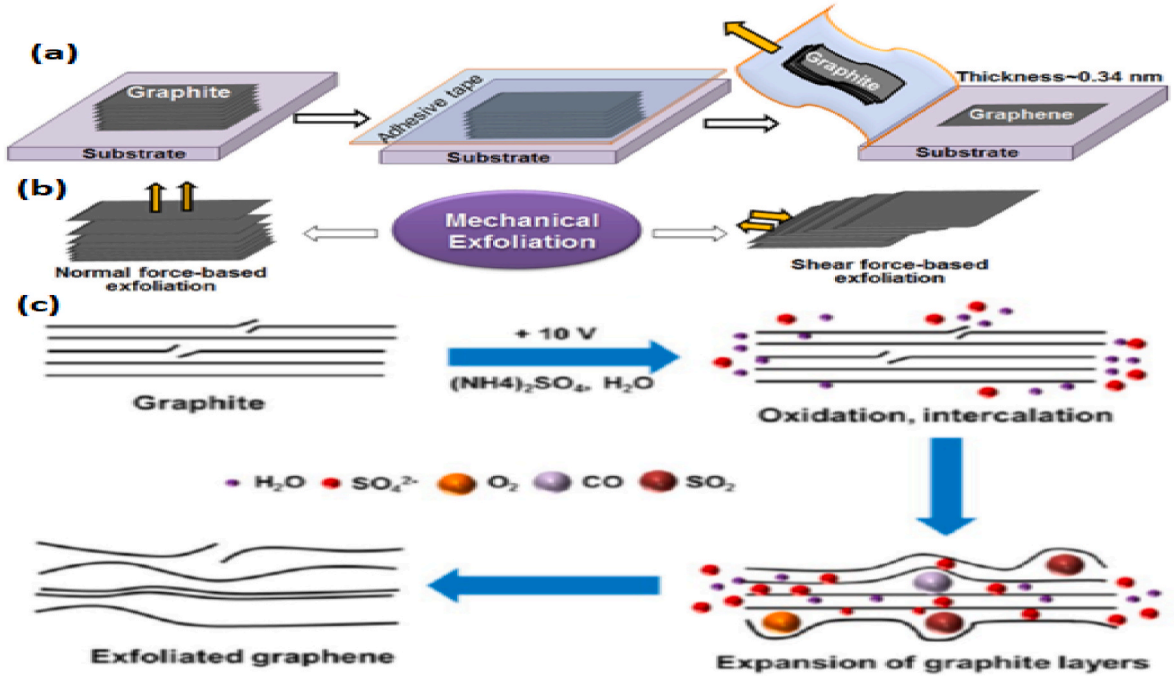


Fig. 2. **(a)** Graphical presentation of the process of graphene layer extraction from bulk graphite using adhesive tape **(b)** Mechanical exfoliation methods for graphene production based on normal and shear forces. Reprinted with permission, copyright, 2020, Elsevier [19] **(c)** Illustration depicting the mechanism of electrochemical exfoliation. Reprinted with permission, copyright, 2014, American Chemical Society [26].

ordered pyrolytic graphite. This method is crucial for obtaining graphene flakes with a larger surface area and enhanced efficiency. However, this process is time-consuming and limited to small-scale laboratory research. Several agents also can help perform this technique as electric field [20–22], epoxy resin and printing technique [23].

2.2. Electrochemical exfoliation

Graphene offers a promising alternative to conventional mechanical/oxidation-based approaches that have been investigated for the efficient and large-scale synthesis of graphene from its precursor, graphite [24–26]. Through the application of an electric potential, ionic species present in an electrolyte solution are driven to intercalate into the graphite electrode, causing an expansion of the interlayer spacing [25]. For instance, in the case of using ammonium sulfate as the electrolyte, sulfate ions and water molecules travel to graphite region, leading to the localized generation of gas bubbles comprising species like SO_2 and O_2 (Fig. 2b) [26]. This electrochemical process enables the successful delamination and exfoliation of graphene layers, producing high-quality graphene nanosheets suitable for various applications. This process exerts a separating force on neighboring graphene sheets, facilitating their delamination.

2.3. Chemical vapor deposition (CVD)

The evolution of graphene layers on metallic substrates using CVD is predominantly governed by the solubility of carbon on the specific used metallic surfaces [27–29]. Recent studies have further explored into the influence of metallic substrates on the CVD growth of graphene, exploring various aspects of the process. For instance, the growth of large-area single-layer graphene on nickel substrates through CVD sheds light on the nickel substrate's impact on the nucleation and growing dynamics of the graphene layers [31]. Similarly, the use of platinum substrates in the CVD growth of graphene films elucidates platinum's effects on the nucleation and grain size of graphene [32].

In modern laboratory, alternative methods are using for graphene synthesis. These methods including ball-milling exfoliation, solvothermal synthesis, thermal decomposition of SiC and high-temperature annealing of carbon-containing materials. These techniques are very much useful to produce graphene with controlled characteristics and desired properties.

3. Characteristics of graphene

Graphene has attracted significant consideration for their excellent properties and applications in several fields along with medical applications [30,31]. From the discovery of graphene, it has been a building block for developing novel carbon-based materials [32]. Graphene has fascinating characteristics, including atomic structure, electronic and thermal conductivity, mechanical strength and unique physical properties (Fig. 3). Due to the high surface area and interesting optical properties, graphene is useful to enhance the contrast in various imaging technology, such as MRI and fluorescence imaging, enabling more accurate and sensitive detection of diseases [33]. It has large surface-volume ratio that allows for efficient loading and precise release of therapeutic agents, while their exceptional mechanical strength confirms stability during transport and delivery.

However, graphene is a potential material in tissue engineering and regenerative medicine [34]. The biocompatibility and the ability of their composites support cellular growth and differentiation that make them an ideal scaffold material for promoting tissue regeneration. Graphene-based scaffolds also can mimic the extracellular matrix, facilitating cell adhesion, proliferation, and tissue growth, thus offering new opportunities for repairing damaged tissues and organs. On the other hand, the antimicrobial properties of graphene have opened a new way against drug-resistant bacteria [35]. Graphene-based materials also have antibacterial activity against various pathogens, including multidrug-resistant strains. The ability to disrupt bacterial cell membranes and inhibit bacterial growth makes graphene a promising candidate for developing new antimicrobial agents and coatings for medical devices, reducing the risk of infections.

4. Graphene based microfluidics in biomedical industries

Graphene and graphene-derived materials have garnered significant attention for their potential biomedical applications. The antimicrobial properties exhibited by graphene make it a promising candidate for various medical fields necessitating the use of antiseptics. However, it is crucial to note that the safe concentration thresholds of graphene for human cells have not been definitively determined. The inherent capacity to functionalize the fundamental lattice structure of graphene enables scientists to fabricate sensors based on graphene that are capable of detecting biochemical molecules. Similarly, the synergistic integration of graphene and microfluidics amplifies their individual advantages, leading to enhanced and more valuable applications. Numerous recent reports and advancements pertaining to this subject are presented below, accompanied by detailed information.

4.1. Microfluidics virus and disease detection

Microfluidics has emerged as a prominent research area within the fields of analytical chemistry and bioscience. Graphene-based microfluidic chips have exhibited a diverse range of significant applications. The integration of graphene membranes with microfluidics holds the potential to facilitate advancements in both domains. Numerous studies have been conducted utilizing microfluidics techniques for the detection of viruses and diseases. One such investigation focused on the electrochemical detection of norovirus using a polydimethylsiloxane microfluidic chip integrated with a screen-printed carbon electrode [36]. A study demonstrated the detection of multiplex quantitative loop-mediated isothermal amplification using a paper/poly(methyl methacrylate) hybrid CD-like microfluidic Spin Chip integrated with DNA probe-functionalized GO nano sensors [37]. Furthermore, another study reported the development of a signal-on photoelectrochemical sensing system for the detection of prostate-specific antigen by employing reduced graphene oxide/$BiFeO_3$ nanohybrids [38]. Oh et al. conducted a study involving the utilization of a GO quenching-based

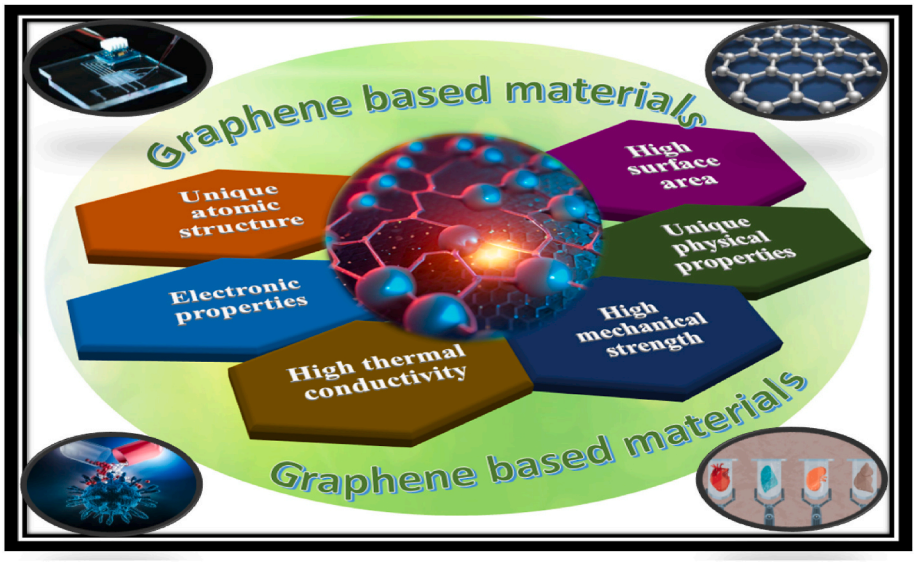


Fig. 3. The graphical presentation of characteristics of graphene including its atomic structure, electronic/thermal conductivity, mechanical strength, and unique physical properties.

molecular beacon imaging technique for investigating the exosome-mediated transfer of neurogenic miR-193a [39]. Singh et al. developed a microfluidic immunochip with high sensitivity and selectivity for the detection of Salmonella typhimurium bacterial cells. In a similar way, Zhao et al. successfully integrated anti-E. coli antibody-coated graphene into microchips for the purpose of detecting E. coli bacteria [39]. The concentration of E. coli in the sample solution was determined by measuring the resistance of the graphene. This immunochip employed specific antibodies to selectively capture and detect the target bacteria, offering a reliable and efficient method for bacterial detection (Fig. 4).

4.2. Microfluidics biomolecules detection

Graphene-based microfluidics has shown a promising role for the detection of biomolecules. By integrating graphene into microfluidic devices researchers enhanced the performance of biomolecule detection assays. Various strategies have been used in graphene-based microfluidics for biomolecule detection. For an example, an electrochemical microfluidic approach was studied for the separation and detection of D-methionine and D-leucine enantiomers [42]. Perry et al. used GO in droplet-based microfluidic microsystems and explored as a strategy to inhibit protein biofouling [43]. Bao et al. studied the immobilization of trypsin via a GO-silica composite as a method to obtain efficient microchip proteolysis [44]. This approach involves incorporating trypsin within a GO-silica composite coating on the surface of a microchip, enabling the creation of microfluidic bioreactors for proteolysis.

A magnetic microfluidic device composed with graphene nanosheet has been developed for the homogeneous online monitoring of pyrophosphatase activity [45]. The integration of graphene into a microfluidic platform allows for real-time monitoring and analysis of individual cells as they pass through the channel. Therefore, the graphene transistor array integrated microfluidic flow for the sensing of malaria-infected single-cell level red blood cells was reported [46]. The capacitively coupled changes in the conductivity of graphene induced by malaria-infected red blood cells, along with the characteristic conductance dwell times, enable the acquisition of specific microscopic information about the disease state with high sensitivity (Fig. 5a–c) [46]. However, disposable paper-based microfluidic immunosensor has been studied using a rGO-tetraethylene pentamine/gold nanocomposite decorated carbon screen-printed electrode [47]. This immunosensor offers a portable and cost-effective platform for sensitive and selective detection of target analytes (Fig. 5d). Furthermore, Zhihua Pu et al. [48] developed monitoring device for a continuous glucose detection using a graphene-based electrochemical sensor integrated into a microfluidic system. This device offers a reliable and real-time monitoring solution for glucose levels that electrochemical sensor is modified with graphene to enhances the sensitivity and selectivity towards glucose detection.

4.3. Microfluidics toxicity detection

Graphene-based microfluidics has emerged as a highly promising platform for the detection of contaminants in diverse applications. Researchers have been able to enhance the performance of contaminant detection assays when combined graphene based microfluidic devices. Functionalization of graphene surfaces with specific receptors, such as antibodies or aptamers are useful for selective capture and detection of target contaminants. The interaction between the impurities and the graphene surface led to detect through various methods, including electrical, optical, or electrochemical techniques. Park et al. introduced an advanced approach for the detection of trace lead ions (Pb^{2+}) by integrating a microfluidic device with a DNA aptamer-linked photoluminescent GO QD sensor (Fig. 6A) [49]. Additionally, Fig. 6B shows a digital image and a cross-sectional view of the assembled microfluidics device providing a visual representation of itstheir structure and configuration. This technique allows the efficient extraction of trace

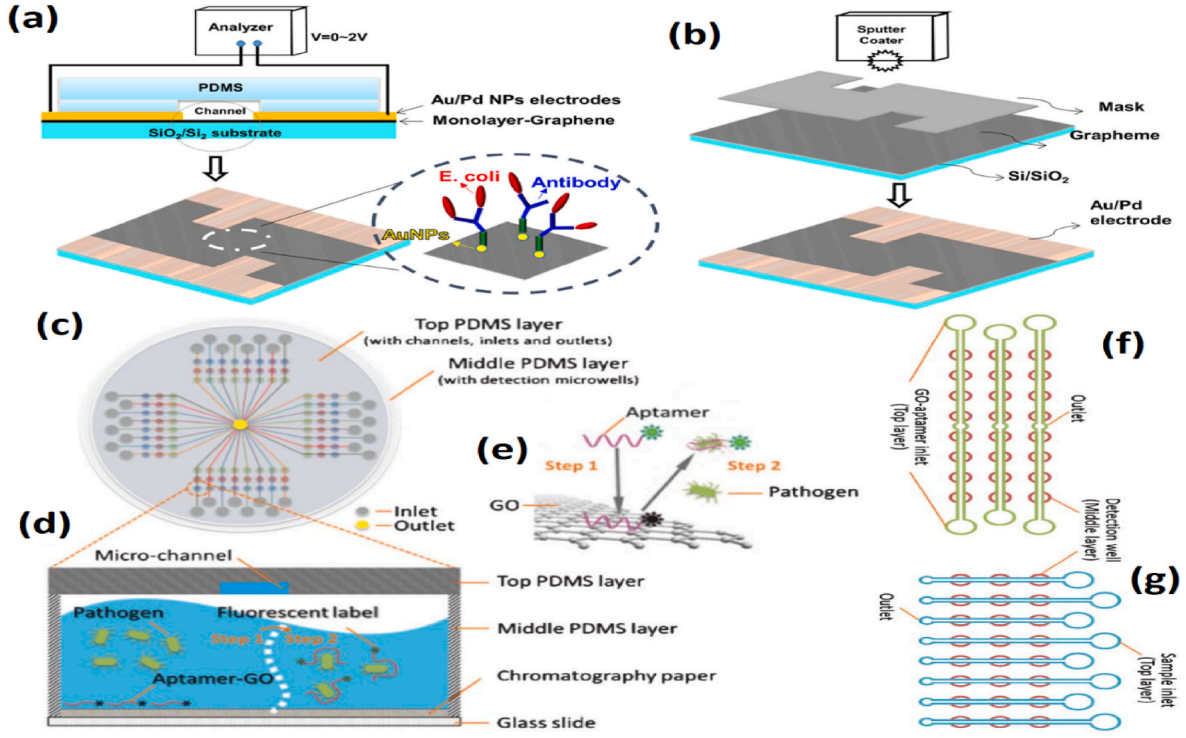


Fig. 4. **(a)** Schematic structural presentation of PDMS microchannel with electrodes affixed to monolayer graphene. The biosensor is located at the center of the microchannel under the PDMS structure. **(b)** Applied sputter coater for both sides coating of the electrodes, with a mask covering the upper surface of the graphene. Reprinted with permission, copyright, 2020, Elsevier [40] **(c)** Illustration of designed PDMS/paper-based hybrid microfluidic system for pathogen detection considering GO biosensors. **(d)** Microfluidic biochip layout **(e)** Illustrate the principle of the aptamers and pathogens detection. **(f)** Schematic diagram of the protocol to introduce the functionalized GO and **(g)** test samples in microchannels. Reprinted with permission, copyright, 2013, Royal Society of Chemistry [41].

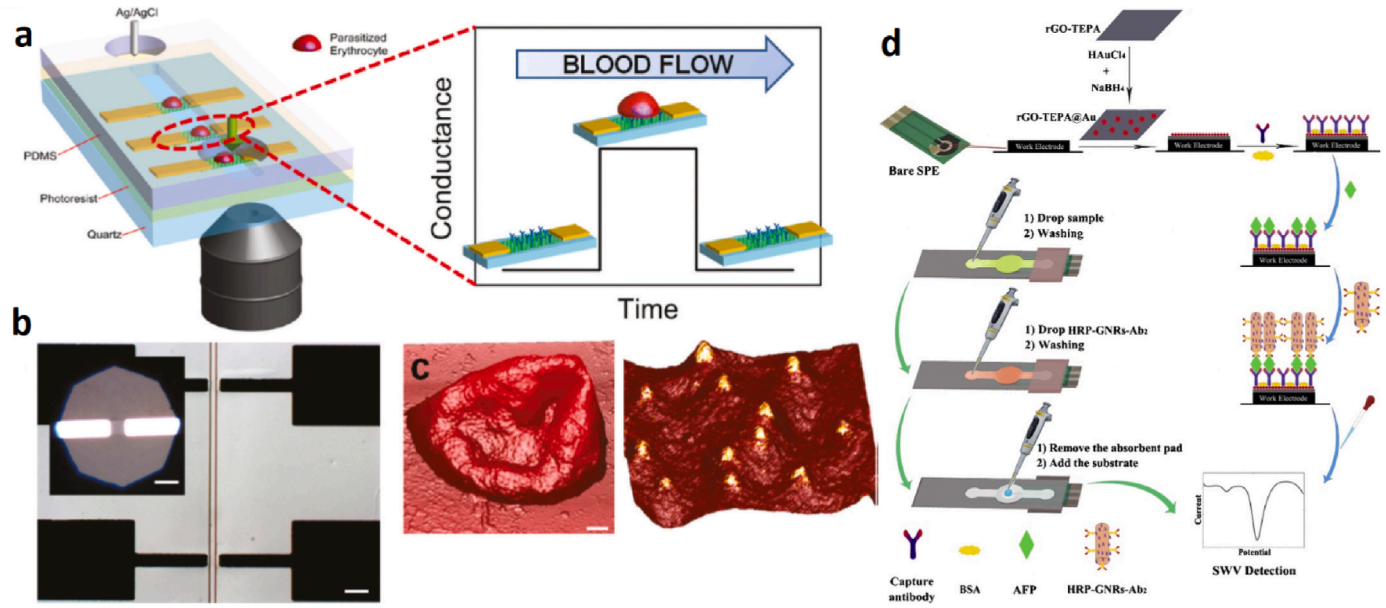


Fig. 5. The detection of single Plasmodium falciparum-infected erythrocyte using graphene-based materials **(a)** Graphica representation of on quartz surface graphene transistors. **(b)** DIC picture of independent graphene transistors integrated with the microfluidic device. **(c)** 3D AFM images of parasitized erythrocyte. Reprinted with permission, copyright, 2011, American Chemical Society [46] **(d)** The schematic illustration of the modification and assay procedure of the immunosensor. Reprinted with permission, copyright, 2017, Elsevier [47].

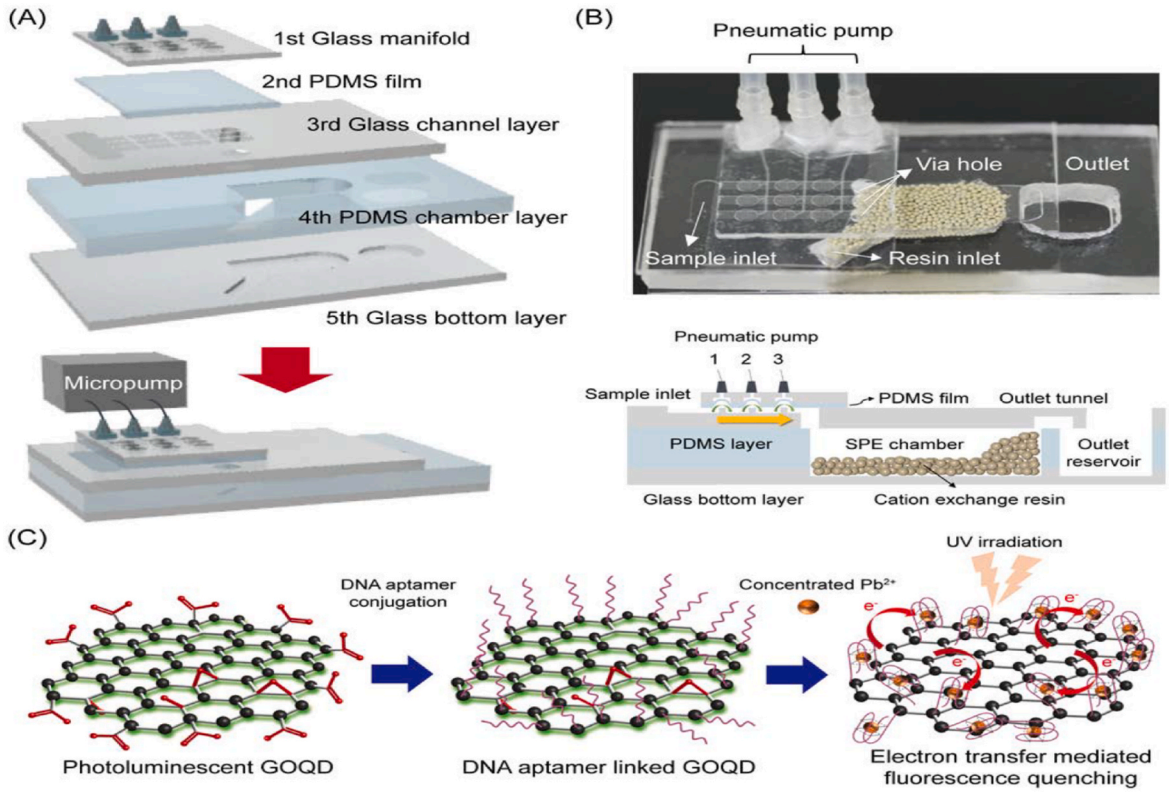


Fig. 6. (A) Graphic design of a 5-layered sample microfluidics device. (B) A visual representation of the microfluidics device consists of resin (top), and a side view of the fully assembled microdevice (bottom). (C) The setup for the detection of Pb^{2+} using a GOQD sensor, facilitated by fluorescence quenching. Reprinted with permission, copyright, 2015, American Chemical Society [49].

metal ions from large-volume samples (Fig. 6C). Furthermore, an investigation was conducted to explore microfluidic flow passing through a polyaniline matrix supported by lamellar-structured graphene, with the aim of enhancing mass transfer during the electrocatalytic reduction of hexavalent chromium [50]. However, using a microfluidic system, GO microspheres were fabricated with precise control over their size and morphology [51]. The microfluidic approach allowed the formation of uniform and monodisperse GO microspheres, which is useful for the removal of perfluorooctane sulfonate from polluted water. Zhang and colleagues presented an inexpensive and

straightforward paper-based microfluidic device designed for concurrent multiplex analysis of various chemical contaminants in food [52]. The efficacy of this apparatus has been effectively demonstrated in the simultaneous identification of the heavy metal mercury (II) ion (Hg^{2+}) and silver (I) ion (Ag^{+}), as well as the detection of aminoglycoside antibiotics residues in food. Furthermore, its utilization exhibits significant promise for the advancement of environmental surveillance and clinical diagnostics.

4.4. Microfluidics based biosensors

Biosensors represent invaluable instruments for the detection of diverse biological entities, encompassing cells, pathogens, proteins, and other biological molecules. The integration of biosensing devices with microfluidics not only facilitates streamlined sample preparation, portability, and diminished detection time and cost but also imparts distinctive attributes, including label-free detection and heightened sensitivity [53] In graphene-based microfluidics, graphene is integrated into the microfluidic channels or as a sensing element on the surface of the channels. This integration allows for efficient transport of fluids and analytes, as well as sensitive detection of target molecules. The high electrical conductivity of graphene enables the development of electrochemical sensors, where graphene serves as the electrode material. Additionally, the large surface area of graphene provides ample binding sites for immobilizing biomolecules or functionalizing with specific receptors, enhancing the sensor's specificity and enabling the detection of specific targets. Jiao et al. [54] introduced a novel approach involving wearable graphene sensors integrated with microfluidic liquid metal wiring for applications in structural health monitoring and human body motion sensing. Dou et al. [55] reported interfacial nano-biosensing in microfluidic droplets for high-sensitivity detection of low-solubility molecules. Besides, modified graphene-polyaniline-based electrochemical droplet microfluidic sensor has been reported for the determination of 4-aminophenol [56].

In recent studies, the utilization of nanoengineered materials in conjunction with microfluidic platforms has demonstrated remarkable progresses in sensing and detection. One such example involves the application of a nanoengineered mesoporous L-cysteine-graphene hydrogel on a microfluidic surface plasmon resonance chip for the detection of human cardiac myoglobin molecules [57]. Another notable development involves the incorporation of 1-layer graphene, obtained through a exfoliation technique into a microfluidic device for the effective detection of chlorpyrifos, a pesticide, at femtomolar concentrations [58]. Moreover, the incorporation of nanosheets of graphene oxide into a microfluidic system demonstrated precise enhanced isolation of natural killer cells [59]. This approach shows promise in the context of cancer diagnosis. Additionally, graphene field-effect transistors have garnered significant interest in the field of biosensor development, primarily for their exceptional properties that make them well-suited for DNA detection applications [60,61]. In a very recent development, real-time monitoring of biochemical processes on a microfluidics chip was achieved by integrating a graphene field-effect transistor, specifically for DNA detection [62]. The studied programmable device content integrated setup, microfluidics flow, microfluidics chips has exhibited crucial versatility in the detection of biomolecules within a fully portable-automated platform (Fig. 7).

5. Conventional graphene in biomedical industries

Conventional graphene, with its exceptional properties has shown significant potential in various biomedical applications. Current advanced materials such as gold nanoparticles, silicon-based materials, and polymers like PLGA (poly(lactic-co-glycolic acid)) have been widely used in biomedical applications. These materials are effective in drug

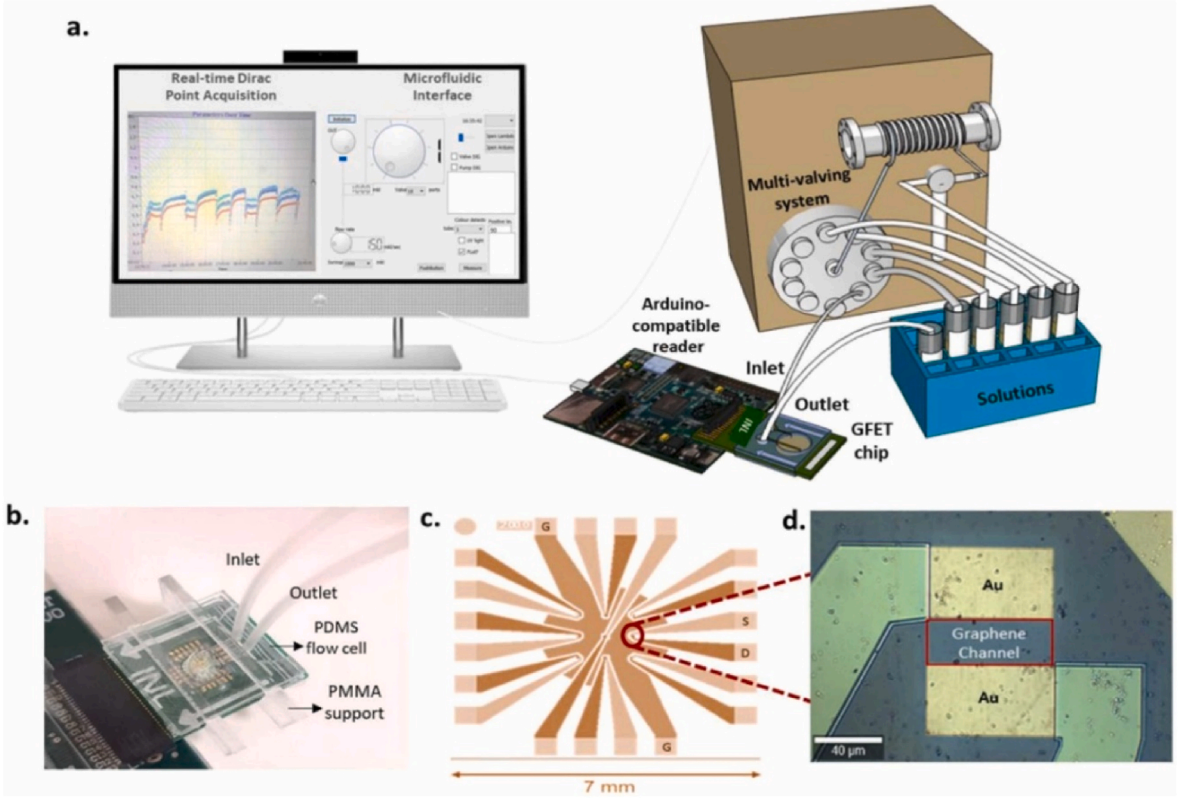


Fig. 7. **(a)** The integrated graphene chip and microfluidic system for DNA detection **(b)** A visual representation of a graphene chip installed within a PDMS flow-cell and connected to an Arduino-compatible reader board for the acquisition of transfer curve data **(c)** The optical micrograph illustrates the position of a graphene channel located between gold contacts within the chip. Reprinted with permission, copyright, 2022, Elsevier [62].

delivery, tissue engineering, and biosensing. However, they have some limitations over graphene-based materials. Such as gold nanoparticles are extensively used in drug delivery and photothermal therapy due to their biocompatibility and ease of functionalization. However, they can suffer from issues related to stability and potential toxicity at high concentrations and also expensive. Graphene-based materials, with their high surface area and robust mechanical properties, offer enhanced stability and a larger loading capacity for therapeutic agents, which can reduce the required dosage and moderate toxicity concerns. Again, silicon-based materials are popular in biosensing and microfluidics due to their excellent electronic properties and compatibility with existing semiconductor technologies. Yet, silicon can be hard and may require complex fabrication processes. In contrast, graphene has exceptional electrical conductivity, flexibility, and mechanical strength provide a more durable and versatile alternative. Graphene is flexible and transparent electrodes also allows for the development of more advanced and miniaturized biosensors. Besides, polymers like PLGA are widely used in tissue engineering and drug delivery due to their biodegradability and biocompatibility. However, their mechanical properties and drug release profiles can sometimes be suboptimal. Graphene-based materials can enhance the mechanical strength of polymer composites and provide more controlled and sustained drug release due to their large surface area and ability to form strong interactions with drug molecules. Here are some key areas where conventional graphene-based materials have been explored. A lot of interest has been evaluated to graphene-based drug delivery systems in biomedical research because of their special qualities and potential uses [63]. Future medicine will greatly benefit from the usage of graphene-based materials due to their distinctive properties, which include an high surface area, exceptional mechanical strength, superior biocompatibility and less toxicity [64,65].

5.1. Transportation of drugs

Drug delivery is the process of controlling therapeutic substances to the body in order to obtain a desired therapeutic effect. It involves the transportation of drugs from their site of administration to the target site within the body, where they can exert their pharmacological action [64]. Increased drug loading efficiency and stability can be achieved by using GO with oxygenated functional groups. To counteract the acidic microclimate of tumor tissues, GO can be programmed to release drugs in increments according to their pH [78]. Drug delivery characteristics have been improved by the creation and testing of scaled-down GQDs that are biocompatible and photostable [66]. As an innovative approach to targeted medication administration and effective anti-cancer therapy, tri nanocomposite combines gelatin/gum arabic with graphene-oxide [67]. Ibrahim et al. sheds light on the potential of Gr nanosheets for use in the delivery of therapeutics [68]. Graphene nanoparticles have been conjugated with a wide range of tumour and anticancer drugs for delivery including Rituxan, doxorubicin, hypocrellin A, and camptothecin (see Table 1).

5.2. Gene transfer

Gene transfer refers the introduction of foreign DNA or RNA into an organism for the purpose of studying or treating the organism. Transfection involves the introduction of external genetic material into cells with the purpose of studying gene function, treating genetic illnesses, altering cellular processes, producing therapeutic proteins, or investigating gene function [84]. Gene therapy's promise to heal rare hereditary and single-gene disorders through genetic engineering and regenerative medicine has received attention. Gene therapy kills tumor cells without chemotherapy by blocking cell pathways with DNA or RNA [81–84]. This method can remove, replace, or add disease-fighting genes [85]. Some examples of nanocarriers based on graphene that have been used for gene delivery are included in Table 2.

5.3. Tissue regeneration & restoration

When human tissue or a scaffold sustains an injury, tissue biologists engage in the development of biological alternatives and safe materials with the aim of facilitating the healing or replacement of the damaged tissue. The importance of creating an optimal composite material with all necessary properties cannot be overstated. The extensive utilization of graphene nanomaterial in the fields of medical science and tissue engineering can be attributed to its remarkable ability to interact with various biomolecules such as DNA, enzymes, proteins, and peptides. This capacity has significantly contributed to the advancement of regenerative medicine [94]. Tissue engineering is a science that uses graphene-based materials to improve cellular development, tissue rejuvenation, and repair by incorporating graphene and its derivatives into scaffolds or substrates. Graphene has a number of properties that make it a good contender for improving the field of tissue engineering. These characteristics include its high mechanical strength, large surface area, and exceptional electrical conductivity [95]. In bone tissue

Table 1
Successive graphene-based materials for drug delivery systems.

SL.	Nanoscale structures made of graphene	Targeted Cell	Drug medium	Results	Ref.
1.	GQD	PC12 cell line	artesunate and mefloquine	Drug resistivity and toxicity condition improved	[69]
2.	GONR-PEG-DSPE	Glioblastoma multiforme cells	Lucanthone	Toxicity improvement	[70]
3.	GO/AuNS-PEG/Ce6	EMT6	Heat and ROS disrupted lysosomal membrane	Inducing Cell death	[71]
4.	GO-polyacrylic acid	Mouse glioma GL261 cancer cells	1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU)	Higher DNA interstrand cross-linking and lower IC(50) value.	[72]
5.	GO-sterculia gum-poly	Colon Cells	Vancomycin	Network density, characteristics, and swelling media pH were impacted.	[73]
6.	PEGylated-GO	Carcinoma cell	pGO-Pt/DOX	Decreased Pt and DOX toxicity	[74]
7.	GO-maltodextrin	Human breast carcinoma cells (MCF7)	Folic acid	Excellent tumor inhibition with chemo-phototherming	[75]
8.	GO-PEG	Osteosarcoma cell and glioblastoma cell.	Cisplatin, carboplatin and oxaliplatin.	Breast cancer migration inhibition	[76]
9.	GO-chitosan	MGC-FU	FI-Nanostay	Drug loading and pH-dependent sustained release improved.	[77]
10.	GO	HeLa cells	Hypocrellin A and EZNA reagent	Suppresses tumors	[78]
11.	rGO	NIH3T3 cell	CS-rGO-CeO_2	Superior cell adhesion	[79]
12.	carboxymethyl cellulose (CMC)/starch/ reduced graphene oxide (RGO)	Tumor Cells	Curcumin	Long-lasting, pH-sensitive curcumin delivery with low toxicity.	[80]

Table 2
Applications for transporting genes using graphene and related materials.

SL.	Gene	Graphene nanomaterial	Study's primary focus cell	Ref.
1	anti-GAPDH siRNA	Dox-loaded PAMP-CP-rGO	EPPT1	[86]
2	Enhanced green fluorescent protein (EGFP)	Graphene-polyethylenimine (1, 2 and 10 kDa)	HeLa cells	[87]
3	Tolerogenic dendritic cells	GO nanosheets	allogeneic hematopoietic stem cell	[88]
4	Luciferase reporter gene	Graphene-polyethylenimine (25 kDa)	HeLa cells	[89]
5	Glycyrrhetinic acid	GA-PEG-NGO-Dendrimer, GPND	hepatocellular carcinoma	[90]
6	CpG oligodeoxynucleotides	GO-β-D-glucan	RAW264.7 cells	[91]
7	anti-miRNA21	PEI-modified GO	TNBC cells	[92]
8	survivin-siRNA (GCE/siRNA)	GO modified with chitosan an d Anti-EpCAM	MCF-7	[93]

engineering, electrospun fibres of GO-reinforced polycaprolactone biocomposites showed that scaffolds might increase physico-mechanical properties and attain considerably enhanced biological features compared to bulk PCL [96]. Nair et al. discovered that incorporating 0.5 and 1.0 wt% of GO nanoflakes into the gelatine-hydroxyapatite matrix increased the mechanical strength and osteogenic differentiation [97]. Aparicio-Collado et al. finds that rGO enhances the electrical conductivity of nanohybrid hydrogels to muscle tissue levels. confirming the validity of the examined scaffolds for use in bone tissue engineering [98]. Fig. 8 demonstrates Improved and scalable stem cell culture, osteoinduction, and tissue engineering using a 3D-printed graphene electrode device [99]. A 3D microporous scaffold from an Functionalized graphene oxide based nanocomposite and adipose-derived stem cells was recently reported for advanced tissue engineering [100,101].

5.4. Theranostics

Theranostics are cutting-edge methods of treatment and diagnosis that can be combined into a single nano-system [102] where the goal is better patient care through more targeted and efficient drug customisation in real time according to diagnostic data [103]. Graphene-based nanocomposites have seen increased investigation into potential suited for the creation of theranostic tools for the recent year [104]. Graphene and its derivatives have gained a lot of interest because their beneficial surface qualities allow for the integration of multiple modalities onto a single platform [105]. Nano-theragnostic systems based on graphene that have broad biomedical implications have been synthesised and studied. Combining imaging with other therapeutic modalities including gene or drug delivery, heat-based PTT, and light-based photodynamic therapy is the focus of these systems [106].

6. Recent advanced of graphene in implants

Graphene has emerged as the favoured form for biomedical application [107]. Among the family of graphene-based nanomaterials, there exist various members including reduced graphene oxide, multilayer graphene, graphene nanoribbons, and other graphene-family materials with varying degrees of functionalization [108,109]. Owing to their exceptional properties, graphene and its derivatives have widespread utilization in the biomedical sector. Notably, they have found extensive application in the domain of medical implants, owing to their remarkable properties.

6.1. Biocompatibility of implants

Biofilms are an essential part of a bacterium's or fungus's survival in the natural world, and they may also be found on the surfaces of teeth, prostheses or implant-anchored restorations [110]. Biocompatible and highly antibacterial, graphene-based products can be used to stop the spread of germs [111–113]. Decorating GO with AgNPs results in a GO-Ag nanocomposite enhanced their antibacterial properties [114,115]. The interaction between microbial biofilms of Streptococcus mutants, Enterococcus faecalis, Pseudomonas aeruginosa, and Candida albicans was investigated by Agarwalla et al., who also examined the

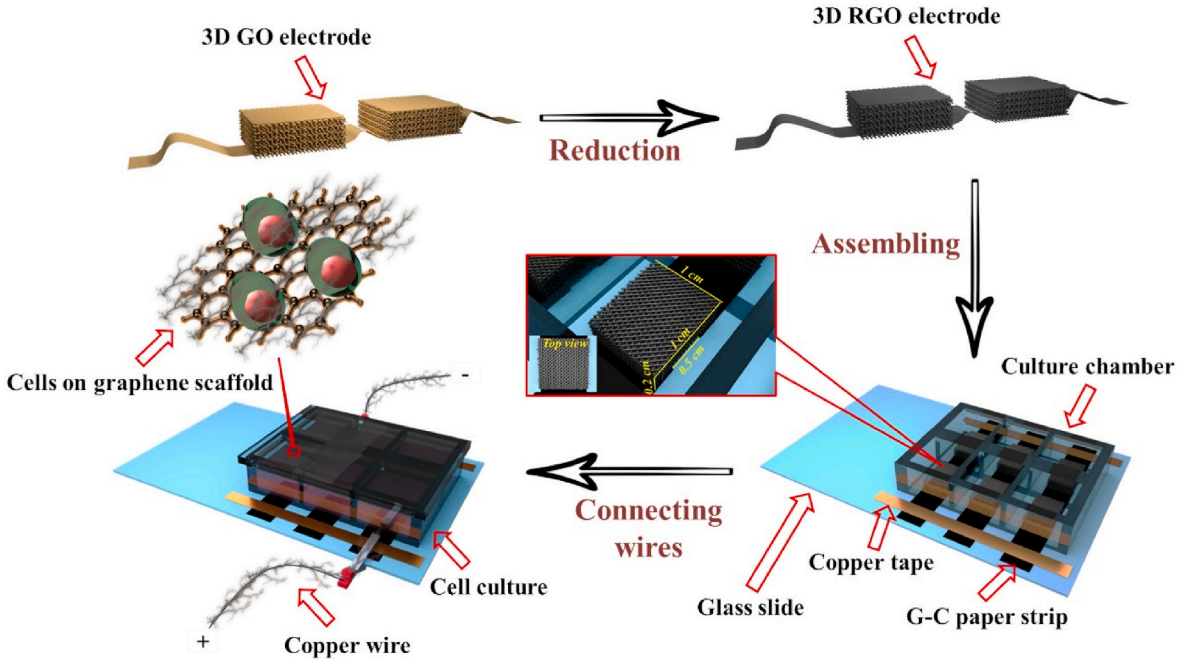


Fig. 8. Electrode device using 3D-printed graphene for enhanced and scalable stem cell cultivation, osteoinduction, and tissue engineering [99].

surface and wettability features of graphene covering on Ti. Depositing graphene on Ti (Control) once, twice, and five times using a liquid-free method [113]. Using nitinol as a base, Zhao et al. created a coating made of gelatin-functionalized GO (GOGel). Biocompatibility and antibacterial efficacy were investigated. The osteoblastic cells isolated from mice performed best when exposed to GOGel regarding adhesion, proliferation, and differentiation. They also discovered that GOGel and GO could suppress E. coli [116].

6.2. Anti-corrosion coating

Joint replacements, dental implants, orthopaedic fixations, stents, and orthodontic and endodontic applications are just some of the many places metallic biomaterials are put to use [117]. Inhibitors, coatings and nanocoating of various sorts are applied to these metals and alloys [118,119]. Graphene's properties as a chemically inert, atomically stable, and very robust coating make it a promising candidate for application as a corrosion barrier layer [120–124]. Coating implants with graphene might boost their surface characteristics and reduce corrosion [128–130]. Additionally, GO coating has excellent potential as a regenerative dental material. Human periodontal ligament stem cells were tested in vitro for their bioactivity on either a GO-coated Ti substrate or a sodium titanate substrate, with the latter receiving a more positive evaluation [124–128].

6.3. Surface refinement of implants

Polymers, hydrogel, chitosan derivatives, silicone, protein lubrication, and ZnO NPs are only some of the biomaterials that have been investigated for their potential to reduce friction in biomedical applications. However, the findings suggest that the coating is unstable and does not have the predicted friction-reduction characteristic. Therefore, further work is needed to create a coating with good lubricating qualities [128–130]. Graphene film coatings have shown promise in reducing friction thanks to extensive research into their lubricating and friction-reducing characteristics [131–133]. A friction coefficient of 0.05 was found to be significantly reduced when GO was dissolved in water. Graphene coverings yielded similar outcomes in other investigations [132,133]. Further decrease friction with a coating made of GO/AgNPs [134].

7. Applications of graphene in bio imaging technology

Bio-distribution of medicines may be tracked reliably using electromagnetic spectrum subsets, and biological processes like cellular uptake can be seen with tailored administration [135–137]. By using the physiochemical features of GO, such as its large surface area, high electrical conducting ability, and remarkable capacity for stacking various biomolecules via chemical or physical interaction, biosensors based on GO have been produced [138–140]. Bioactive GQD-based polymer composites have several desirable properties, including their use as appropriate imaging probes in various bioimaging techniques and their high level of biocompatibility [141]. Graphene biomolecules, both self-assembling and tuneable, make it possible to construct ultrasensitive biosensors for recognizing DNA and other atoms [138,142]. Graphene-ultrathin films make superior biosensing and electrochemical sensors more accessible [143]. An improved biosensing platform for the detection of motile bacteria is presented in a new paper by Bing Li et al. (see Fig. 9) that makes use of two-photon polymerisation and graphene. Bio-inspired 3D printing and 2D materials are put to use in a novel way in the suggested platform, allowing for the creation of sensing devices with potential biomedical applications [144].

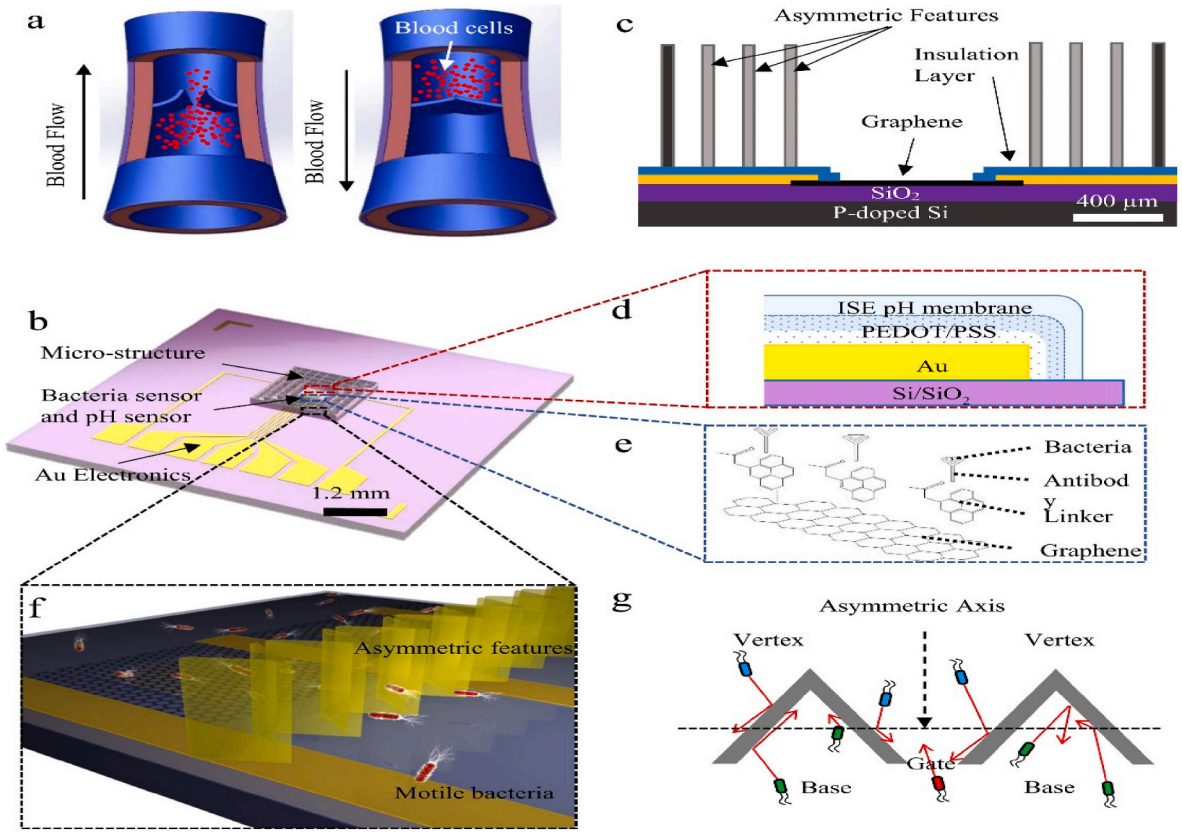


Fig. 9. Micro-structured graphene boosted by biological inspiration shown in schematic form. (a) Venous valves in a blood vessel shown schematically. (b) Sensor on SiO_2/Si substrate, shown in three dimensions. (c) Slice through the bacterium sensor made of graphene. (d) pH sensor cross section and (e) bacteria sensor chemical functionalization. (f) The Focusing Process, Seen in Three Dimensions (g) The 2D focusing mechanism and asymmetrical characteristics, seen from above [144].

Because of its high electrochemical and photochemical activity as carbon nanotube, is an excellent material for sensor-based applications in the pharmaceutical industry. Table 3 shows a few examples of where it has been useful. Graphene's utility extends beyond biosensors to the realm of medical diagnosis. Graphene may soon be at the forefront of biomolecules for detecting illness and response to treatment. On the other hand, using biosensors allows for the non-invasive diagnosis of glucose, glutamate, cholesterol, and haemoglobin [145–147]. Moreover, the biosensors would readily detect smaller/lighter markers because of the use of graphene [148]. Comparable sensors strengthened graphene, which expedites the process with quick detection and increased sensitivity in a cost-effective method.

7.1. Advantages

Graphene-based materials offer significant advantages in biomedical applications due to their interesting properties [157,158]. Their high surface area, excellent mechanical strength, and remarkable electrical conductivity make them ideal for modern biomedical applications [159–161]. In conventional biomedical technologies, graphene and its derivatives are used in drug delivery systems, where their high surface area allows for the efficient loading of therapeutic agents [162]. The ability to functionalize graphene with various biomolecules enhances their biocompatibility and specificity, making targeted drug delivery efficiently [160]. Additionally, graphene has strong antibacterial properties that contribute to use in wound dressings and implants, reducing the risk of infection and promoting faster healing.

Considering the microfluidics, graphene-based materials have advantages by enhancing the sensitivity and functionality of lab-on-a-chip devices. The exceptional electrical conductivity of graphene enables the development of highly sensitive biosensors, capable of detecting minute concentrations of biological markers which is crucial for early diagnosis and monitoring of diseases. Moreover, the thin and flexible nature of graphene allows to fabricate microfluidic devices with complex, miniaturized channels that can efficiently manipulate small volumes of fluids. This capability is particularly beneficial in personalized medicine, where precise control over fluid flow and reaction conditions is essential for accurate diagnostics and tailored treatments. The integration of graphene in microfluidic technology thus opens new avenues for advanced biomedical applications, combining high sensitivity, rapid analysis, and the potential for portable diagnostic tools.

8. Current challenges

The research on graphene-based materials and their medical applications has made significant progress, although remains several challenges. Some of the current challenges in this field include: biocompatibility and safety, tissue-specific targeting, biodegradability, scalability and production, stability in biological environments, drug delivery challenges, imaging and detection sensitivity, long-term effects etc. Besides, graphene-based microfluidics encompass a range of critical issues that need to be addressed to unlock the full potential of this innovative field. Biocompatibility and cytotoxicity concerns must be thoroughly understood, especially in biomedical applications, to ensure the safe use of graphene-based materials. Achieving precise fluidic control and minimizing surface interactions remains a challenge, affecting the efficiency of microfluidic operations. The scalability and consistent production of high-quality graphene materials for microfluidic devices, as well as integration with existing microfluidic systems, present significant hurdles. Regulatory compliance and standardization of protocols for device design and evaluation are essential for widespread adoption. Enhancing detection sensitivity and specificity for various analytes and improving the durability and long-term stability of graphene-based microfluidic devices are also pressing concerns. Addressing these challenges, requires interdisciplinary collaboration and ongoing research to explore the full potential of graphene-based microfluidics across various fields. In healthcare system, such collaboration can help to the develop the advanced diagnostic tools and therapeutic systems that influence the unique properties of graphene for enhanced sensitivity and specificity. For example, researchers from materials science, biology, and engineering can work together to create graphene-based biosensors integrated into microfluidic platforms that enable early detection of diseases and real-time health monitoring. In diagnostics, the interaction between graphene-based materials and microfluidics can lead to the creation of lab-on-a-chip devices that perform complex analyses with minimal sample volumes. Researchers from diverse fields such as physics, medicine, and microengineering can collaborate to optimize these devices for a wide range of applications, from blood tests to genetic screening, ultimately making diagnostics more accessible and affordable.

9. Conclusions and prospects

Graphene-based nanomaterials have shown significant advancements in synthesis processes and material characteristics, making them promising for healthcare applications. Different forms of graphene-based materials, produced using environmentally friendly methods and the latest advancements in graphene nanotechnology, are emerging as ideal electrode materials in biomedicine. The integration of graphene-based materials with microfluidics offers great potential to revolutionize healthcare and diagnostics. The unique properties of graphene such as high surface area, excellent electrical conductivity and biocompatibility

Table 3
Overview of graphene as a pharmaceutical sensing material.

Sl.	Modifier	Electrode	Detection method	Target	Linear range	Sample	Recovery %	Ref.
1	GO	Glassy carbon electrode (GCE)	Cyclic voltammetry (CV), LSV	Midecamycin (MD)	0.3- 200 μM	Serum, urine	95.6–104.3	[149]
2	Ni0.5Zn0.5Fe2O4/ graphene	GCE	CV, Differential pulse voltammetry (DPV)	Omeprazole (OMZ)	0.03–100 μM	Serum	97.5–101.5	[150]
3						OMZ capsule	98.6	
4	Graphene	GCE	DPV	L-dopa	0.04–79.0 μM	Tablet, mouse brain extract	101.4–109.42	[151]
5	GNRs-GO-CNTP	GCE	Square Wave Voltammetry (SWV)	Indomethacin	0.2–0.9 μM, 2.5–91.5 μM	Human blood serum, urine, pharmaceutical	98.0–103.5	[152]
6	Graphene/TiO2/ polyaniline (PANI)	GCE	SWV	Aripiprazole (ARP)	0.0112–0.0893 μM	Pharmaceutical formulations	99.0–101.6	[153]
7	Graphene nanoparticles-Bi	GCE	CV, LSV	Dopamine (DA)	1.0–30.0	Commercial injection	98.2–98.4	[154]
8	Graphene/2,7-BF	Graphene paste electrode (GPE)	CV, SWV, Cetrimide (CA)	Methyldopa	0.09–500.0	Tablet	97.6–102.0	[155]
9						Urine	98.7–103.2	
10	Graphene-AuNPs	Screen printed carbon electrode (SPCE)	CV, SWV	Rutin	0.1–15.0	Tablet	96.52–102.97	[156]

make it well-suited for a wide range of biomedical applications. When combined with microfluidic systems, which provide precise fluid control at the microscale, graphene-based devices enable rapid, cost-effective, and sensitive diagnostics. These integrated platforms hold promise in point-of-care diagnostics, personalized medicine, drug delivery, and tissue engineering. Graphene-based sensors integrated into microfluidic devices can detect biomarkers with high specificity and sensitivity, facilitating early disease detection and real-time monitoring. While graphene-based materials hold significant promise in biomedical applications, there are several challenges that need to be addressed as below to fully realize their potential.

1. ***Biocompatibility and Toxicity: S***urface functionalization of graphene with biocompatible molecules can be used to overcome this problem. Coating graphene with polymers, proteins, or other biocompatible materials can enhance its compatibility with biological tissues and reduce potential toxicity.
2. ***Scalability and Reproducibility:*** Developing standardized, scalable production methods such as CVD and improving quality control measures can help achieve consistent graphene materials. Collaborative efforts between industry and academia can also help in scalable production techniques.
3. ***Integration with Biological Systems:*** Advancements in nanotechnology and bioengineering can facilitate better integration of graphene with biological systems. Optimizing the design of graphene-based devices and employing bio-inspired engineering approaches can improve compatibility and functionality.
4. ***Complex Fabrication Processes of chips:*** Simplifying fabrication processes through innovative techniques such as inkjet printing or 3D printing can reduce costs and complexity. Utilizing self-assembly methods and developing new lithography techniques can also streamline the production of graphene-based microfluidic devices.
5. ***Stability and Durability of chips:*** Enhancing the chemical stability of graphene through surface treatments and protective coatings can improve its durability. Employing robust material designs and incorporating stabilizing agents can also extend the lifespan of graphene-based microfluidic devices.
6. ***Sensitivity and Specificity of Biosensors:*** Functionalizing graphene with highly selective recognition elements, such as antibodies or aptamers, can enhance specificity. Developing advanced signal processing algorithms and integrating complementary sensing techniques can further improve the accuracy of graphene-based biosensors.

CRediT authorship contribution statement

Mohammad Aminul Islam: Writing – original draft, Conceptualization. **Aslam Hossain:** Writing – original draft, Conceptualization. **Nayem Hossain:** Supervision, Formal analysis. **Md Mir Shakib Ahmed:** Software, Investigation. **Safiul Islam:** Software, Data curation. **A.M.A. Henaish:** Writing – review & editing. **A.V. Soldatov:** Writing – review & editing, Project administration. **Mohammad Asaduzzaman Chowdhury:** Writing – review & editing, Project administration.

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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