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Review

Revolutionizing biomedicine: Aptamer-based nanomaterials and nanodevices for therapeutic applications

Rajkumari Urmi [a], Pallabi Banerjee [a], Manisha Singh [a], Risha Singh [a], Sonam Chhillar [a], Neha Sharma [a], Anshuman Chandra [b], Nagendra Singh [a], Imteyaz Qamar [a,*]

[a] School of Biotechnology, Gautam Buddha University, Greater Noida, U.P. 201312, India
[b] School of Physical Sciences, Jawaharlal Nehru University, New Delhi, 110067, India

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ABSTRACT

With the progress in two distinct areas of nanotechnology and aptamer identification technologies, the two fields have merged to what is known as aptamer nanotechnology. Aptamers have varying properties in the biomedical field include their small size, non-toxicity, ease of manufacturing, negligible immunogenicity, ability to identify a wide range of targets, and high immobilizing capacity. Nevertheless, aptamers can utilize the distinct characteristics offered by nanomaterials like optical, magnetic, thermal, electronic properties to become more versatile and function as a novel device in diagnostics and therapeutics. This engineered aptamer conjugated nanomaterials, in turn provides a potentially new and unique properties apart from the pre-existing characteristics of aptamer and nanomaterials, where they act to offer wide array of applications in the biomedical field ranging from drug targeting, delivery of drugs, biosensing, bioimaging. This review gives comprehensive insight of the different aptamer conjugated nanomaterials and their utilization in biomedical field. Firstly, it introduces on the aptamer selection methods and roles of nanomaterials offered. Further, different conjugation strategies are explored in addition, the class of aptamer conjugated nanodevices being discussed. Typical biomedical examples and studies specifically, related to drug delivery, biosensing, bioimaging have been presented.

1. Introduction

With the advent of biotechnology, there have been tremendous advancements in various fields such as genetic engineering, omics technology, modern biology, biomaterial science, which undoubtedly have impacted on the population as seen by the breakthroughs in the biomedical field. A noteworthy development in biotechnology involves the emergence of addressing ligands, which bind to physiologically active molecules or receptors which are produced differently in diseased targets like cells or tissues. These specialized ligands play a key role in advancing both the diagnosis and therapeutics of diseases, wherein enhances sensitivity and specificity contributing to the refinement of diagnostic assays, particularly bio-imaging, delivery of drugs to diseased or target cell called targeted therapeutics, bio-sensing, biological analysis [1]. Consequently, as biotechnological innovations continue to unfold, the integration of targeting ligands stands as a key strategy in the quest for improved healthcare outcomes. Aptamers thus behave like ligands, in which they are single stranded short DNA or RNA sequences or amino acid sequences that are designed to bind to specific target molecules with high binding affinity and specificity. A reasonably rapid and affordable way to produce aptamer having slow rate of decomposition, little toxic effects and negligible batch-to-batch inconsistencies is the SELEX method (Sequential Evolution of Ligands by Exponential Enrichment) [2]. In SELEX selection method, aptamers are identified to select from a large random library and, then amplified obtaining a strand which have affinity to bind to various molecules such as proteins, peptides, drugs, chemical organic and inorganic compounds and whole cells [3]. RNA and DNA nucleic acid aptamers have been proposed as potentially new therapeutics and detection elements. The apparent benefits of aptamers have made it even superior than antibodies due to properties include their small size, non-toxicity, ease of manufacturing, versatility in chemical alteration, negligible immunogenicity, ability to identify a wide range of targets, and high immobilizing capacity. Aptamers have gained promising applications in the biological field, however conjugating aptamers to other molecules like nanomaterials have provided potential evidences of becoming one of the most useful

* Corresponding author.
E-mail address: imteyazqamar@gbu.ac.in (I. Qamar).

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devices in the therapeutic and diagnostic field.

Aptamer nanotechnology represents a cutting-edge convergence of two dynamic fields, aptamer technology and nanotechnology which contributes a platform for innovative applications in diverse domains of biomedical and therapeutics. Nanotechnology has generated widespread foundation in the biotechnological sector. Regulating the molecules at nanoscale level makes enormous differences and possibilities of modification of chemical and physical properties of substances according to their target applications. Nanomaterials like carbon nanomaterials, metallic nanoparticles, nanostructures, magnetic nanomaterials, in represent a major breakthrough in medicine and material science to precisely communicate with the human tissue at cellular level. Attributes of nanomaterials such as having electronic, thermal, optical, magnetic, photocatalyst properties, makes them excellent choice to be utilized in biological filed like in sensing and imaging [4]. The integration of aptamers with nanomaterials has emerged as a transformative approach, leads to the development of engineered aptamer nanodevices and nanostructures. These hybrid entities harness the unique characteristics of aptamers, such as their high binding affinity and selectivity, and combine them with the tailored functionalities of nanomaterials, resulting in a powerful synergy that enables applications ranging from targeted drug delivery and imaging to sensing and therapeutics. Owing of the enormous surface area of nanomaterials, aptamers can have a substantial loading efficacy and binding affinity, which increases the sensing intensity by a number of times and enhances target identification performance through collaborative contact. Importantly, aptamer conjugated nanomaterials are advantageous in diagnostic purposes as most nanomaterials exhibit extraordinary biocompatibility helping aptamers to be shielded from damage brought on by nuclease degradation [5]. Aptamer nanotechnology is thus a field that has great promise, to such extent, more research and development are necessary, even though considerable success has been performed.

This review provides an insight on how the aptamers are generated and classification of nanomaterials with the conjugation strategies involved in the construction of aptamer immobilized nanomaterials and their implementation in the biomedical applications. Different types of roles acted by nanomaterials in the conjugated system, such as role as electrocatalyst, photocatalyst, optical transducer and carrier molecule have been discussed with the various strategies of conjugation of aptamer with nanomaterials includes covalent and non-covalent strategies. Diverse nanodevices constructed by the aptamer immobilized with nanomaterials have been addressed and categorized ranging from aptasensors types based on nanomaterials to nanorobots to nanomotors. Most importantly, it explores all the constructed devices utilization in varying biomedical applications such as drug delivery system, gene therapy, bioimaging, biosensing and even cancer therapy.

2. Aptamer nanotechnology

2.1. Aptamers

Aptamers are single stranded short oligonucleotides, whether it can be DNA either RNA, therein having ability for high attractive to bind and target the molecules corresponding to it. Aptamers have capability to bind to proteins, small organic or inorganic molecules, drugs, toxins resulting in modulation of target molecules [6]. The name aptamer has been from a Latin word “aptus” meaning “to fit” and “meros” which means “part”, and was introduced in 1990 by Andrew Ellington and Jack Szostak [2]. These nucleic acid-based ligands can be generated and identified by a synthesis approach called SELEX (Sequential Evolution of Ligands by Exponential Enrichment). In SELEX specified selection method, aptamers are selected from a large random library and, then amplified obtaining a strand of 10–100 nucleotides [3]. Aptamers are analogous to antibodies functionally, however they vary structurally as well as physically. Due to this differential, aptamers are considered to be superior replacements for antibodies in therapeutic applications. Unlike antibodies, in terms of having advantages aptamers have high stability, small size, does not cause immunological rejections, minimum variation in batch-to-batch production, low toxicity [7]. Being a new research area, a medication called “pegaptanib” or “Macugen” which originated from aptamer commercialized by company Pfizer and they were given US FDA approval as it had potential to treat age-related maculopathy that affects a person’s vision, over the last two decades [8]. Binding sites of aptamers resemble such kind of features that serve as sites for target molecules to bind. Aptamers when they bind to target molecules behaves like a three-dimensional structure, from a single stranded turns into a loop like structure, making binding to the target molecules easy. This self-folding through electrostatic forces, hydrogen bonding, makes aptamers ability that bind to wide variety of targets such as organic, inorganic, proteins, nucleic acids, drugs, toxins, especially small molecules [9]. This form of aptamers gives better accommodation for binding to the binding pocket of the target molecules. Due to this, they have extremely focused drug like properties which makes them easier to incorporate them into drug target validation and drug screening activities [1]. Aptamers have capability of modifications such as chemical modifications of affinity tags for identification of molecules, ring modifications, modifications to make them nuclease resistant, above all, chemical modification to facilitate conjugation to nanomaterials like thiol groups [10].

2.2. Advantages of aptamers

Aptamers has been emerging as one of the class of molecules which has found various benefits and primary employed in the biological field. Most biomedical applications uses antibodies, however aptamers are molecules with several important advantages. There are aptamers effective in binding both large molecules such as proteins, cells, and smaller ones molecules such as amino acids or metals, concurrently antibodies in general can bind mainly to larger molecules. Aptamers known to be superior to antibodies due to their less immunogenicity and no immunological rejections, they function similar to antibodies however, starting from their structure they differ from each other in their nucleic acid contents. [6] Synthetic aptamers have a number of advantages over antibodies, including time and control over production in addition to design flexibility, perhaps the most significant benefit of aptamer technology, despite the fact that antibodies are more evolved and understood (Panigaj et al., 2020; [3]). While the design and production of antibodies necessitates a biological system with inherent stochasticity and can take several months, the selection of aptamers can be completed in a matter of weeks under carefully monitored experimental settings, with the possibility of automation. Selective aptamers can be produced at scale using a fully synthetic process, which reduces batch-to-batch variability. (Panigaj et al., 2020) Since aptamers are chosen under laboratory condition, they can be employed where we can determine the aptamer selection through their binding affinity to a variety of targets, such as harmful or antigens with low immunogenic substances. In addition, the screening procedure carried out in non-physiological conditions, such as excessively high or low pH levels or temperatures making it challenging to obtain them with antibodies. The greatest advantage of aptamers is their durability at high temperature than the protein-based antibodies. [11] Aptamers, we know can be of two types either oligonucleotides or protein based, where it is known that oligonucleotide based are more stable than the protein-based aptamers. Proteins easily get denatured losing their structure at high temperature, so antibodies being proteins readily lose their structure in high temperature making oligonucleotide-based aptamers to be the greatest advantage over antibodies. While antibodies readily experience irreversible denaturation, aptamers readily regain their original shape and can bind to targets upon re-annealing. Aptamers can therefore be applied in a variety of test scenarios [11]. Aptamers can offer further benefits when it comes to nanostructures, which also hold great promise

for diagnostic applications. For instance, aptamers have a higher surface density and less steric hindrance than antibodies since they are considerably smaller even than antibodies aiding in boosting the binding yield (Lee et al., 2011). Aptamers can withstand reversible denaturation and be transported at room temperature and stored for an extended period of time under the right circumstances [12]. These distinct characteristics make aptamers a great option for applications in biomedical field.

2.3. *Selection of aptamers*

The selection of aptamers having preference for the target sequence can be identified through a method as already mentioned through SELEX. This is a promising technique that allows the production of aptamer affinity agents without the need to initially select a target In the 1990s, Gold and Ellington's independent research groups conducted the first SELEX studies. Gold and their team called their process "systematic evolution of ligands by exponential enrichment," or SELEX; the latter term was universally used for subsequent research. Szostak and their team referred to their technique as "in vitro selection" [2,13]. In order to find an aptamer with a high affinity for the target, SELEX first screens a sizable or a generated oligonucleotide pool. Typically, this oligonucleotide is composed of two sequences; a constant sequence and a randomly generated sequence. The aptamer is contained on the random sequence, which attaches to the target molecules. It is bordered by conserved sequences, which bind to the primers used in polymerase chain reaction (PCR). The primer-driven PCR amplification of the oligonucleotide pools for the upcoming SELEX round requires the conserved part with a constant sequence. [3,14] The library's size is sufficient to fill the appropriate sequence space. After that, the target molecule is added to the library and allowed to bond properly. Subsequently, the nucleic acids that are not bound are separated from those that are specifically bound to the targeted molecule. The required sequence is subsequently eluted by chromatography techniques and amplification via PCR. Further, selection protocol is shown in Fig. 1. Until the final sequences are greatly enhanced, this selection process is repeated multiple times. After being chosen, the nucleic acids are evaluated for possible binding affinities and put via DNA sequencing. Aptamers with high binding affinity and specificity are produced by SELEX technology. [3,15]

2.3.1. *The SELEX technology*

The fundamental aspect of the SELEX process and subsequent applications relies on the interaction between an aptamer and the target molecule of interest. This aspect interaction influenced by the type and size of the target molecule. In cases where aptamers exceed the size of their target, they typically incorporate it into their own structure. Such SELEX process for aptamer selection can be based on different types of methods and molecules utilized to produce aptamer of targeted size. This diversity in SELEX variants, in turn, provides a spectrum of aptamers with unique characteristics that can be harnessed for aptamer-nanoparticle conjugation. Over the course of its development, SELEX has undergone numerous iterations and enhancements. Aptamers are selectable in either DNA form or RNA aptamer form, and the selection conditions tailored to closely resemble the condition of target species or molecule to their interest [3]. For the isolation process of either DNA or RNA aptamer, protocol steps can be varied. For DNA aptamer isolation, the initial pool of oligonucleotides is composed of DNA sequences featuring a variable region spanning 30 to 60 nucleotides. The purpose of these flanking regions is to facilitate PCR amplification during subsequent steps of the selection process. The initial round involves the use of DNA, where they are during the incubated with our target specific to application like cells, separates the strands of DNA effectively to become single stranded, a common approach involves biotinylating the 3′ primer. This biotinylated primer enables immobilization on streptavidin-coated beads, followed by denaturation using chemical methods. The resulting library of ssDNA is then subjected to incubation, allowing for the binding of aptamers. The bound sequences are subsequently collected and purified. The partitioned DNA, comprising the of our interest DNA sequences, is utilized for the next subsequent cycles of SELEX protocol [1,16]. Each successive round refines the pool of aptamers, enhancing their specificity and affinity for the target.

For the isolation of RNA aptamer, the initial step involves the generation of DNA template to produce ssRNA, and annealing of 5′ primer is required instead of 3′ primer annealing, therefore results in the generation of a double-stranded DNA (dsDNA) template. This creation of dsDNA template is achieved through the extension of the primer using the Klenow fragment or through multiple cycles of polymerase chain reaction. Further, dsDNA template which have been obtained is converted into single-stranded RNA (ssRNA) using a transcription process, in which ssRNA, now synthesized from the dsDNA template, becomes available for interaction with the desired molecule. The 3′ primer annealing performed with reverse transcriptase enzymes. This annealing process results in the formation of complementary DNA (cDNA) from the RNA sequence, then is subjected to amplification via PCR to generate a double-stranded DNA (dsDNA) template, which can be used for subsequent rounds of the SELEX process. So, for the RNA aptamer, RT-PCR is utilized for this purpose, whereas conventional PCR utilized in case of DNA aptamer isolation. [16]

In the SELEX process, a negative selection or counter selection and a positive selection has been incorporated intended to eliminate sequences that may have non-specific binding affinities for components other than the desired target. Basically, in negative selection, the goal is

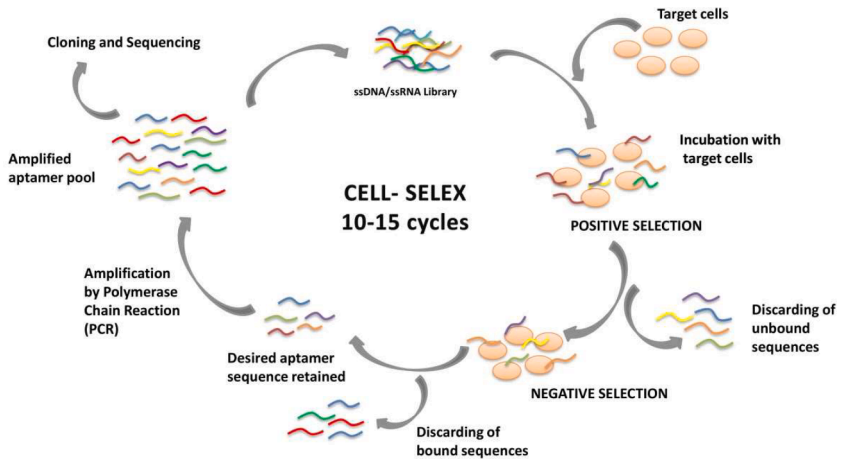

Fig. 1. Selection of aptamer by Cell-SELEX.

to check the binding of the target to enhance the specificity of the selected aptamers for the desired target. Negative targets are chosen to represent components or features that aptamers should not bind to, where untargeted cells like parental PC12 cells are selected for such purpose in case of cell-based SELEX. This Cell-based SELEX process is illustrated in Fig. 1. The aptamer library generated is exposed to the negative target during a counter-selection round, in which the untargeted cells are incubated with the aptamer library so as to allow potential non-specific binders to interact with the negative target. (Zhou et al., 2017; [1]). Techniques like affinity chromatography, magnetic bead separation, or other methods specific to the experimental design are employed for the separation of bound and unbounded sequences, having introduced to distinguish between sequences that have bound to the negative target and those that remain unbound. Sequences that have bound to the untargeted cells are discarded eventually ensuring that sequences with unwanted binding characteristics are removed. [15,17] Positive selection is followed afterwards, where in this case positive target specific to the molecule or entity that the aptamers are intended to bind are utilized, as demonstrated in Fig. 1. Similarly, the targeted or desired cells are incubated with the library of aptamers followed by separation of bound and unbound sequences. The required sequences bound to the positive target are retained, often through methods like chromatography that allow for the isolation of the target-bound aptamers. [17].

The iterative nature of SELEX, combining both negative and positive selection, helps enhance the specificity of the aptamer pool over successive rounds.

SELEX process is subject to various influencing factors that can impact its outcomes. Understanding and addressing these factors are essential for optimizing the selection and enrichment of aptamer sequences with desired properties. Due to the structural complexity inherent in proteins, the ways in which they can engage with aptamers are more diverse compared to the interactions observed with small molecules. The nature of the target molecule is a prime factor influencing the selection of appropriate SELEX variants. The specific characteristics of the target, including its molecular type, may necessitate a selection process conducted in solution, while others may benefit from immobilization on a matrix. The choice of an immobilization matrix introduces additional considerations. The manner in which the target molecule is immobilized can impact its conformation, potentially influencing the binding interactions with aptamers. One of the simplest and cost-effective matrices employed for target immobilization is a nitrocellulose filter, favoured for its uncomplicated nature and affordability [18]. The incorporation of modified nucleic acids may enhance the probability of a successful selection. When modifications are needed to extend the half-life of aptamers, it is advisable for these modifications to be present during the selection process however addition in post-selection could potentially disrupt the structure and functionality of the identified aptamers. Molecules characterized by strong hydrophobicity or possessing prominent surface charges may present limitations in terms of their interaction with aptamers [18,19]. These properties could potentially diminish the likelihood of successful SELEX outcomes. SELEX variants can be based on immobilized targets used such as Bead-based SELEX can be utilized for beads with different sizes and material, microarray-based SELEX having aptamer immobilized to microwell plate, Capillary electrophoresis (CE) SELEX with both targets and aptamers in solution and Cell SELEX involves use of cells or tissues for generation of aptamers [20].

Nevertheless, there are challenges with SELEX like any other methods have. The efficacy and success of SELEX depends on the accessibility and stability of the target molecule. Aptamer degradation by nucleases is one of most problems. Depending on the conformational structure and oligonucleotide content, the typical duration of oligonucleotide degradation in blood and cells can vary from time to time [21]. Chemical alterations and other methods to increase nuclease resistance can alter the characteristics of aptamers, necessitating further adjustments. Scientists have further developed ways to make aptamers resistant to such nucleases. A typical approach is to alter the aptamer while they are being created. Several chemical groups, such as fluorine (F), amino (NH_2) groups, can be added to the aptamer structure as part of these alterations [22,23]. Aptamers may be shielded against degradation by these modifications, but their ability to adhere to their target may also be compromised. Such changes must be carefully tailored to achieve the intended purposes. Aptamer cross-reactivity may pose a challenge to the practical implementation as aptamer in contact with other proteins may result in adverse effects By using structurally comparable compounds in a SELEX-negative selection stage, this issue can be addressed, where a highly specific aptamer can be created by applying a rigorous SELEX technique [24]. Aptamer production appears to be a fairly straightforward procedure, but in practice it is a labor-and time-intensive approach.

3. Nanomaterials

The term ‘nanotechnology’ is a field of science and technology that involves the application of materials and devices at the nanoscale, typically at dimensions less than 100 nm. It is the utilization of technology for the synthesis, manipulation, characterization of the nanoscale range molecules for its wide variety of applications [25]. Unique properties have been incorporated in such materials allowing for control and regulation of its chemical, biological, physical properties at macroscopic level. Applying nanotechnology in the field of aptamers presents distinct opportunities for the advancement of medicine, influencing the diagnosis, monitoring, and treatment of diseases, while also contributing to the control and comprehension of biological systems. To unlock the complete capabilities of nanomaterials in biomedical field, they must exhibit biocompatibility and possess the ability to specifically target biomolecules. This specificity is crucial to enable sensing and imaging, and specifically drug delivery within intricate conditions including animals, and humans apart from living cells or tissues. The immobilization of nanomaterials with aptamers represents a potent strategy for constructing versatile materials and devices with sought after properties, wherein nanomaterials can be readily customized for functionalization depending on the wide applications. This kind of modification with the aptamers improves binding affinity specifically attributed to their capability to absorb cellular constituents and metabolites. Nanomaterials involves extensive classifications having diverse properties, on which nanomaterials are defined as materials or substances having structure and components at nanoscale range of 1–100 nm where they exhibit defined dimensions [26]. Nanomaterials are known to exhibit large surface area and excellent biocompatibility allowing for attachment of large number of aptamers and depending on its size each nanomaterial properties can be varied. At the nanoscale, materials can exhibit properties that give significance for their size range less than 100 nm. They exhibit unique quantum effects within which confines the behavior of electrons and other particles, where they are is restricted in its range. Different optical, electrical, and magnetic properties that are not present in bulk materials can result from these quantum effects. Increased surface area of the nanomaterials than bulk matters allow for more interactions with surrounding environments, making them useful for applications like catalysis, sensing, and drug delivery [27]. During synthesis, one can manipulate the size, shape, and content of nanomaterials to fine tune their properties. Materials with certain properties can be modified for a variety of uses, like for precise medication delivery systems or highly detectable sensors, due to their tunability.

Nanomaterials can be classified based on the dimensions, structural configurations and nucleic acid nanomaterials as shown in Fig.2. Such diverse types of nanomaterials have its distinct properties unique for their applications. Zero-dimensional nanomaterials (0-D) includes nanoparticles, quantum dots, where all are in the nanoscale range of 1–100 nm and as name suggests they are not extended in any dimensions

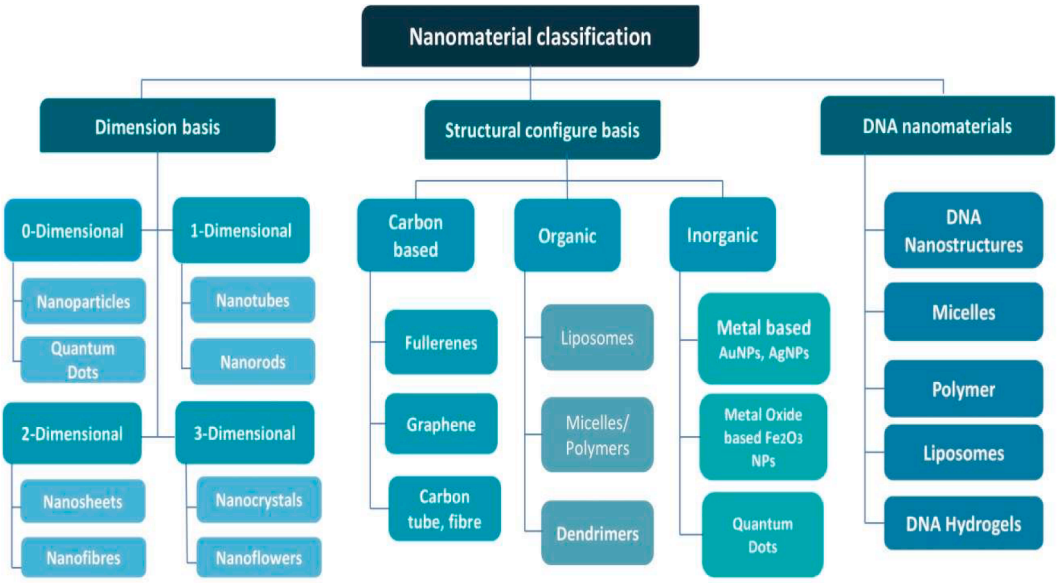

Fig. 2. Classification of nanomaterials on different basis.

and behave as point like structures. Nanoparticles are defined as minute scale particles existing at the nanoscale, characterized as particles with dimensions less than 100 nm in at least can have one direction or materials constructed from these diminutive units. Gold nanoparticles, silver nanoparticles, liposomes, capable of penetrating deep in tissues and interacting at molecular level due to their small in size. One dimensional nanomaterial (1-D) consists of nanotubes, nanorods, nanowires characterized by at least one dimension in nanoscale range. As the dimensions of nanowires decreases, they generally demonstrate enhanced mechanical properties with increased strength and toughness [26,28,29]. Nanosheets, nanofibers, graphene are two dimensional nanomaterials (2-D) arranged like sheets or layers having flexibility property. Lastly, three dimensional nanomaterials (3-D) have all dimensions from 1–100 nm in range, which can be of nanocrystals, nanostars, nanobulk materials. Nanoclusters possess characteristics that harmonize well with the attributes of aptamers. Additionally, they exhibit advantageous demonstrate low toxicity, making them particularly suitable for applications in biological contexts, where their unique properties can be leveraged for imaging and sensing purposes without posing significant risks to living systems [30]. On structural configuration basis, nanomaterials can be organic, inorganic or carbon based, where components primarily composed of carbon atoms in carbon-based nanomaterials like fullerenes, carbon nanotubes, having unique electronic, mechanical, thermal properties. Organic nanomaterials are specifically used in drug delivery and imaging due to their biocompatibility with cells and tissues, such organic nanomaterials can be of liposomes, polymers, dendrimer. Inorganic, on the other hand are metal based like gold and silver nanoparticles, iron oxide nanoparticles, in which gold nanoparticles are known best to conjugate with aptamers. In addition to possessing large surface area and versatile chemical modification, gold nanoparticles exhibit surface plasmon resonance resulting in exploiting these properties in conjugation with aptamers to have sensing and imaging abilities [31,28]. DNA nanomaterials are new concept in the field of DNA nanotechnology, where it utilizes the properties of nucleic acid (either DNA or RNA), its self-assembling ability, capability of base pairing functioning as the building block of nanostructures [29]. They are highly programmable with the aptamers which can be engineered to carry and deliver drugs at cellular level, hence nanocarriers, nanodevices, nanorobots designed to execute its functions to their applications. DNA nanostructures possess inherent water solubility, rendering them well-suited for creating biosensors in homogeneous solution environments [32]. Corresponding to this, nanomaterials can be synthesized by top-down and bottom-up approaches, featuring various chemical, physical and biological methods. In top-down, smaller nanoparticles generated by division of bulk materials, employing physical methods like mechanical milling and electro explosion. The chemical and physical methods for synthesis of nanoparticles like thermal techniques, and by lithography and milling processes are under this approach that provides the essential energy for the synthesis process. Nanomaterials are assembled from smaller components in bottom-up approach adopting chemical method such as sol-gel method and green synthesis by utilizing different plants and fungi mediated synthesis have been developed [25,26]. Under this approach, it often includes the biological method of synthesis such as produced from plants, algae, bacteria, fungi, actinomycetes, and also includes some chemical methods like sol-gel process, aerosol-based process [25]. Most bottom-up techniques make use of naturally occurring, well defined structures. However, because the generated nanostructures are positioned randomly at this point in their growth, they are unlikely to create organized and intricately linked patterns. Consequently, challenging materials could be created by combining top-down and bottom-up techniques. Various roles of nanomaterials they present when conjugated with aptamers have been discussed.

3.1. *Role of nanomaterials*

3.1.1. *Electrocatalyst*

Nanomaterials with special conducting properties utilized to engineer electrochemical biosensor. Nanomaterials based on carbon like graphene, fullerenes, quantum dots, carbon nanotubes, are majorly favoured acting as conducting transducers due to their exceptional electronic properties. These materials are renowned for their high conductivity, making them effective in carrying and transmitting electrical signals [33]. Electroresponsive polymers are kind of nanomaterials having significant number of charged groups, converting electric energy into mechanical energy. This further, alters their size or shape when electric current applied to give a slight modification [34]. An immunosensor based on aptamer modified graphene was demonstrated by Ohno et al. to receive electrical signal for detection of IgE protein, where IgE aptamers were conjugated on the graphene surface [35]. So, for the need to integrate such useful electric properties with the living system, Abidian et al. engineered low-impedance, biologically active polymer nanotubes on surface of gold electrode allowed for a slow breakdown, which allowed for the continuous release of biologically active

substances [27]. A novel biosensor composed of gold nanoparticle conjugated aptamer was engineered for the detection of a tumour biomarker like carcino-embryonic antigen [36]. Combining electroactive nanomaterials with aptamers in diagnostics increased potential to broaden applicability and enhance sensitivity, allowing for detection at low target concentrations.

3.1.2. Photocatalyst

Light sensitive materials serve as biomarkers, indicating drug sites, showcasing targeting capabilities, and visualizing tumors across various parameters precisely controlled with on/off modes [4,34]. Nanozymes have been recently developed, are nanomaterial possessing enzyme like properties having significant promise in a range of biomedical application [37]. Cheng et al. designed a new single atom nanozyme (SAN) where there is presence of Fe atoms immobilized to the carbon nanotube, resulting in noticeable colour changes in the presence of various substrates. It showed catalysing abilities for the oxidation of different substrates, such as 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS); 3-amino-9-ethylcarbazole (AEC), 3,3',5,5'-tetramethylbenzidine (TMB), o-phenylenediamine (OPD), and di-azo-aminobenzene (DAB), resulting in green, red, blue, yellow and grey colours, respectively [38]. Most modern phototherapeutic systems effectively employ NIR-sensitive nanopolymers, which are comparable to UV/VIS-sensitive fluorophores, NIR fluorescence is being used in new diagnostic or treatment systems to observe deep tissue cancer tumours. Nanoclusteres synthesized by Thangudu et al. showed exhibition of remarkable photophysical properties, featuring characteristic emission peaks, displaying effective co-localization in the cytoplasmic level, while a notable part or section translocated into the nucleus, thereby acted as fluorescent markers for cancer cells that helped in visualization intracellularly [39]. This further made advantageous for the nanomaterials to be acting as a photocatalyst when coupled with aptamers.

3.1.3. Optical transducer

With the integration of aptamer and nanomaterials, optical-based sensing has experienced notable progress in recent years. Blue latex beads made of polystyrene serve as favourable candidates for colour transduction due to their ease of modification, excellent dispersibility, and clear colour signal. Such polystyrene blue bead coated with streptavidin used to enhance the beacon of nucleic acid, resulting in distinct visible detection shown in pattern generated by isothermal strand displacement amplification (iSDA) method [40]. A distinct and vivid black colour is displayed by silver-enhanced gold nanoparticle. This occurs as the silver ions in the solution undergo catalytic reduction, binding to the surface of gold nanoparticles and creating a silver shell, producing an intensified black signal, effectively amplifying the overall signal strength [4]. Graphene, carbon nanotubes, carbon nanoparticles also show black colour, providing outstanding resolution and robust signal contrast [41]. Nanomaterials often serve as quenchers called as nano-quenchers in cases when using FRET (Fluorescence Resonance Energy Transfer) technology so aptamers frequently employ nanomaterials like quantum dots (QDs) or gold nanoparticles with strong fluorescence characteristics as fluorescent probes [42,43]. Additionally, superior surface area in nanomaterials changes more fluorescent molecules or increase fluorescent dye loading, enhancing their sensitivity in biosensing and bioimaging. Song et al. generated dansyl (DNS) conjugated with nanotube and nanoflower shaped nanomaterials for fluorescence in the cell imaging process [44].

3.1.4. Magnetic signal

It is possible to distantly regulate cells both in vitro and in vivo using magnetic nanoparticles, which include iron, cobalt, nickel, and metal oxides like iron oxide nanoparticles, allowing for a better insight onto cell signalling and functions [34]. Compared to traditional techniques, magnetic nanomaterials offer greater edge in terms of imaging. Conventional techniques like thermal ablation, which at first involves exposing the area of tumour growth to a high temperature, and magnetic hyperthermia employs ultrasounds or microwaves to raise the body's temperature to kill cancer cells, have certain drawbacks, including low ability to target and deep tissue infiltration [45]. Variable kinds of nanomaterials when paired with aptamer have the potential to enhance magnetic separation, cellular magnetic labelling, magnetically administration of drugs, immunoassays, and MRI (magnetic resonance imaging) diagnostics [7]. A system created by Antman-Passig and Shefi is an illustration of the application of magnetic signal responsive by nanomaterials. They provided a novel approach to remotely and dynamically control gel orientation in situ, having incorporated magnetic nanoparticles into collagen hydrogels and subsequently applied an external magnetic field. Significantly, the normal electrical activity and survival of neurons within the 3D magnetically generated gels and formation of an elongated morphology by neurons developed after weeks hence, demonstrated neuronal regeneration in the system [46].

3.1.5. Thermal signal

Nanomaterials not only exhibit magnetic signal, electrochemical properties or act as photocatalyst, but generates excellent thermal signal facilitating in the diagnostic field. Detection techniques based on the excellent photothermal responsiveness can be seen in aptamer conjugated gold-palladium nanopopcorns designed for thermal reading detection [38]. Au has been incorporated with Pd as Au is known to have limiting surface plasmon resonance (SPR) absorption band so Au alone is not the best option for the photothermal signal [47]. As a result, to improve the efficiency of thermal detection by Au-based nanomaterials, a particular type of Au-Pd nanocomposite created wherein, leading for excellent thermal performance [4,48]. Tamaki and Kojima recently reported a thermos-sensitive dendrimers, where they developed and produced a range of zwitterionic dendrimers modified with phenylalanine (Phe) as thermal and pH-sensitive polymers using polyamidoamine (PAMAM) dendrimers showing upper critical solution temperature (UCST)-type thermosensitivity [49]. Newly developed injectable zwitterionic thermosensitive hydrogel shows promise as a substrate for a range of biomedical uses. The PNS nanogels wherein PNS is for poly (N-isopropylacrylamide-co-sulfobetaine methacrylate), were modified containing polydopamine nanoparticles (PDA NPs), when upon injection observed substantial anticancer effects leveraging a combination of photothermal therapy and local chemotherapy [50].

3.1.6. Carrier molecule

Nanomaterials can function as nanocarriers by transporting and delivering various substances at the nanoscale and in the field of aptamer nanotechnology, they are employed as aptamer carrier due to their variable properties. Unique features such as enhanced targeted drug delivery, increased stability makes nanomaterials acting as a carrier molecule to be important. Moreover, enhanced wide surface area of the nanomaterials like in case of nanosheets, nanoflowers facilitates aptamer immobilization on surface, therefore boosting its biosensing and bioimaging ability [51]. Various kinds of nanocarriers are used to transport hydrophilic and hydrophobic drugs to the directed location. These include inorganic nanocarriers, consisting of carbon nanotubes, magnetic nanocarriers, quantum dots, and organic nanocarriers, like liposomes, dendrimers, and polymeric nanocarriers [52]. Among nanomaterials employed, particularly organic nanomaterials like liposomes with different therapeutically feasible compositions proven to be the most effective [53]. The lipid bilayer surrounding liposomes assist in transportation, targeting and extending in vivo circulations as therapeutic agents [54]. Additionally, the binding affinity of protein-like nanomaterial for mRNA molecules is more persistent and prolonged, facilitating efficient cytosolic transport of mRNA and cellular absorption, leading to robust gene expression [4].

4. Aptamer conjugated nanomaterials

Delving into the aptamers and nanomaterials in the field of biomedical, numerous applications have become feasible by the range of nanomaterials coupled with aptamers constructed through various approaches. The development of functionalized nanomaterials conjugated to aptamers designed for specific applications like bioimaging, biosensing, drug delivery relies on the capacity to manipulate the size, shape and composition of these nanomaterials and aptamers. Likewise, it depends on what properties the nanomaterials have that can function in sync with the aptamer conjugated to functionalize and enhance specificity. This permits a customized adjustment of their physical, chemical properties, enabling a targeted and precise tailoring to meet the requirements of the intended application. Aptamers can be readily modified facilitating their assembly on the nanoparticles surface through covalent conjugations strategies (Fig. 3) like Au-S linkage (Mirkin et al., 2020). The Au–S covalent interactions play a crucial role in ensuring a durable and specific binding between the aptamers and the nanoparticles allowing precise control over the orientation of aptamers on the nanoparticle surface, thereby enhancing the overall stability and efficacy of the functionalized nanoparticles. It is possible to target the transmembrane protein found elevated in prostate cancer, using nanoparticle and A10 aptamer conjugates as reported by Farokhzad et al. showing drug-encapsulated nanoparticles [55]. Aptamers have been identified to inhibit autoimmune antibodies suggesting significant implications for insulin resistance treatment. These instances highlight the potential for aptamers in pioneering targeted nanotechnology-based treatment methods to disrupt disease pathogenesis across various conditions [56,1]. Nevertheless, by developing aptamers that can bind to VEGF, researchers gain a powerful tool to modulate angiogenesis process essential for the formation of new blood vessels, offering potential applications in treating various diseases which is one of the foremost achievment in aptamer research [57].

Aptamer conjugated nanomaterials possess a combination of aptamer and nanomaterial properties, along with additional features like high affinity and specificity, robust conformational modification, large surface area and biocompatibility [28]. They exhibit new properties apart from its native attributes for better playing its role in different applications. a) High affinity and specificity; the aptamer conjugated nanomaterials showed enhanced specificity and affinity due to their covalent and non-covalent interactions. A study reported fluorescent probes utilizing ruthenium (Ru) complexes and quantum dots (QDs) to demonstrate a dynamic fluorescence response [58]. b) Conformational modifications; aptamers change conformation when bind to target modifying their structure into secondary or tertiary conformation, inducing high affinity and specificity. This further enabled the construction of more sophisticated devices in the medical field by changing their specific sequences for stabilized behaviour [10, 28]. c) Large surface area; smaller the nanomaterial higher is the surface area, so increase in the surface atoms produce plenty of unsaturated bonds. Thereby, gold nanoparticles when conjugated with aptamers show high catalytic property and expansive surface area allows for a higher aptamer density, facilitating increased interaction with target analytes [59]. d) When choosing materials for particular uses, the characteristics of bulk nanomaterial must be carefully taken into account in addition to aptamer making surface biocompatibility crucial. A number of methods aimed at improving biocompatibility through surface modification have been established however, there are still a lot of obstacles to get beyond [28,60].

4.1. Conjugation strategies

4.1.1. Covalent strategies

In this kind of strategies for functionalization, they are immobilized with the help of covalent bonds resulting in a stable molecule. Covalent techniques are employed commonly to conjugate aptamers and nanomaterials, which are known to be the most stable strategy than non-covalent techniques [4]. Furthermore, strategies involving covalent coupling chemistries are extensively utilized in the synthesis of a wide array of nanomaterials, imparting distinct surface properties and functional groups. In covalent conjugation, a thiol group is typically used mostly affixed to the aptamer as functional moeity. This functional group then engage in chemical reactions with corresponding functional groups, such as carboxylic acid or aldehyde groups, situated either on the surface of the nanoparticle or on extremes or directly with the nanoparticles like organic or inorganic nanoparticles [17] as demonstrated in Fig. 3. There is use of a linker molecule as shown in Fig. 3 that serves as a bridge between the aptamer and nanomaterials playing key role in flexibility and accessibility, where they can be of thiol linkers, polyethylene glycol (PEG), maleimide-modified linkers. Covalent conjugation methods encompass various interactions, such as the bonding of the carboxylic acid with the amino forming an amide linkage, the interaction between the carboxylic acid and the thiol group resulting in a thioester bond, ester bond formation, the interaction between two thiol groups leading to a disulfide bond, and the bonding of the thiol group resulting in an Au–S or Ag-S bond where, among this thiol linker is

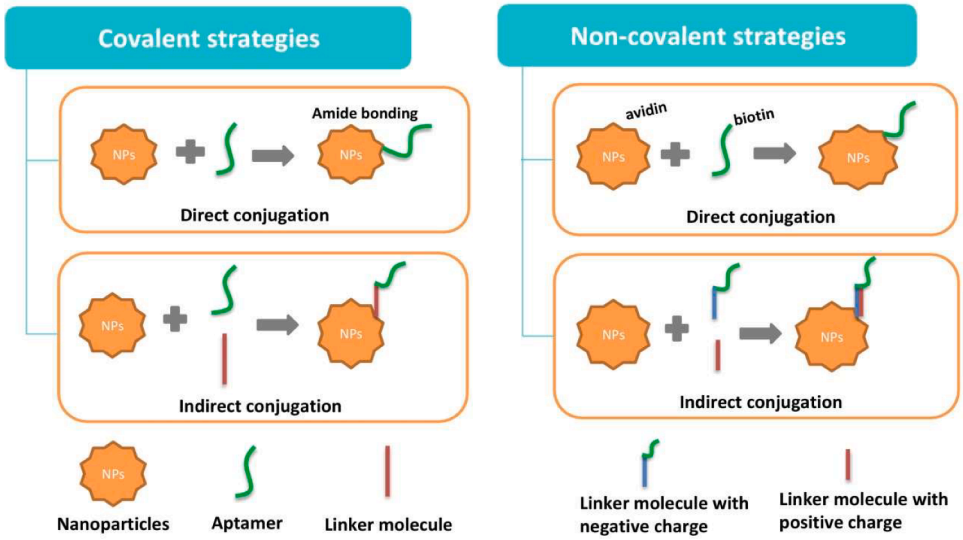

Fig. 3. Conjugation strategies of aptamer and nanomaterial.

the most used and studied when using gold nanomaterials [4,17,61].

Through this type of sophisticated Au-S chemistry reaction, immobilization of thiolated aptamers on the surface of porous gold nanocages (AuNCs) electrostatically attached to a screen-printed carbon electrode (SPCE) enabling efficient aptamer coupling [62]. A study described the invention of a unique multicolor fluorescent gold nanoprobe that combines the ultrahigh quenching capacity of gold nanoparticles (AuNPs) with the precise binding abilities of aptamers for the homogenous detection of small-molecule targets, therein using thiol conjugations [63]. This type of conjugation between aptamers and nanomaterials through covalent linkage as example just described above, significantly enhanced the stability of the aptamer-nanoparticle complex, ensuring prolonged functionality in biological environments. Further, covalent conjugation prevents the leaching or detachment of aptamers from nanomaterials over time, which is essential for maintaining the integrity and functionality of the bioconjugate. Direct conjugation in case of covalent strategies occurs without the utilization of linkers and directly coupled using amide bonding, while indirect conjugation in covalent strategies, there is use of linker molecule where, functional group on aptamer and nanomaterial conjugate to immobilize on surface of the nanomaterials [17] (Fig. 3). A10 aptamers commonly used where they are conjugated with cationic nanobubble with the direct conjugation by covalent strategies for targeted drug delivery [64] as shown in Table 1 with the size of nanocomposite formed. In addition, Si-based nanomaterials surfaces are abundant with hydroxyl groups, while graphene oxide surface have carboxyl, carbonyl and hydroxyl groups [65]. Using the thiol conjugation, DNA aptamer namely, sgc8 was effectively bonded to the liposome surface, where sgc8 aptamer-liposomes were prepared by first adding a maleimide polyethyleneglycol (PEG-Mal) to the liposome membranes during liposome production. This further research on the cellular uptake of sgc8 aptamer-liposomes showed that targeting was essential for cellular utilization. Sometimes, overnight incubation at 4 degrees Celsius allows sufficient time for the covalent linkage between the aptamer and liposomes to ensure strong and durable binding [66]. The covalent immobilization of aptamers onto magnetic nanoparticles (MNPs) for efficient and stable capture of cancer cells have also been researched, showing covalent linkage resulted in a robust and long-lasting capture system with high specificity and sensitivity. Amine groups are commonly subjected to reactions with various reagents such as 2,4,6-Trichloro-1,3,5-triazine (TCT) [67], p-nitrophenylcarbonate (NPC) [68], N-hydroxy-succinimide esters (NHS esters) [69]. These reactions enable the functionalization of amine groups and can involve the formation of stable linkages with other molecules or surfaces, expanding the versatility of amine containing linkages in the conjugation. Apart from functional groups, the optimal reaction conditions such as temperature, pH, and solvent are critical for promoting efficient covalent bond formation while maintaining the stability and functionality of both the aptamer and the nanoparticle.

4.1.2. Non-covalent strategies

The formation of aptamer-nanomaterial conjugations can be achieved by using the non-covalent techniques, which primarily rely on interactions like hydrogen bonding interactions, π-π stacking, van der waals interactions, ion-ion electrostatic interactions and hydrophobic and hydrophilic, whereby mainly includes electrostatic interactions and high affinity interactions [4,98]. Similarly, in non-covalent approach as demonstrated in Fig. 3, there is direct and indirect conjugations, where aptamers and nanomaterials are directly conjugated with high interactions in case of direct conjugations while linkers are employed in indirect conjugation. In indirect conjugation by non-covalent strategies, aptamers immobilized to nanomaterials with presence of charges, where linker molecules with positive charges interact with aptamer having negative charges, thereby conjugating with the nanomaterials like polymers, hydrogels [17].

A variety of uses in medicine and biology have arisen from the ability of DNA to assemble into nanoscale range to form what is known as DNA nanostructures [99]. Avidin is a tetrameric protein that binds to biotin, and has a high degree of specificity and affinity for binding to biotin. The avidin–biotin complex is one of the strongest known non-covalent bindings. Similar to avidin-biotin relation, streptavidin-biotin complexes are exceptionally stable under a wide range of conditions, including variations in pH, temperature, and chemical environments. This stability ensures that the aptamer-nanomaterial conjugates remain intact and functional during experimental procedures or biological applications. Aptamer-conjugated nanoprobe coupled with iron nanoparticles and aptamer shown in Table 1, has been tested for hyperthermia cancer treatment. This nanoprobe was made by streptavidin–biotin coupling between biotin-labeled aptamer with streptavidin-functionalized iron nanoparticles. Nanoprobe constructed via streptavidin and biotin amplification interactions results revealed that the complex could be more effective in diagnosing leukemia at the early stage and has the potential to image tumor cells in vitro or in vivo for early diagnosis of disease [70]. Besides, DNA bases can engage in interactions with graphene oxides nanomaterials through the utilization of hydrogen bonds and π-π stacking [69]. Moreover, DNA and Au nanoparticles interact primarily through the nitrogen atoms, which create a strong coordination contact in the arrangement of affinity [21]. These fundamental interactions serve as the foundation for a number of intriguing and useful techniques, such as using high affinity interactions like avidin-biotin interactions [17,100], supramolecular chemistry [101] and employing imidazolium ring groups (Ding et al., 2017) to produce multi-interactions (Fig. 3). Employing the direct conjugation and covalent strategies, the majority of aptamer-nanoparticle conjugates reported thus far have done so. Farokhzad et al. stated that covalently linked conjugates may result in improved salt and pH stability to eliminate the unwanted inclusion of cellular components that can lead to toxicity (Farokhzad et al., 2006). Due to this reason, covalent strategies are more stable than the non-covalent strategies.

4.1.3. Other strategies

Encapsulation is one way for the conjugation of aptamer and nanomaterial, involves methods to enclose or entrap these entities within a protective carrier or matrix. Utilizing silica, polymers or gels for the encapsulation represents a highly effective approach to shield against enzymatic degradation during transportation across cell membranes as DNA and RNA molecules are sensitive to degradation [102]. MOF-based chlorin e6-modified DNAzyme based therapeutic nanosystem have been created for combined therapeutics of gene therapy and photodynamic therapy (PDT) by Wang et al. They managed to release the doped DNAzyme within a new ZIF-8 generated with chlorin e6-modified DNAzyme, due to its effective pH sensitivity. The therapeutic DNAzyme had the potential to be effectively delivered to cancer cells using ZIF-8 nanoparticles without causing any degradation [59]. Streptavidin-biotin interactions are a kind of biological based affinity interactions, therein includes antibody-antigen interactions, lectin-glycan interactions, hormone-receptor interactions [4,103]. A novel aptamer based nanoprobe where combined with fluoro-graphene nanohybrid and aptamer coupled with AuNPs as designed by Adegoke et al for the detection of cocaine. In this system, streptavidin was utilized for absorbtion onto the QDs-GO-AuNP nanocomposite, facilitating to bind with anticocaine DNA aptamer receptor. This adeptly designed aptamer-based fluorescent nanoprobe demonstrated successful application in determining cocaine levels in confiscated adulterated cocaine samples (Adegoke et al., 2020).

5. Aptamer conjugated nanodevices

5.1. Aptasensor based on nanomaterials

In consequence of the key properties, which include compact size, a high degree of specificity, superior affinity, excellent sensitivity, bioavailability and robust immobilization, aptamers can be employed as

Table 1
Aptamer conjugated nanomaterials with conjugation strategies for various biomedical applications.

Aptamer	Type	Nanomaterial	Type	Conjugation	Target	Size	Clinical use	References
MA3	DNA	Iron nanoparticles (FeNPs)	Metal	Streptavidin – biotin, Direct conjugation	Mucin - 1	296 nm approx.	Hyperthermia cancer treatment	[70]
TLS11a	DNA	PtNPs	Metal	Covalent strategies, Direct thiol conjugation	HepG2 cells	N/A	Biosensing, Nanocarrier	[71]
NH2-TGGGGGTTGAGGCTAAGCCGAC,	DNA	Conducting polymer/AuNPs nanocomposite	Metal	Covalent strategies, Direct conjugation	Kanamycin	8–12 nm	Biosensing, Detection	[72]
As42	DNA	Gold nanoparticles (AuNPs)	Metal	N/A	Ehrlich's ACC	37 nm approx.	Photothermal cancer therapy	[73]
AS1411	DNA	Gold nanoparticles (AuNPs)	Metal	Dithiolene linker	Nucleolin		Anticancer therapeutics	[74]
AS14	DNA	Gold coated magnetic Nanoparticles	Metal	Thiolated ONT primer	Fibronectin protein	50 nm approx.	Magnetodynamic nanotherapy	[75]
S2.2	DNA	Zinc oxide nanoparticles	Metal oxide	APTES linkage	Mucin - 1	5–10 nm	Targeted photocatalytic and chemotherapy in cancer	[76]
DNA- RNA Hybrid	DNA-RNA	SPION (Super paramagnetic iron oxide nanoparticles)	Magnetic	Streptavidin - biotin, DNA linker	PSMA		Prostate Tumour Targeted Drug Delivery	[77]
5TR1	DNA	SPION (Super paramagnetic iron oxide nanoparticles)	Magnetic	Covalent strategies, Direct conjugation	Mucin -1	57–58	Bioimaging	[78]
AS1411	DNA	Graphene oxide (GO) nanosheets	Carbon	N/A	Nucleolin	30–40 nm	Drug deliver for tumour treatment	[79]
AS1411	DNA	GQD-FMSN	Carbon	Direct conjugation through amide bond	Nucleolin	72.5 nm	Drug delivery	[80]
5′-NH2- (CH2)6-GGGTGGGTGGGTGGGT-3		Graphene quantum dots (GQDs	Carbon	Non covalent strategies, electrostatic attraction and π–π stacking interaction	Lead (Pb^{2+}) ions	N/A	Biosensing	[81]
5′- (SH)-(CH2)6-ACT TCA GTG AGT TGT CCC ACG GTC GGC GAG TCG GTG GTA G-3	DNA	graphene oxide (rGO) and silver nanoparticles (AgNPs	Carbon	Covalent strategies, Direct conjugation	Chloramphenicol (CAP)	15 nm	Biosensing	[82]
PD-1 aptamer	DNA	DNA hydrogel	DNA nanomaterial	Covalent strategies, Direct thiol conjugation	Spenocytes	N/A	Cancer immunotherapy	[83]
AS1411	DNA	DNA Nanotrains	DNA nanomaterial	Base pairing	CD30		Targeted drug release	[84]
A10–3-2	RNA	Cationic nanobubble	Nanostructures	Covalent strategies, Direct conjugation	PSMA	479.8 ± 24.5 nm	Target specific deliver of dexorubicin	[85]
Thiolated apatmer	DNA	Molecularly imprinted polymer (MIP) cavity	Organic	Covalent strategies, Direct thiol conjugation	Human Kallikrein 2 protein	~10 nm	Biosensing	[86]
Osteosarcoma (OS)-specific aptamer (LC09)	DNA	PEG-PEICholesterol (PPC) lipopolymer	Organic	Covalent strategies, Direct thiol conjugation	Osteosarcoma cell	N/A	Gene therapy	[87]
AS1411	DNA	Liposome	Organic	Covalent to cholesterol	Nucleolin	220 nm	Targeted delivery in cancer	[88]
A10	RNA	PLGA-PEG-COOH	Organic	Covalent strategies, Direct conjugation	PSMA (Prostate specific membrane antigen)	155–168 nm	Prostate Cancer diagnostics	[89]

(*continued on next page*)

Table 1 (*continued*)

Aptamer	Type	Nanomaterial	Type	Conjugation	Target	Size	Clinical use	References
AS1411	DNA	PEG-PLGA	Organic	Covalent strategies, Direct conjugation	Nucleolin	156 nm	Drug Delivery for glioma treatment	[90]
sgc8c	DNA	PAMAM dendrimer	Organic	Covalent strategies, Direct conjugation	CCRF-CEM cell	8 nm approx.	Bioimaging, Detection	[91]
GMT8	DNA	PEG-PCL	Organic	Covalent strategies, Direct conjugation	U87 cells	11.9-64.2 nm	Glioblastoma cancer therapy	[92]
Endo28	DNA	3WJ-RNA	Organic	Covalent strategies, Direct conjugation	Annoxin A-2	8.1 nm	Targeted drug delivery of doxorubicin	[93]
5TR1	DNA	PLGA - Chitosan	Organic	Non covalent strategies, Electrostatic interaction	Mucin -1	222.7 nm approx.	Bioimaging in cancer	[94]
A15	RNA	PLGA	Organic	Covalent strategies, Direct conjugation	CD133	143.7 ± 24.6 nm	Hemangioma treatment	[94]
Wy5a	DNA	PLGA-PEG-COOH	Organic	Amide bond with spacer	PC3 cells	154.3 nm approx.	Drug delivery system	[95]
TLS1c	DNA	Liposome	Organic	Avidin-biotin interaction	MEAR cells	90.10-92.70 nm	Targeting of tumour	[38]30
AS1411	DNA	TD-PEC chitosan	Organic	Non-covalent strategies, Electrostatic bonds	Nucleolin	40–270 nm	Targeted cancer treatment	[96]
XEO2 mini	RNA	Hybrid – lipid polymer	Organic	Direct conjugation, maleimide-thiol	PC3 cells	50–100 nm	Cancer therapy	[97]

biosensors. Fluorescently labelled aptamers are used in aptasensors, wherein aptasensor is defined as a biosensor that employs aptamers as the recognition element to assist in detection the presence of a specific target molecule. Since they are flexible in terms of chemical alteration and probe engineering design, aptamers have proven to be attractive for the detection of tiny compounds. However, most anti-small molecule aptamers have weak binding affinity, which translate to limited sensitivity of detection. Binding affinity of aptamer has never been easy to increase, and the approaches that are frequently employed have only slightly improved their binding affinity. Combination of aptamers with variety of nanomaterials opens new doors in the sensing domain to explore new grounds for developing future biosensors. Varieties of existing aptasensors have been exploited to engineer with nanomaterials to construct diagnostically and clinically usable nanodevices with improved properties. Considering such advancements, the aptamers conjugated or functionalized with nanomaterials can be used therapeutically as aptasensor for sensing, detecting and targeting. Table 2 gives an overview of the various types of aptamers and nanomaterials with their conjugation strategies and their utilization in the clinical and diagnostics. Different types of aptasensors present and when coupled with nanomaterial provides varying aptasensors, which can be metal based aptasensors, magnetic based aptansensors, carbon based aptansensors also mentioned.

5.1.1. *Metal nanomaterials based aptasensors*

Metal based nanomaterials mostly gold (Au), silver (Ag), platinum (Pt) has been employed significantly due their properties as we have discussed, for the construction of aptasensors to explore various target biomolecules. Mahmoudpour et al. mentioned that so far, metal-based aptasensors have demonstrated a strong ability to increase tailored signal sensitivity and selectivity [4]. In a study for detection of kanamycin, an aptasensor, which is based on using a conducting gold nanocomposite, providing highly sensitive was designed. Zhu et al. selected a DNA aptamer in vitro and conjugated covalently AuNP where it was further encompassed with a polymer, poly-[2, 5-di-(2-thienyl)-1*H*-pyrrole-1-(*p*-benzoic acid)] (poly-DPB) as mentioned in Table 1 [104]. It is frequently stated that the electrochemical sensor substrate is important for both immobilizing the target biomolecules and converting the signal. Conducting polymers are used as biocompatible with biomolecules hence, have widespread application in case of electrochemical sensors [4]. We are familiar that gold nanoparticles directly and covalently conjugate by thiol linkers, however it may compromise their recognition capability on surface, resulting in decreased binding constants and limitations in the aptamers' structural conformation when immobilized on the surface of AuNPs [118]. Consequently, a noble approach known as sandwich type detection has been depicted by Zhu et al., in which involves the use of two aptamers; one immobilized on the sensor surface to capture the target analyte and the other with a signal-generating moiety for detection, forming a sandwich that helped in differentiating negative HER2-cells from -positive HER2 breast cancer cells [104]. Additionally, Ag NPs can be integrated into dendrimers, polymers and graphene to improve the sensor durability and efficiency. A recent study introduced a nanoprobe composed AgNPs and reduced graphene oxide (rGO) for the electrochemical detection of chloramphenicol (CAP). The aptasensor was created using an electrostatic assembly technique on a polyelectrolyte-functionalized rGO surface, which was subsequently used to modify a glassy carbon electrode (GCE). Following this, attached the CAP-specific aptamer to the modified electrode giving a detection limit of 2 nM and concentration range of 0.01 to 35 μM [119].

5.1.2. *Magnetic nanomaterial based aptasensors*

In view of the distinct advantages over other types of nanomaterials, including several advantages including faster processing, higher

Table 2
Aptamer conjugated nanodevices for biosensing, bioimaging, drug delivery.

Aptamer	Nanomaterials	Nanodevices	Application	Description	References
DNA aptamer	AuNPs	(DPB) poly-DPB(AuNP) nanocomposite and DNA aptamer	Biosensing	Detection of kanamycin by the nanomaterial based electrochemical aptasensor	[104]
DNA aptamer	AuNPs	Hyd−AuNP−Apt	Biosensing	Detection of HER2 breast cancer cells and distinguishes HER2-negative cells and HER2-positive	[105]
DNA aptamer	Graphene oxide and AgNPs	rGO/AgNP nanocomposite	Biosensing	Selective determination of the antibiotic chloramphenicol (CAP)	[106]
TLS11a aptamer	Platinum and AuNPs	DNA-PtNPs with attached AuNPs	Biosensing	Cytosensor used for interaction between the target cells and DNA-Pt NPs for signal transduction to detect tumour cells	[71]
DNA aptamer	Graphene oxide and quantum dots	Aptamer–rGQDs bioconjugates	Biosensing	Detection of lead (II) by the nanosensor	[81]
DNA aptamer	Molecularly imprinted polymer (MIP) cavity	aptamer-PSA complex	Biosensing	Electrochemical detection of prostate specific antigen (PSA)	[86]
AS1411 aptamer	DNA nanostructures	DNA octahedron-based fluorescence nanoprobe	Bioimaging	Detection of cancer biomarkers and more effectively internalising cancer cells and differentiating them apart from healthy cells	[107]
sgc8 aptamer	ZrMOF nanoparticles	ZrMOF/DNA aptamer	Bioimaging	Performed target-induced imaging and photodynamic therapies	[21]
switchable aptamer micelle flare (SAMF	Nanostructure	Switchable aptamer micelle flare nanostructure	Bioimaging	Ability for real time image of internal biomolecule expression as well accessibility of delivering drug payloads into living cells	[108]
sgc8c and sgc4f aptamer	DNA nanostructure	DNAlogic gate triangular prism (TP)	Bioimaging	Identification of biomarkers through use of boolean turn on-off mechanism	[109]
DNA aptamer	DNA nanoflowers (NFs)	NF-aptamer conjugate	Drug delivery	Improving drug retention in cancer (MDR) cells and inhibiting drug efflux, NF-Dox generates strong cytotoxicity in target chemosensitive cells	[110]
EpCAMAp	PEI (Polyethyleneimine)	Aptamer-PEI-siRNA nanocomplex	Drug delivery	siRNA is specifically delivered to positive cancer cells, thereby inhibiting the growth of tumour cells for breast cancer therapy	[111]
SYL3C aptamer	DNA origami sheet (DOS)	Tetrahedral DNA nanorobot (TDN)	Drug delivery	Designed to react to stimuli from outside and undergo a programmed conformal change when exposed to the target molecule for cargo transportation and nanoscale sensing	[112]
sgc8c aptamer	PAMAM dendrimer	PAMAM-sgc8c	Cancer therapy	Target cell labelling on surface showed by fluorescence conjugated with PAMAM-sgc8c in cancer cells	[91]
Sgc8c, Sgc4f, and TC01 aptamers	DNA nanostrctures	DNA Nano claw	Cancer therapy	Capable of analyzing multiple cell molecular signature to get the outcome of targeted therapeutic effects	[113]
A10–3.2	Lipid-polymer hybrid nanoparticles (LPNs)	Aptamer-functionalized, curcumin (CUR) and cabazitaxel (CTX)	Targeted drug delivery and cancer therapy	Possibility of synergistic combination treatment for prostate cancer through drug delivery to the tumour growth and prostate cancer cells in vivo	[114]
AS1411	Single-walled carbon nanotubes (SWCNT)	SWCNT- aptamer nanocomposite	Targeted drug delivery and cancer therapy	Co-delivery mechanism of Doxorubicin at the tumour cells (gastric cancer) that have more surface nucleolin receptors than normal ones	[115]
MUC1- aptamer	Au-SPION	Au-SPION-MUC1	Bioimaging and cancer therapy	Results using modified SPIONs for colon cancer cell photothermal treatment and negligible cellular toxicity revealed	[116]
Dna aptamer	Nanopores	Nanomechanical device	Bioregulation	Concatenated DNA reactions enable the regulation of drug transport across a bilayer to create artificial logical ionic networks for the regulated release of drugs	[117]
DNA aptamer	PEG-PEICholesterol (PPC) lipopolymer	LC09-PPC nanocomposite	Gene therapy	Encapsulation of CRISPR and Cas9 plasmid for targeting vascular endothelial growth factor A (VEGF) for tumour cell targeted delivery	[87]

sensitivity, and lower noise and reduced limit of detection [120], magnetic nanoparticles (MNPs) have attracted a lot of attention in biomedical applications. On account of this, MNPs and magnetic nanomaterials provide advantageous attributes for the construction of next generation sensors. A study revealed that certain magnetic nanoparticles (MNPs), particularly polyethyleneimine (PEI) coated with MNPs, can effectively bind with DNA through electrostatic interactions, resulted in significant fluorescence quenching forming a basis for a novel aptasensor. The aptasensor in turn demonstrates a perceptive detection of lipopolysaccharide (LPS) with a low limit of detection. Compared to traditional graphene oxide (GO) conjugated with ssDNA aptamer sensors, PEI-MNPs-based biosensor exhibits superior resistance offering potential advancements in DNA-assisted bio-analysis [121]. For the detection of tetracycline (TET), MNPs and an ionic liquid (IL) were layered on a microarray electrode for specific immobilization of aptamers. The modified electrode, consist of IL as first layer and Fe_3O_4 MNPs in second layer, showed a significant voltammetric response when aptamers were immobilized on it, enabling the detection of TET [122]. For the same application, Jahanbani and co-worker synthesized an aptasensor involving a magnetic bar carbon paste electrode (MBCPE), modified with oleic acid coupled to Fe_3O_4 MNPs to efficiently attach anti-TET. This executed high sensor performance due to the optimal absorption of MNPs-OA by the magnetic bars in the carbon paste electrode [123]. Moreover, there is ongoing research on encapsulation or detection of bacteria by aptamer conjugated magnetic nanomaterials.

5.1.3. Carbon nanomaterial based aptasensors

A combination of high elasticity, variable bandgap and capacity as nanoquenchers, carbon-based nanomaterials are easily integrated into biosensing systems. In additionally, single-strand DNA molecules have capability to adsorb onto carbon nanomaterials due to the hydrophobicity of their surface and π-stacking interactions [4]. Among the many carbon-based nanomaterials, graphene, quantum dots and carbon nanotubes are the mostly studied nanocomposites due to their surface

modification, high electron transfer efficiency, good interfacial characteristics, biocompatibility which functions as electrochemical sensor with aptamer coupled. Quantum dots (QDs) exhibit the capability to form conjugates with aptamers when excited with a single wavelength, enabling highly efficient sensing of the target. The excitation of QDs at a specific wavelength leads to the emission of light at distinct wavelengths, providing a versatile platform for designing aptasensors with enhanced sensitivity and specificity [124]. Primarily, in the areas of bioimaging, analysis, and administration of drug, graphene quantum dots (GQDs) based nanoprobes have shown great promise. Likewise, a novel aptasensor for lead (II) detection was developed using GQDs and graphene oxide (GO). The aptasensor utilizes Pb^{2+} induced G-quadruplex formation, demonstrating high sensitivity and reproducibility. It achieves an ultralow detection limit of 0.6 nM, making it effective in showing fluorescence on and off capability [81]. From all this, it can be seen that interaction between the aptamer and the target induces changes in the electrical, optical, or electrochemical properties of the carbon nanomaterial, allowing for the detection. When creating such aptasensors, nanomaterials can be used in two different ways: either as quenchers or fluorophores. GO is the most often used nanomaterial as quencher owing to its high surface area, low toxicity, and accessibility of integration for conjugation, making it the best alternative available for these kinds of applications. Fluorophores release radiative energy, which can be captured by the planar structure of GO and used to quench them. This allows for a relatively broad surface area for interactions between molecules [125].

5.2. Aptamer functionalized DNA nanomaterials

Aptamers with DNA nanotechnology emerging as fields with distinct benefits. The multi presentation of aptamers on nanostructures is made possible by DNA nanotechnology. DNA nanotechnology, apart from its original purpose of carrying and transferring genetic information, DNA can be used as the basic element to create various types of nanomaterials as classification seen. DNA nanotechnology offers a very interesting approach to the development of self-assembling drug delivery systems since it may be used to create precise structures that resemble viral capsids or nanoparticles. It is possible to increase the binding avidity overall and boost the effectiveness of aptamer-based sensors, probes, and therapeutics by carefully building several copies of aptamers. Aptamers are conjugated with the different types of DNA nanomaterials such as DNA nanostructures, DNA micelles, DNA hydrogels, DNA liposomes, wherein all of these are based on organic nanomaterial shown in Table 1.

5.2.1. DNA nanostructures

Nucleic acid aptamers can be readily incorporated to create a wide range of DNA nanostructures, facilitating targeted molecular targeting and other applications due to its particular hydrogen-bonding interactions between the DNA bases. Nucleic acid hybridization is one of the primary techniques used to create aptamer-integrated DNA nanostructures. Compared to other traditional or conventional delivery carriers like such as liposomes, DNA nanostructures are enticing due to their versatility in regulating their spatial arrangements and their payloads. Using precise designs and high efficiency, three-dimensional DNA nanostructures are capable of assembling themselves in a solution. In addition, the shape and topology of nanoparticles are known to have a substantial impact on therapeutic bioavailability, such features drive the creation of DNA nanostructures as drug and DNA delivery vehicles assisting in drug delivery. DNA nanostructures can simultaneously transport several therapeutic payloads because of their modular design. Li et al. introduced an approach presenting a designable aptamer-based nanocomposite platform for studying attachments of cell membranes and its cellular mechanism and cellular networks. A versatile and biocompatible DNA probe for manipulating cell connections, utilizing 3D amphiphilic pyramidal DNA with 100-fold enhanced stability was developed improved target infiltration. On this, the anchoring to cell membranes possible due to the programmable nanoplatform by size and structural conformation, revealing the significance of close proximity in cell interactions [126]. This type of nanocomposite similarly showed application to act as a nanocarrirer in drug deliver and targeted system as seen by Apt-ND-ABP nanoplatform. AS1411 aptamer was used with miR-21 and miR-150, which are antisense oligonucleotide sequences and an anti-biomarker probe. This miR-21 and miR-150 would be transported with the help of this system inside the cell target. Upon binding on specific cell, the nanodevice Apt-ND-ABP internalized through cytoplasm and multiple antisense oligonucleotides including miRNAs released. This led to apoptosis of the target cell inhibiting the therapeutic target [127]. There have been many studies regarding DNA origami and DNA nanoflowers since functional sequences can be substituted for the programmable origami building blocks. Like to transport chemotherapy medications, Pan et al. developed a nanocarrier based DNA origami called as Apt-Dox-origami-ASO for the delivery of doxorubicin [128]. Zhu and colleagues created self-assembling DNA based nanoflowers by the use of a rolling circle amplification (RCA) technique, wherein eliminated the traditional drawbacks of complex preparation processes that impacted biostability [105]. The beauty of DNA nanotechnology lies in its programmability. By manipulating these nanostructures, scientists can make them release their contents in certain ways for use in drug or cargo delivery. For precision medication delivery, they can be made, for instance, to only open and release the pharmaceuticals in response to specific biological signals. Thus, functionalization of aptamers with DNA nanomaterials allows aptamer to bind to their desired target and enables the nanomaterials to recognize and interact with the biological molecules in cell and to perform desired functions.

5.2.2. DNA micelles/polymers

A spherical DNA micelle framework can organise and assemble themselves from amphiphilic oligonucleotides, hereby have a hydrophobic core with a hydrophilic shell making them appropriate for drug uptake. Polymer are known to have huge scope in the biosensing acting as a biosensor. Nevertheless, methacrylamide used to connect aptamer and lipid fragments in a condition of photoillumination, this branch covalently joins aptamer-lipid units. The aptamer-lipid micelles were thereby given increased stability for imaging applications by this covalent bonding technique [127]. The ambiguous property that these DNA micelles display greatly improves their ability to bind to certain targets with aptamers, therefore have a lot of promise for use in biosensors and gene delivery systems [129,130]. Various imaging molecules can be loaded onto polymer nanostructures for applications where polymers such as poly (D,L-lactic acid) or poly (D,L-glycolic acid) are mostly used [9,131]. Yang et al. on the other hand, developed nanoscale coordination polymers (NCPs) for photodynamic therapy, primarily constructed using G quadruplex DNA aptamer AS1411. Polymer when conjugate with aptamers are known to protect from enzymatic degradation and shows improved antitumor efficacy. So, a nanodevice or nanocomposite called CACH-PEG (Ca-AS1411/Ce6/hemin/pHis-PEG) nanostructure was developed with usage of photosensitizer like chlorin e6 (Ce6) integrated with polymers and hemin as a DNAzyme with iron-containing porphyrin and further modification of PEG improved antitumor efficacy [132].

5.2.3. DNA hydrogels

DNA hydrogels which are gel like structure having high water content and improved, enhanced flexibility generated for a variety of biotechnological uses. These DNA hydrogels are highly biocompatible and have outstanding moisture content, making them appropriate for a variety of purposes. Moreover, the DNA modules incorporated into the hydrogel had distinct detection skills in detecting and targeting biomarkers [129]. Structures like employing three chemical substances to create the DNA nanohydrogels prepared where, Y-shaped monomer A

(YMA), Y-shaped monomer B (YMB) and DNA linker, in which one can regulate the size of DNA nanohydrogel. Further, such kinds of Y-gels used to create structures like Y-gel-Apt, which aptamer conjugated important in GSH-gene therapy. The Y-gel-Apt demonstrated a substantial suppression during cell division with minimal damage, attributed to its fast incorporation and improved biological compatibility [133]. Aptamer-based hydrogels also have the intriguing potential to be employed in the acquisition of certain live cells for cell-based treatments and cancer diagnosis, wherein using a technique known as aptamer-triggered clamped hybridization chain reaction (atcHCR), created an aptamer-based hydrogel in view to identify and detect circulating tumour cells (CTCs). In this approach, the epithelial cell adhesion molecule like EpCAM on the surface of tumour cells is uniquely recognised by DNA aptamer which in turn initiates subsequent atcHCR. CTCs can be directly captured with minimum damage to the cells attributed to a porous DNA hydrogel-based cloaking technique as reported. The capacity to recognise a minimal number of CTCs in blood using DNA hydrogel made it possible for a high level of specificity and sensitivity for cancer diagnosis [134]. In addition, by creating stimuli-responsive hydrogels, useful cargo can be delivered, as discussed where researcher have designed the Y-gel-Apt which forms DNA hydrogel for gene regulation [133].

5.2.4. DNA liposomes

Liposomes are spherical, tiny molecules that resemble lipid bilayer of which have a diameter of 50–500 nm and can hold a variety of chemicals and drugs foe encapsulation. DNA, thus functionalized making them suitable for a variety of uses, such as the administration of drugs or genes, cancer therapy. An aptamer functionalized liposome system was synthesized by researcher for targeted administration of drugs. According to this structure, sgc8 aptamers may make it easier for liposomes to identify target cells since they are known to immobilize on the membrane surface of those cells. The drug to be delivered are incorporated inside the liposomes, where the sgc8 aptamers conjugate to liposomes by PEG linkage and hence, during confocal imaging analysis showed that drug is delivered to target cells with excellent specificity and efficacy [135]. This system overcomes the challenge of delivering of drug to the diseased target without interfering with the proliferation of healthy cells. A novel class of treatments for a range of disorders is being developed by utilising the CRISPR/Cas9 system to limit the expression of a specific gene. This system employed the A10 aptamer, known for its specific binding to prostate cancer cells, along with the DNA liposome having lipid content carrying Cas9 and gRNA plasmid DNA. Here, for the selective binding of prostate cancer cells, the RNA aptamer i.e A10 aptamer having specificity to prostate-specific membrane antigen [136]. Enhanced cellular uptake by such kind of nanostructures and high specificity and binding affinity with increased stability can be seen.

5.3. Nanorobots

There is a growing interest and anticipation in the scientific and medical communities regarding the potential use of nanorobots as a promising device for delivering drugs specifically to tumour sites within the body. Nanorobots are minute robotic devices designed to operate at the nanoscale range constructed using nanotechnology principles intended to perform specific tasks at the molecular or cellular level. Therapeutic agents can be encapsulated in a variety of stimuli-responsive materials to create nano-formulations that, when exposed to particular stimuli within Tumour Microenvironment (TME), can undergo protonation and conformational changes at molecular level while remaining stable in normal tissue and blood. Wang et al. addressed the challenge of limited efficacy in immune checkpoint blockade (ICB) therapy, specifically addressing programmed cell death protein 1 (PD1) and programmed death ligand 1 (PDL1). While ICB therapy using monoclonal antibodies have shown significant tumour inhibition, but trials only few patients benefited, potentially due to tumour immunological tolerance. To overcome this limitation, the researchers developed a matrix metalloproteinase-2 (MMP-2)-responsive nanorobot. This nanorobot was designed to co-deliver the photosensitizer ICG and PDL1, aiming to enhance the effectiveness of ICB therapy and overcome immunological tolerance in tumors [59]. In fact, on the rise of DNA nanostructures, DNA nanorobots having enhanced drug loading ability and targeting capabilities have been developed and used extensively in drug delivery. A recent study employed DNA nanotechnology to create a precision breast cancer therapy using a DNA nanorobot that target human epidermal growth factor receptor 2 (HER2), wherein an aptamer syntheized on anti HER2 i.e. HApt was immobilized onto a tetrahedral framework nucleic acid (tFNA), at last forming the functional DNA nanorobot (HApt-tFNA). The formation triggered endocytosis and lysosomal digestion mediated with HER2, thus reducing HER2 on cell surfaces, inducing apoptosis, and halting cell growth [137]. Nanorobots having magnetic characteristics have also been on rise for precise administration of drug inside the cell. In context, researcher developed a magnetic-responsive nanorobot with a FeGa alloy core and a piezoelectric shell. The core-shell nanowire is formed inside the tubes by electrically deposited FeGa, an alloy with a high magnetostrictive efficiency. The nanorobots surface was prepared with polydopamine (PDA), which allowed them to communicate reversibly with paclitaxel, an anticancer medication, and carry out magnetically drug delivery system. The magnetic field induced a polarization change, which hence cuts the connection of drug and PDA molecules, facilitating drug release. In summary, this nanorobot achieved accurate drug release using in vitro supplied external power generation source [106]. Nanorobots are thus can be known as minute or tiny vehicles that have a function to perform as been designed through that specific application. They utilize a power source for their operation like using magnetic field supplied and have robust application the delivery of drug system through the cell where, further conjugation with aptamer enhances target and binding affinity to execute the task given at molecular and cellular level.

5.4. Nanomotors

Nanomotors are small-scale devices designed to convert energy into mechanical motion at the nanoscale, empowered by various energy sources, including chemical reactions, light, or magnetic fields. They are a type of nanorobots where functionally varied. They exhibit autonomous movement and can perform tasks such as transportation, rotation, or manipulation of objects at the nanoscale. In addition, it offers an adaptable method for combining different parts to create uniformly sized and shaped miniature buildings. Catalytic engines or imaging substances can be readily put into the motors during the assembly process, giving them several functions for a variety of uses. Layer-by-layer (LBL) assembly and self-assembly of molecules are the two types of assembly methods utilised to form nanomotors. The process of self-assembly involves molecules spontaneously rearranging into structures and patterns [138]. Employing this assembly, a study presented the first instance of a multilayer hollow capsule made of Janus polyelectrolyte that is self-propelled and can function as both intelligent cargo and nanomotor. This Janus capsule motor was created by combining a microcontact printing technique with template-assisted LBL self-assembly to create dendritic platinum nanoparticles (Pt NPs). They autonomously move at speeds exceeding 1 mm/s and can exert substantial forces, while external magnetic fields enable directed movement [139]. Similarly, they necessitate the power supply consumption that can either come from chemical reaction, magnetic field or energy from environment. Further, nanomotors can be categorized into two main types based on how they move; chemical-propelled nanomotors and external field-propelled nanomotors stated by Lin and coworkers. Chemical-propelled nanomotors get their power source through chemical reactions, like bubble propulsion or self-diffusiophoresis [140], conversely external field-propelled nanomotors are get their power supply by physical fields that is to be applied from external source. They

can be powered by magnetic field, light, electricity and ultrasound (Gao et al., 2020). Besides moving on their own, it is crucial to be able to control nanomotors dynamically, adjusting their speed and direction particularly important for delivering drugs precisely to tumour cells. However, keeping in mind, whenever such biomolecules like nanomotors enters the human environment, multiple factors must be taken into account such as biodegradability, biocompatibility, adhesion, immunological response and toxicity. Consequently, nanomotors with aptamers have been designed in such a way that have the ability to self-destruct after their given task corresponding to an environment. In order to limit the possibility of off-target effects and unwanted gene expression alterations, precise control mechanisms are crucial in ensuring that nanomotors carry genetic material exclusively to the intended target cells or tissues, such as of gene therapy and drug delivery mechanisms. Meanwhile, influenced by biological motors, there have been progressively designed chemical and physical micro/nanomotors from a bionics context. This involves fusing synthetic and natural biological materials, such as platelet and red blood cell membranes, so that the biocompatibility and the design can be leveraged to improve implications [141].

6. Biomedical applications

Aptamer functionalized nanomaterials have made significantly notable progress in the range of biomedical field. Due to the diverse unique properties of each fields combined makes it to yield a superior targeting properties and smart responses to various targets owing to their unique molecular recognition ability. The development of advanced procedures and characterization approaches has made it possible for researchers to create a wide range of non-biological materials designed with specialized sizes and shapes having unique properties. These features make the aptamer functionalized nanomaterials makes an excellent prospect for variety of applications. Hence, the following sections addresses the biomedical applications for aptamer functionalized nanomaterials in drug delivery, gene therapy, bioimaging and biosensing.

6.1. Drug delivery

This type of technology also known as, drug delivery systems accurately target infection cells or infectious organisms with medications at the therapeutic dose in vivo by utilising a variety of chemical techniques and materials. In spite of this, it is difficult to regulate the stability of drugs and its particular targeting. Nanomaterials have shown a lot of promise as transporters in drug delivery over the past few years and drug molecules can be incorporated or assembled inside nanomaterials by attaching to surface and encapsulating thereby lowers side effects and increases therapeutic impact [4]. Targeted drug delivery can lessen the undesired effects of traditional or untargeted pharmaceutical mechanisms. This allowed for accurate delivery to the target cells or tissue by acting as a carrier. Thus far, a multitude of frameworks exploiting aptamers based on AuNPs, AgNPs, magnetic nanomaterials, quantum dots, dendrimers, carbon nanomaterials, polymeric, hydrogels, DNA nanomaterials, have been devised to administer a wide range of therapeutic compounds, encompassing multiple chemotherapeutic medications, Fig. 4 depicting various applications in the biomedical field.

Upon this, in order to distribute hydrophilic nucleic acid integrating medications in a targeted manner and incorporate hydrophobic drugs within poly (D,L-lactic-coglycolic acid)-block-poly (ethylene glycol) i.e. (PLGA-b-PEG) NPs, which is a kind of drug delivery nanosystem based on aptamer conjugation has been created [142]. The intricate mechanism of aptamer-conjugated nanomaterials in drug delivery epitomizes an approach to achieving targeted therapeutic outcomes. The aptamers functions as targeting ligands, guide the nanomaterials with precision to specific cells or biomolecules, thereby enhancing the selectivity of drug delivery and mitigating collateral damage to healthy tissues [17]. On subsequent interaction with target cells, the aptamer-conjugated nanomaterials facilitate internalization through endocytosis, optimizing the efficiency of drug delivery. Intracellularly, the nanomaterials orchestrate the release of encapsulated drug payloads, a process often modulated by triggers responsive to specific intracellular conditions or stimuli [1]. This meticulous approach ensures that the therapeutic agents are selectively dispensed at the intended sites of action. Furthermore, Table 2 provides an overview of additional devices in biomedical applications, specifically focusing on drug delivery systems. Advanced systems may integrate aptamers that are engineered as sensors, enabling real-time monitoring capabilities and the ability to adapt to dynamic physiological conditions. A kind of innovative targeted medicine known as aptamer-drug conjugates or ApDCs, has garnered a lot of attention. ApDCs are small molecular therapeutics agents or conjugates, where they have been constructed by conjugating aptamers with different types of drugs where they act as a target ligand to bind to specific target

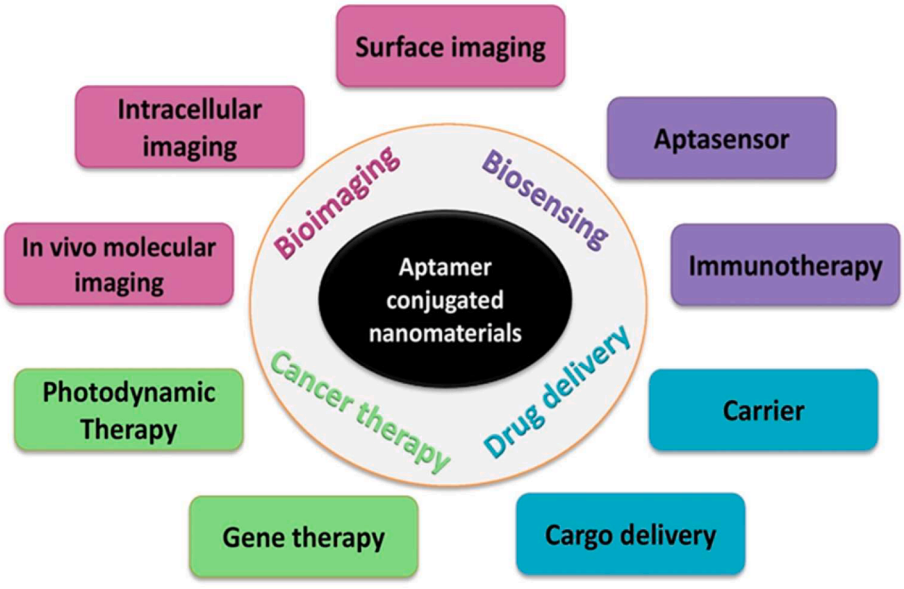

Fig. 4. Biomedical applications of aptamer conjugated nanomaterials.

molecules with affinity and specificity. These drug carriers, such as polyprodrugs are polymer based designed to encapsulate therapeutic substances like drugs and for controlled release kinetics and offer the cargo a stable and regulated environment. ApDCs have advantage on having multifunctionality where, it allows for simultaneous targeting of specific cells or tissues while delivering therapeutic payloads. These molecules are able to carry one or two drug molecules showing high stability and deep penetration with improves therapeutic efficacy when conjugated with aptamers (Deng et al., 2019). Through the coupling of cell-targeting aptamers with polyprodrugs, a highly loaded Aptamer-Polypro Drug Conjugates (ApPDCs) created (Deng et al., 2019), having several benefits, including their potent cytotoxicity, extended in situ recirculation duration and strong nuclease tolerance.

6.2. Gene therapy

Gene therapy is a therapeutic approach that involves the alteration or replacement or addition of genetic material for an individual at cellular level to treat or prevent diseases, which is the method of correcting genetic mistakes by transferring therapeutic genetic elements into sick cells. Pharmacological nucleic acids such as small interfering RNA (siRNA), miRNA, and short hairpin RNA (shRNA) can be presented at the transcriptome level [4,143]. Several advanced techniques have been devised in order to achieve this objective, falling into the two main categories of viral vectors and non-viral vectors. Here, viral vectors have the potential to cause insertional mutagenesis, which raises the risk to patients even more, as well as severe inflammatory and immunological reactions (Dolatabadi et al., 2016), on the other hand, non-viral gene delivery methods can address these issues, the primary challenge of avoiding endosomal breakdown following endocytic uptake persists [144]. Apart from this, effective therapeutic modalities can be delivered by a variety of techniques combined with DNA nanotechnology, such as drug delivery, gene-silencing, incorporated into DNA nanostructures. Anticancer therapeutics can be combined with DNA nanostructures and allow proper binding efficiency and correct formation without causing any stress. Nevertheless, despite being effective as a medication, when it builds up off-target, it can have major adverse effects such cardiomyopathy, which can result in congestive heart failure. Consequently, it is imperative to prevent off-target or premature delivery, so there has been utilization of aptamers to functionalize targeted ligands and remove any undesirable off-targeting. Additionally small interfering RNA (siRNA) has been used by numerous studies for therapeutic gene silencing and can be tailored to be target specific in order to prevent off target silencing effects [4,145]. In such context of DNA nanomaterials functionalized with aptamers, they have ability to encase or protect therapeutic molecules like genetic molecules within their structures. By preventing cargo degradation during internal circulation, this protection makes sure the therapeutic payload is preserved until it reaches its target site.

With the advancement of nanotechnology, a variety of non-viral vectors have been developed, including conjugate-based aptamer-NPs vectors. The physical characteristics of nanoparticles (NPs), including their size, shape, charge density, and colloidal stability, are crucial factors that influence how well the NPs function as possible non-viral carriers, wherein mostly inorganic nanomaterials are utilized such as silica, gold, magnetic. When contrasted to other non-viral vectors, peptide-based vectors are also present where, have the advantage of delivering genetic materials directly to the nucleus, enclosing and safeguarding DNA, and rupturing the membrane of the cell. They utilize peptide sequences derived from viral proteins, to facilitate the transportation of genetic material into the nucleus [143]. Consequently, peptides like polyethyleneimine (PEI) [144] employed to enhance the functionality in gene delivery applications. It is possible to transfer CRISPR/Cas9 into particular tissues or cells using potent in vivo targeted delivery systems enhancing the effectiveness of CRISPR/Cas9-based therapies. Upon this, Zhang et al. reported a significant study involving the coating of polyamidoamine (PAMAM) conjugated with anti-EpCAM aptamer (P-Apt) onto hollow mesoporous silica nanoparticles (HMSN). This innovative approach facilitated the delivery of sorafenib creating a gene therapy system for treating liver cancer, hepatoma. This non-viral delivery system, effectively inhibited EGFR expression both in vitro and in vivo showcasing a potent anti-angiogenesis effect through binding to EpCAM receptors on HCC cell membranes (Zhang et al., 2020). As a consequence, the targeted delivery of CRISPR/Cas9 using the aptamer-NPs conjugate was coined "magic scissors" by Mahmoudpour et al. having great potential for gene therapy treating hereditary disorders [4].

6.3. Bio-imaging

Monitoring the arrangement of macromolecules within cells is crucial for understanding pathophysiology, illness diagnosis, medication exploration, and cell function. Analysing the spatial arrangement of biomolecules in cells can be accomplished through the application of cell imaging techniques. Imaging performed using aptamer conjugated nanomaterials help to get information quantitatively and qualitatively. Bio-imaging can be categorized as cell surface imaging, intracellular imaging and in-vivo molecular imaging [32] (Fig. 4). Cell surface imaging is the visualization of the outer membrane or surface of cells using various imaging techniques. It is a crucial aspect in aptamer functionalized nanomaterials to view the immobilization that provides insights into the organization, composition, and dynamics of the cell membrane, where interactions with the external environment cells occur. A group of researchers developed a method for real time imaging of dimerization of protein on surface cell membranes. Using carboxyfluorescein labelled with aptamers, they monitored receptor protein states (monomer or dimer) in real time. They also introduced a proximity-induced HCR strategy for fluorescence imaging of in living cells receptor dimers [146]. In contrast, intracellular imaging visualizes structures, processes, and molecular events within the interior of living cells. A DNA octahedron based on aptamers was created for the purpose of simultaneously imaging two tumour-related mRNAs using fluorescence. Aptamer AS1411 could be added to the nanoprobe to increase its internalisation into tumour cells and enable it to differentiate them from normal cells [147]. Unlike in-vitro imaging, which involves studying cells or tissues outside of their natural environment, in-vivo imaging allows researchers to observe and monitor biological phenomena in real-time within intact living organisms. Fluorescence probes are widely used for the majority of these techniques because they supply signals with comparatively minimal background noise, thus there is florescence imaging however, radioisotopic imaging is also possible. In this context, 99mTc-labeled aptamer having specificity for human matrix metalloprotease 9 was generated to track real-time tumour slice monitoring [148].

6.4. Bio-sensing

Biosensors are indispensable tools across diverse fields, including biological research, clinical diagnostics, forensic analysis, food safety, and environmental monitoring. Their versatility and sensitivity make biosensors pivotal in advancing scientific understanding, improving healthcare outcomes, enhancing forensic capabilities, ensuring food quality, and safeguarding environmental well-being. As previously mentioned about aptasensors functionalized with nanomaterials, this system provided immense applications in detection of biomolecules in biosensing, wherein various types of aptasensors ranging from carbon based to magnetic based to organic based aptasensor based nanomaterials. Moreover, due to the superior nature of nanostructures, high specificity can be easily attained for solution-based sensors. As DNA nanostructures are naturally very soluble in water, they are perfect substrates for the development of homogenous solution-based biosensors [32]. In their innovative work, a novel approach was introduced known as the 'DNA origami traffic light' designed to detect and sensing

of adenosine triphosphate (ATP). This method involves the incorporation of aptamer onto the two sides of DNA origami structure. As a consequence of ATP binding, the dyes associated with the aptamer are brought near each other, facilitating energy transfer from the donor to acceptor emissions [149]. Biosensors that sense on diverse surfaces are among the most significant biosensor types. Target molecules are still less accessible to interfacial probes than their counterparts in homogeneous solution, despite the fast advancements in surface chemistry [32]. To overcome this, an aptamer-dependent DNA tetrahedron was used to immobilize the electrode surface of their electrochemical biosensor. This design allows for the ultrasensitive and selective detection of cocaine with a limit of detection of 33 nM [150]. The underlying mechanism involves the binding of aptamer to the target molecule, leading to structural changes in the DNA tetrahedron. These conformational alterations are then transduced into measurable electrochemical signals, providing a robust platform for the detection of diverse analytes with high sensitivity and selectivity. Further, biosensor nanodevices have been provided in Table 2 with their brief application. This versatile sensing strategy demonstrates the potential for aptamer-based electrochemical sensors in a broad range of applications, from drug monitoring to the identification of disease biomarkers.

7. Conclusion and future perspective

The substantial advancements in the aptamer nanotechnology with a great deal of advantages ranging from target specificity, conformational flexibility, enhanced binding affinity, large surface area, biocompatibility to enhanced stability presented revolutionizing the biotechnological and along with the healthcare domain. In this review, we have discuss aptamer conjugated nanomaterials provided promising technique that can be utilized as tool or device for wide array of applications in biomedical field including, drug delivery systems, biosensing, bioimaging for diagnosis and therapeutic treatments. Aptamer identified through SELEX methods provided minute size, excellent binding sensitivity and specificity, and easy chemical alteration making it appealing as a recognizable component. Concurrently, nanomaterials demonstrated role as electrocatalyst, photocatalyst, optical transducer, carrier molecule producing magnetic and thermal signal. Even though, they have unique characteristics of their own, when combined together creates a new type of attributes offering a potent platform in the field of biomedical. Such therapeutic approaches may be able to improve the detection and targeting diseased cell to boost the therapeutic results.

Despite resolving the issues regarding the targeting of cell, delivery of drug, biosensing and gene therapy by the aptamer conjugated nanodevices engineered as we have discuss, it is no doubt that there are some challenges regarding this. Nanomaterials are not stable in complex environments, particularly living ones, which significantly reduces their efficacy and can have unfavourable outcomes. In the meanwhile, in-vivo sensing and imaging require consideration of the cytotoxicity and longevity implications of nanomaterials. Explore modifications to the surface, such as immobilization using biocompatible substances, as a potential solution to these problems [5]. Furthermore, maintaining the stability of aptamer-nanomaterial conjugates under varying physiological environment particularly, to target sites in vivo remains a challenge. The efforts concentrated on finding pertinent protein targets, can then be applied to create pertinent aptamer for usage in nanotechnology complexes targeting various illnesses and ailments, makes them promising tools for advancing precision medicine, tailoring treatments to individual patients based on their molecular profiles. In summary, research on the integration of aptamers with nanomaterials is still ongoing. While there are obstacles, the growing endeavors are expected to propel the rapid advancement of this emerging area allowing to play more significant roles in various biomedical applications.

Disclosure statement

The authors have nothing to disclose.

Author declaration

We hereby declare that there are no known conflicts of interest associated with this publication. We also affirm that the manuscript has been reviewed and approved by all named authors. Additionally, there are no other individuals who meet the criteria for authorship but are not included in the list. Furthermore, the order of authors presented in the manuscript has received unanimous approval from all of us.

CRediT authorship contribution statement

Rajkumari Urmi: Writing – original draft. **Pallabi Banerjee:** Validation, Formal analysis. **Manisha Singh:** Validation. **Risha Singh:** Formal analysis. **Sonam Chhillar:** Data curation. **Neha Sharma:** Writing – review & editing. **Anshuman Chandra:** Validation. **Nagendra Singh:** Methodology, Investigation. **Imteyaz Qamar:** Writing – review & editing, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare no relevant financial or non-financial interests to disclose.

Data availability

No data was used for the research described in the article.

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