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Point-of-care testing based on DNA nanotechnology for pharmaceutical analysis

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ABSTRACT

The integration of DNA nanotechnology advances the development of Point-of-care testing (POCT) by the design of programmable nanostructures and various signal amplification strategies. In this review, we systematically elucidate the structural design strategies of DNA nanotechnology for POCT, and the engineering of diverse POCT devices, including paper-based diagnostics, microfluidic chips, electrochemical sensors, and optical systems integrated with smartphone-compatible interfaces. The particular emphasis is placed on their transformative applications in pharmaceutical analysis, including real-time drug monitoring and metabolic profiling, drug delivery tracking, safety assessment, as well as quality control of traditional Chinese medicines. Future perspectives explore the expanding applications in pharmaceutical analysis with the emergence of new technologies such as artificial intelligence. Overall, this review provides a comprehensive overview of recent progress in DNA nanotechnology based POCT for pharmaceutical analysis and offers valuable insights for its continued development and clinical translation.

1. Introduction

POCT (Point-of-Care Testing) is a kind of rapid testing technology carried out in the vicinity of the patient or on-site. Characterized by its core feature of "instant, on-site, on-demand", it offers unique advantages including minimal sample requirements, rapid results, elimination of complex pre-processing, and high portability for clinical use [1,2]. These features make POCT a powerful complement to traditional laboratory-based testing. In the context of pharmaceutical analysis, POCT enables real-time monitoring of drug safety, pharmacokinetics, and therapeutic efficacy.

The pivotal role of POCT in pharmaceutical analysis is exemplified by its application in real-time therapeutic drug monitoring (TDM) [3,4], such as NIR-guided warfarin dosing and chemotherapeutic drug concentration tracking [5], which facilitates personalized dose adjustment and minimizes toxicity risks. POCT also enables rapid screening for drug abuse and toxicology assessment in forensic and addiction management, achieving high accuracy rates [6]. In emergency toxicology, POCT allows rapid detection of drug and alcohol levels in blood or urine, enabling timely intervention for overdosed or poisoned patients [7]. It can also be used on-site for detecting pesticide or heavy metal poisoning, which accelerates clinical decision-making regarding antidote

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administration [8]. In clinical trials and individualized therapies, POCT facilitates dynamic monitoring of biomarkers like circulating tumor DNA (ctDNA), allowing for real-time assessment of drug response [9]. Furthermore, microfluidic chip-based POCT platforms support high-throughput pharmacokinetic analysis with minimal sample volumes and enhanced efficiency [10]. With the advancement of equipment manufacturing technology, three-dimensional (3D) printing has emerged as a transformative fabrication technology, enabling rapid prototyping and customization of miniaturized POCT devices with complex geometries and integrated functionalities [11,12]. For example, a low-cost, disposable 3D-printed electrode modified with gold particles has been developed for simultaneous detection of SARS-CoV-2 and creatinine [13]; the incorporation of a 3D print with a microfluidic chip or microneedle array patch achieved portable and rapid detection [14,15], and the integration of smartphones further enhances the readout portability [16].

Importantly, POCT also plays a critical role in the quality control of Traditional Chinese Medicine (TCM). It enables rapid on-site detection of pesticide residues, heavy metals, active ingredients, and genetic authentication markers [17]. With its portability and operational simplicity, POCT significantly enhances field-based TCM inspection, supports rapid screening for counterfeit or substandard products, and promotes regulatory compliance-effectively bridging the gap between laboratory testing and real-world application.

The application of DNA nanotechnology in POCT has remarkable suitability. The unique advantages make it a key technology to enhance the performance of POCT. DNA nanotechnology is an interdisciplinary field that takes advantage of the molecular properties of nucleic acids to artificially design and build nanoscale structures or functional devices [18]. Its flexible structural design and multifunctional integration provide dynamic response characteristics as well as signal amplification capabilities [19]. Through rational base sequence design, DNA molecules can self-assemble into precisely controlled two- or three-dimensional nanostructures, such as nanotubes, polyhedra, and nanosphere [20–22], which can serve as scaffolds or signal amplifiers in diagnostic sensors.

In POCT platforms, DNA nanostructures enable the development of enzyme-free, highly specific, and sensitive detection strategies, offering significant advantages in miniaturization, multiplexing, and adaptability for diverse pharmaceutical and clinical applications. Functional nucleic acids such as aptamers and G-quadruplex DNAzymes enable rapid, low-cost, and label-free detection without relying on complex instruments [23]. DNA logic circuits support multiplex analysis, while DNA nanomachines like walkers and tweezers offer dynamic sensing or therapeutic functions [24]. These systems remain stable in complex biological fluids, including blood and urine, making them well-suited for real-world POCT applications in drug monitoring, toxicity screening, and quality control of pharmaceuticals and traditional medicines.

Conventional DNA biosensors often require multi-step operations for real sample analysis, including sample preparation, amplification, and signal generation, however, the microfluidic integration offers a pathway toward miniaturized and automated lab-on-chip systems [25–27]. Furthermore, the pump-free fluid manipulation strategies (such as centrifugation, capillary action, and magnetic fields) coupled with cost-effective materials to enhance manufacturability and user accessibility [28]. These advances are paving the way for the further promotion of DNA nanotechnology-based POCT platform.

Although DNA-based point-of-care testing (POCT) platforms have been systematically reviewed, covering aspects from device engineering to detection technologies, a comprehensive review specifically focusing on its innovative applications in pharmaceutical analysis (especially for traditional Chinese medicines) is still lacking. To bridge this gap, based on the structural design strategies and signal response mechanisms of DNA nanotechnology in POCT, this review summarized recent advances in the integration of DNA nanotechnology with innovative detection devices used in POCT systems, such as paper-based diagnostics, microfluidic chips, electrochemical sensors, and smartphone-compatible interfaces. Furthermore, we highlight the transformative applications of these DNA nanotechnology-based POCT platforms in pharmaceutical analysis, including drug safety and toxicity assessment, pharmacokinetic monitoring, and quality control of Traditional Chinese Medicine (TCM) (Scheme 1). Finally, we explore future perspectives, emphasizing the integration of emerging technologies such as artificial intelligence to enable automated analysis, intelligent data interpretation, and further optimization of POCT in clinical and pharmaceutical settings.

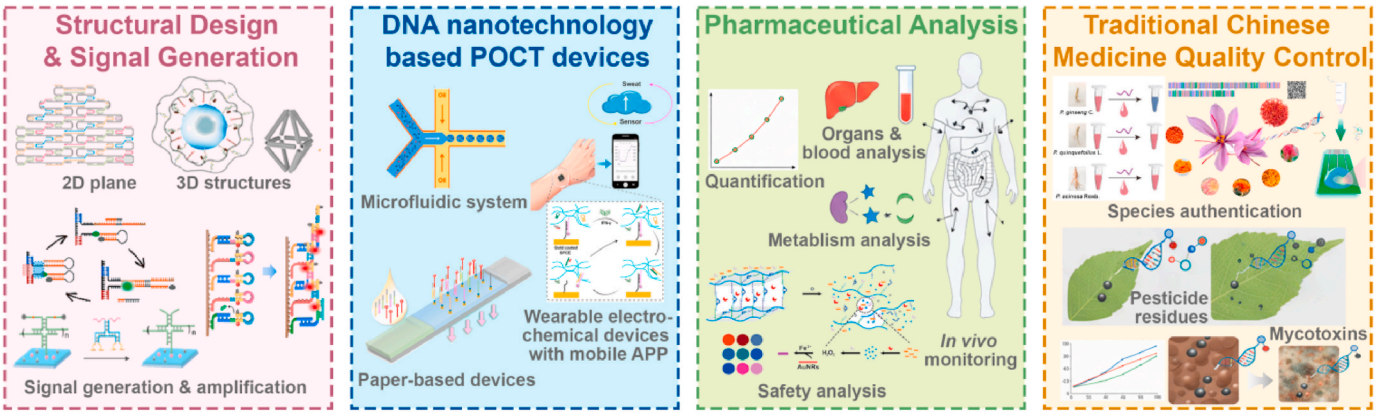
2. Design and construction of DNA nanostructures

2.1. Types of DNA nanostructures

The DNA nanostructures can be divided into two main categories based on the classification of geometrical forms, including two-dimensional planar structures and three-dimensional stereo structures. 2D planar structures are usually assembled from periodic lattices or non-periodic structures. Periodic lattice is the formation of ordered two-dimensional arrays by self-assembly of sticky ends of repeating units. For example, Seeman constructed fixed Holliday linkage tiles with several short single-stranded DNA oligonucleotides, and assembled a number of 2D arrays and DNA cubes with these tiles [29,30]. Such structures can be used to build computational logic units, such as generating fractal patterns. Non-periodic structures, on the other hand, are designed to achieve complex patterns by specific sequences. For example, Rothermund used a long single DNA strand as a scaffold and a large number of short DNA oligonucleotides as a staple to assemble various shapes (Fig. 1a) [31]. Three-dimensional structures are divided into polyhedral structures, nanotubes and nanocages, and three-dimensional lattices. In our previous work, a DNA nanotube was constructed through annealing mixture of DNA single strands, and the photocleavable unit as well as the enzyme-assisted strand displacement amplification were incorporated to trigger strong resonance Rayleigh scattering signals for microRNA-126 detection (Fig. 1b) [32]. Using DNA strands as modular building blocks, our group constructed a DNA nanocage directly on the surface of T-cell membranes. This nanocage, assembled through hybridization of acrylamide-based DNA copolymers, encapsulates single cells to spatially confine cytokine secretion, thereby enabling real-time monitoring of interferon-gamma (IFN-γ) at the single-cell level (Fig. 1c) [33]. Through the hybridization of long skeleton strand with staple strands, our group developed a spheroidal DNA nanohydrogel architecture for near-infrared II fluorescence imaging of early-stage tumor. Under the activation of highly expressed ATP or cytokine in tumor cells, the staples were.

Liberated to generate fluorescence recovery for tumor imaging. This straightforward design offered the advantages in terms of low cost and ease of adaptation for multitarget detection, underscoring its potential for advancing DNA nanotechnology toward clinical translation and commercial production (Fig. 1d) [34]. Dynamic reconfigurable structures include nucleic acid nanomachines and environmentally-responsive structures, for example, Z-DNA conceived to switch from B-type to left-handed helix under specific ionic concentration or super-helical tension, which can be used for designing smart sensors or logic gates [35,36].

Hybrid composite structures, such as DNA-nanoparticle complexes and DNA-protein hybrids, offer enhanced functionality through synergistic integration. For instance, combination with gold nanoparticles or quantum dots improves optical and electrical properties for bioimaging and electronic sensing. Similarly, the integration of DNA nanostructures with protein systems like CRISPR Cas systems enables precise gene editing and highly specific nucleic acid detection, expanding the application scope of POCT technologies. There are also application-oriented DNA nanostructures in biomedicine, such as drug carriers and diagnostic probes. In addition, there are some DNA nanostructures that are artificially designed and simulated based on non-classical DNA



Scheme. 1. Schematic illustration on the design and devices of DNA nanotechnology based POCT and applications in pharmaceutical analysis and traditional Chinese medicine quality control.

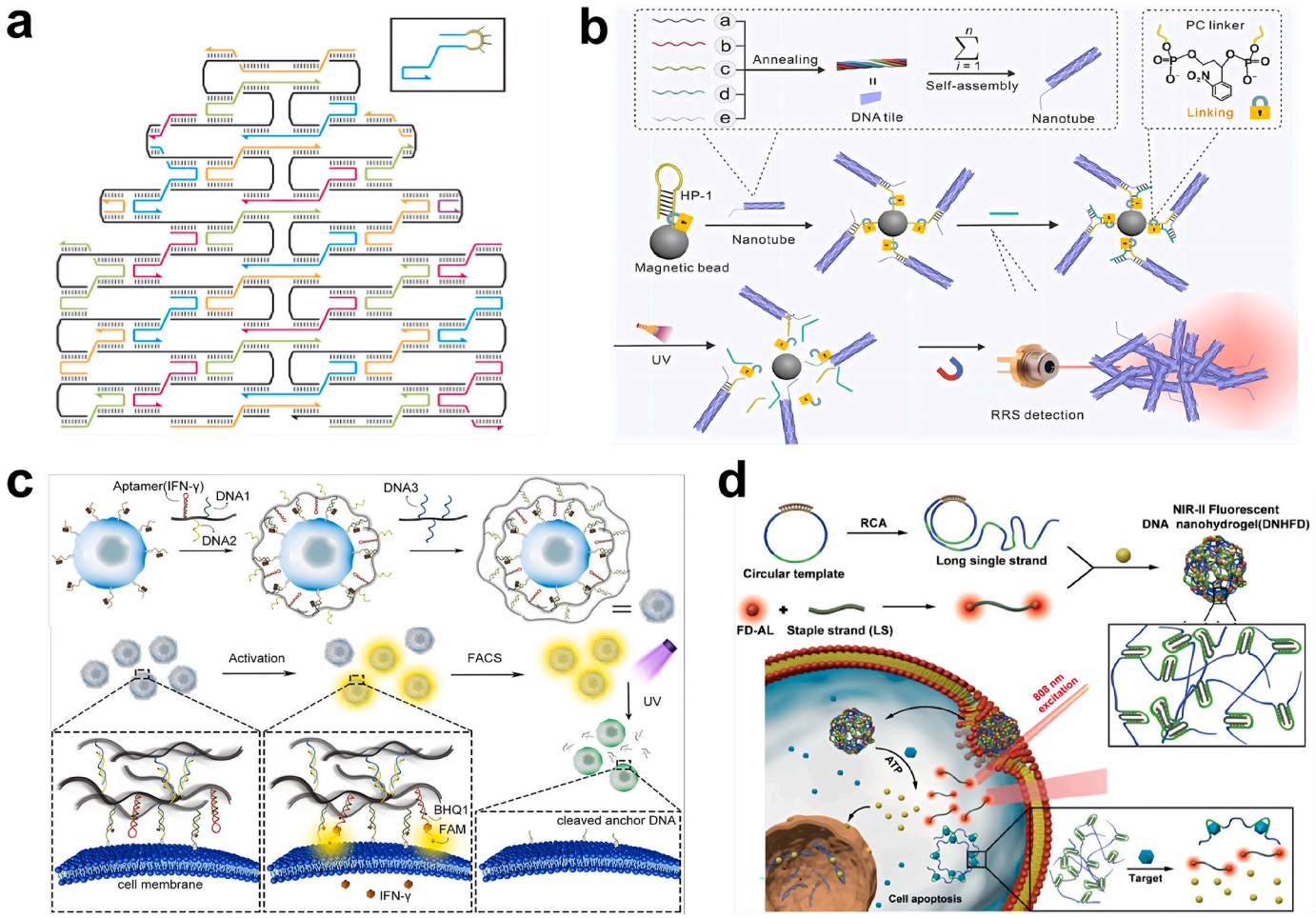


Fig. 1. Schematic illustration of different types of DNA nanostructures: (a) a two-dimensional shape through long, single-stranded DNA molecules folding [31], (b) photocleavable DNA nanotubes for microRNA-126 detection [32], (c) DNA-copolymer nanocage constructed on the cell membrane [33], (d) spheroidal DNA nanohydrogel assembled from long skeleton strand with staple strands [34].

structures that exist naturally in organisms. It breaks through the paradigm of the traditional double helix (B-type DNA) to build nanomaterials with specific functions by mimicking the special folded form of nucleic acids in nature. Nature-inspired atypical structures provide rich design inspiration for DNA nanotechnology, and the combination of their biological properties and engineered functions is driving breakthroughs in fields such as precision medicine and synthetic cells [37–39].

2.2. *Functionalized modifications*

Functionalization modification (FM) refers to the modification of a material's surface or body by chemical, physical or biological means to give it a specific function or property that it did not originally have. This

process is widely used in the fields of materials science, nanotechnology, biomedicine, energy, etc., and its core objective is to "tailor the properties of materials" to meet the needs of specific applications. For example, in the field of medicinal chemistry, L0ate-Stage Functionalization (LSF) directly modifies the C–H bond at a later stage of complex molecule synthesis in order to rapidly generate a library of structurally diverse molecules, accelerate the study of structure-activity relationships (SARs), and optimize lead compounds [40]. In our previous work, the high-affinity interaction between streptavidin and biotin was leveraged to conjugate a TAT peptide on DNA nanostructures, enabling efficient cellular uptake and precise transport of the DNA nanostructures into the cell nucleus [41].

Several common functional group modification methods include carboxylation, amino modification, and azide modification. Carboxylation is primarily achieved through three methods: chemical oxidation, plasma treatment, and grafting reactions. In our previous work,we functionalized CSUCNPs-800CW with carboxyl groups to provide covalent binding sites for immobilizing the amino-modified DNA backbone, enabling stable anchoring of the DNA nanobrush on the carrier substrate [42]. Additionally, in prior work, we introduced thiol groups (-SH) at the termini of the DNA frameworks. These thiol-functionalized DNA structures were conjugated to the UCNP surface via amide bonds, achieving robust integration between the DNA nanostructures and UCNPs [43]. This design prevents dissociation in intracellular environments and establishes a stable platform for subsequent logic-gate operations.

Azide modification methods primarily include click chemistry precursors and in situ synthesis. Click chemistry precursors introduce azide groups through thiol-azide exchange or silylation reactions, such as azide-modified chitosan. In situ synthesis involves using azide-containing monomers in material synthesis, such as metal-organic frameworks (MOFs). Karol's group introduced azide groups (-N_3) onto the surface of silicon nanoparticles (Si NPs) via silanization. Subsequently, dibenzylcyclooctyne-modified DNA (DBCO-DNA) covalently bound to the Si–N_3 through strain-promoted azide-alkyne cycloaddition (SPAAC), forming a stable triazole linkage [44].

2.3. Target identification and signal response

Target recognition by DNA nanostructures refers to the design of specific DNA nanostructures that enable them to recognize and bind target molecules with a high degree of specificity. This recognition is based on DNA's molecular complementarity, aptamer binding ability, or dynamic structural changes that enable precise detection, localization or response. The core mechanisms include complementary strand hybridization, aptamer binding and inversion of configuration under acidic conditions. Complementary strand hybridization is the design of single-stranded regions on DNA nanostructures to bind to target nucleic acids through base complementary pairing. For example, circulating miRNAs are present in various body fluids and have become useful diagnostic biomarkers for various diseases. Nucleic acid base complementary pairing recognizes miRNA, triggering a cascade amplification through base complementary pairing, combined with a logic gate design to achieve high sensitivity and specificity detection [45–47]. Aptamers specifically recognize small molecules such as ATP, or proteins like IFN-γ, thereby initiating a strand displacement reaction that induces conformational changes of the DNA nanostructure and subsequently triggers signal generation [33,34].

Signal response mechanisms are currently classified into several broad categories, including optical signal response, such as fluorescent signals, which are detected by Förster resonance energy transfer (FRET) or fluorescent group/quenched group separation [48]. In addition, Rayleigh scattering-based detection offers enhanced selectivity and sensitivity, making it highly suitable for biosensing applications. Electrochemical signal response, the principle of which is to change the electrode surface charge distribution or release electroactive molecules through target binding. Wu's team discovered that $K_2Cr_2O_7$-induced DNA damage in HT1080 cells triggers a metabolic response, releasing electroactive molecules (hypoxanthine, guanine, xanthine) [49]. These purines, detected via linear scan voltammetry, produce amplified electrochemical signals, serving as a novel biomarker. Biological effect response, which has applications in both drug release and immunomodulation. Drug release i.e. the target triggers DNA nanostructures to unfold and release loaded drug molecules, for example, Zhang's group designed a tubular DNA origami paired with an aptamer that releases prodrugs after internalisation in tumour cells [50]. Immunomodulation aspects of DNA nanomachines can activate or inhibit immune pathways. For example, Song's team found that the compact structure of DNA origami inhibits the cGAS-STING pathway, while loose double strands activate the pathway [51].

2.4. Signal amplification strategies

Many techniques have been used for signal amplifications including enzymatic signal amplification, such as polymerase chain reaction (PCR), which mimics the semi-retentive replication of DNA and amplifies the target DNA through thermal cycling to exponentially increase the signal, rolled-circle amplification (RCA) to produce long repetitive DNA strands, loop-mediated isothermal amplification (LAMP), helicase-dependent amplification (HDA), and recombinase polymerase amplification (RPA), enabling low-temperature amplification for point-of-care use. In addition, non-enzymatic signal amplification is also widely used, including catalytic hairpin assembly (CHA), hybridization chain reaction (HCR) and DNA walker designs. These methods enhance sensitivity and specificity in genomics, diagnostics, and biosensing.

Winfree's team proposed the DNA-based catalytic hairpin assembly (CHA) mechanism firstly in 2007 [52], which achieves enzyme-free amplification through target-triggered strand displacement reaction, laying the theoretical foundation of CHA. In our previous work, we combined catalytic hairpin assembly (CHA) with DNA aptamer to design a transmembrane DNA logical computation strategy for precise therapy of solid tumors (Fig. 2a) [43]. Under the combination with sgc8 on the cell membrane, the miRNA-21 recognition region of the DNA nanomachine was exposed for CHA reaction, which activates the photosensitizer Rose Bengal for efficient generation of ROS. You's group, on the other hand, used CHA to construct molecular circuits for sensitive detection of RNA in living cells, promoting the application of CHA in biomedicine [53]. Ye's team combined CHA with CRISPR-Cas12a to achieve one-step detection of miRNA [54]. Yuan's group proposed ordered aggregation of CHA to achieve simultaneous detection and imaging of dual miRNAs through tetrahedral DNA nanostructures, with a detection limit as low as 21 fM [55]. Li's group, on the other hand, localized CHA on the surface of gold nanoparticles (AuNPs) to shorten the detection time to 45 min, with a sensitivity up to 10 pM [56].

The hybridization chain reaction (HCR) was first proposed by R. M. Dirks, N. A. Pierce, who used two DNA hairpin probes to self-assemble into long-stranded double-stranded structures triggered by the target to achieve signal amplification [59]. In our previous work, a near-infrared photoswitched cascade reaction was achieved through incorporation of HCR with multiple upconversion luminances (Fig. 2b) [42]. Under NIR light irradiation, the UV light generated from upconversion nanoparticles (UCNPs) enables the microRNA-responsive HCR between hairpins, facilitating the ROS generation of photosensitizers under the emitted blue light for photodynamic therapy of early-stage cancers. Recently Xu's team proposed to achieve precise control of the degree of HCR reaction by modulating the overhanging region at the end of hairpin DNA, and expanded its application in enzyme activity analysis and secondary structure identification of ultrashort sequences [60]. In recent years, DNA walkers have achieved substantial advances in the design of signal amplification strategies and biomedical applications. The core technology of DNA Walker is based on dynamic DNA nanotechnology, and its core idea can be traced back to dynamic DNA

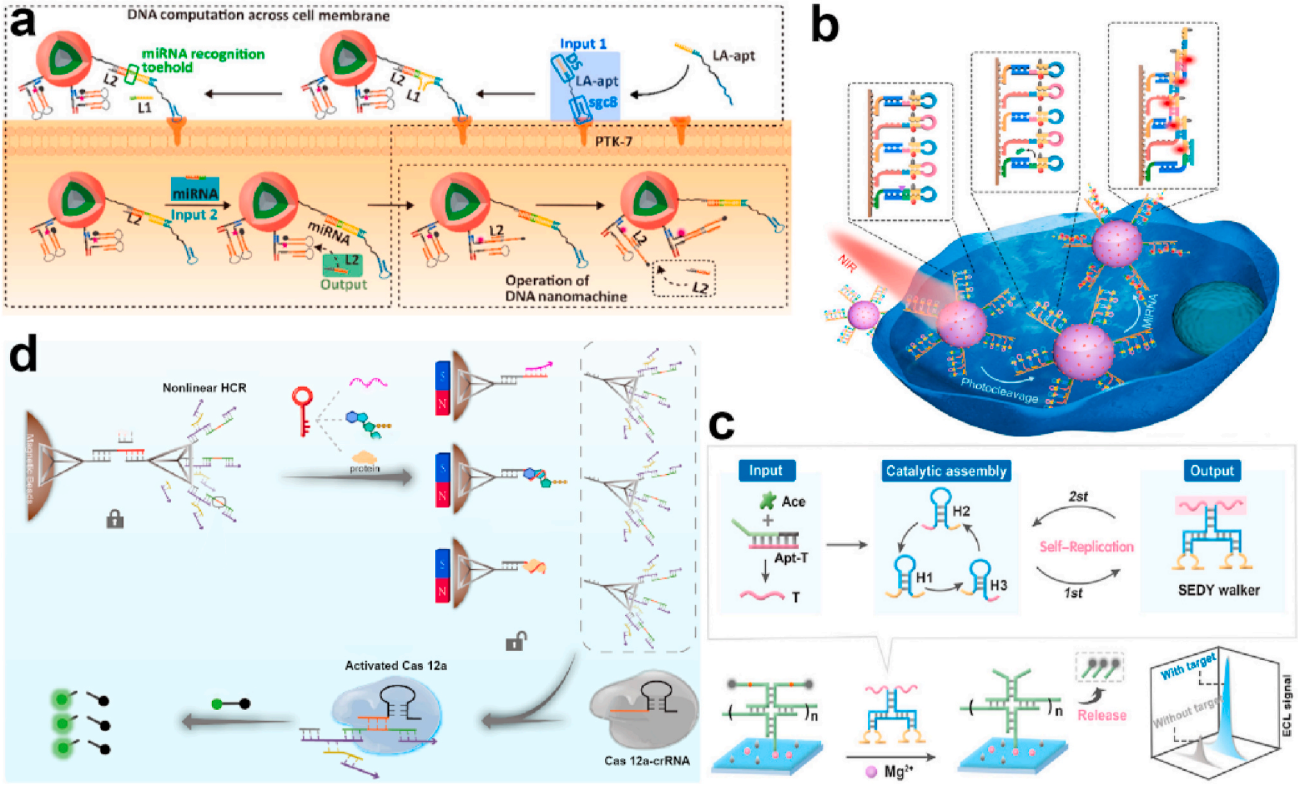


Fig. 2. Schematic Illustration of various signal amplification strategies: (a) catalytic hairpin assembly for efficient photosensitizer activation [43], (b) hybridization chain reaction to facilitate the ROS generation [42], (c) self-replicating bipedal DNAzyme walker to achieve ultra-sensitive detection of pesticide residues [57], (d) HCR and Cas12a-mediated two-stage amplification cascade for highly sensitive multiplex detection [58].

assembly technologies such as CHA and HCR. Zhuo's group from Southwest University proposed to generate a circular DNA walker by ligase chain reaction (LCR) [61], which combined with electrochemiluminescence (ECL) technology to achieve highly sensitive detection of single nucleotide polymorphisms (SNPs). Yuan's group designed a double-stranded interlocked structure of double loop DNA walker, whose anti-entanglement and high stability enable it to achieve Amole level sensitivity in microRNA detection [62]. Lu's team developed a bipedal catalyst-driven DNA walker, which significantly accelerated the reaction kinetics through local concentration enhancement and autocatalytic feedback mechanism and was successfully used for live-cell mRNA imaging [63]. Zhuo's team designed a self-replicating bipedal DNAzyme walker (SEDY), which combined with cross-shaped DNA tracks to achieve ultra-sensitive detection of pesticide residues (Fig. 2c) [57]. Unlike conventional catalytic DNA walkers with a single direction, this SEDY walker employs a target-triggered, enzyme-free self-replicating mechanism. This design enables exponential product amplification through autonomous replication, enhancing the detection sensitivity and reducing signal leakage.

Through the incorporation of the CRISPR-Cas system and enzyme-nanomaterial synergy system, multifarious composite signal amplification systems have been developed and introduced novel technical support for signal amplification in DNA nanotechnology, offering versatile applications in molecular diagnostics and bioimaging. Hu's group integrated nonlinear HCR with the CRISPR-Cas12a system to develop a versatile biosensing platform for the simultaneous detection of diverse analytes (Fig. 2d) [58]. The sensing mechanism relies on two self-assembled DNA tetrahedrons configured into a dumbbell-shaped "lock" structure, which undergoes target-induced dissociation. This event initiates a two-stage amplification cascade involving nonlinear HCR and Cas12a-mediated collateral cleavage, resulting in robust fluorescence signal output suitable for highly sensitive multiplex detection.

3. Development of DNA nanotechnology based POCT devices

Leveraging the unique advantages of DNA nanotechnology (including highly programmable design flexibility, precise molecular recognition capabilities, and efficient signal amplification mechanisms), a diverse array of POCT devices has been developed to enable rapid and accurate on-site analyses. The foundational substrate framework materials for these POCT devices typically include microfluidic chips, paper-based materials, and electrochemical platforms. These substrate platforms serve as the basis for constructing integrated electrical and optical signal response systems.

3.1. Substrate materials

3.1.1. Microfluidic chip

Microfluidic chip technology, also known as laboratory-on-a-chip (Lab-on-a-chip), is a multidisciplinary cross-disciplinary technology [64]. With the support of DNA nanotechnology, microfluidic chips can be equipped with structures such as DNA tetrahedra and nanosphere, combined with CRISPR/Cas system or isothermal amplification technologies, to achieve highly sensitive detection of viruses, bacteria, and gene mutations [26,65]. Within this category, devices can be further differentiated by their driving forces and degree of integration, such as sample-in-answer-out chips vs. detection-only modules.

Microfluidic chips have ultra-high sensitivity and specificity [26], and combined with the signal amplification ability of DNA nanostructures, the detection limit can be up to the single-molecule level. Meanwhile, the microfluidic chip has a certain anti-interference ability, and the nano-restricted domain effect and co-calibrated probe design can eliminate the interference of blood, sputum and other complex matrices [65]. Besides, the portability and low manufacturing cost of microfluidic chips have significantly accelerated their transition into commercial production and broad market application, thereby

promoting their extensive utilization in point-of-care diagnostic systems and decentralized healthcare settings. Representing the pinnacle of integration and manufacturability in microfluidic POCT, Xia's group proposed a fully integrated, sample-in-answer-out microfluidic chip for rapid on-site nucleic acid detection. This device exemplifies the highly integrated category, as it incorporates sample preparation, amplification, and detection modules into a single cartridge. Furthermore, its design for mass production via injection molding at a minimal cost (~$3 per chip) addresses the critical challenge of scalable and cost-effective manufacturing for commercial translation, setting a benchmark for disposable, integrated diagnostic platforms [65].

Alternatively, centrifugal force provides a robust and pump-free driving mechanism for fluid manipulation. Li's group developed a centrifugal microfluidic platform with double rotation axes for sample-to-answer hepatitis B virus DNA detection from whole blood [66]. This work exemplifies the centrifugal microfluidic subcategory, where controlled rotation sequentially drives samples and reagents through different processing chambers, enabling automation and integration within a disc format. This approach is particularly advantageous for processing complex biological samples like whole blood. At the same time microfluidic technology enables the integration of reaction and detection by integrating functional sample pre-processing, its detection methods are diverse and can output results by fluorescence, electrochemical or colorimetric methods. It can even be detected using mobile phones [67].

Using a home-built microfluidic system, Liu's group developed a size-coded hydrogel microbead system that directly uses serum samples to capture target miRNAs for cancer diagnosis (Fig. 3a) [68]. After hybridization between the target miRNA and the capture probe, rolling circle amplification (RCA) is triggered to generate long DNA strands, which subsequently hybridize with TAMRA-fluorophore-labeled reporter chains to amplify the signal. This technology can be extended to multi-miRNA marker panels for other cancers, such as breast cancer and prostate cancer.

3.1.2. Paper-based devices

Paper-based devices are categorized into different dimensions based on functional requirements. 1D (linear) paper-based structures are used for simple assays, 2D paper-based devices enable multi-targeted assays through a larger surface area, whereas 3D origami structures allow for the integration of multi-step reactions, approaching a The 3D origami structure can integrate multi-step reactions, which is close to the function of a “minilab” [23]. These devices use low-cost materials such as filter paper and wax-printed hydrophobic.

Channels, combined with DNA nanostructures and functional nucleic acids to achieve target recognition and signal amplification [23,26].

The core advantages of paper-based devices include low cost and ease of production, portability and ease of operation, high sensitivity and immunity to interference, and a wide range of applications. Its material cost is low, with inexpensive paper-based materials, and combined with the wax-printing process to make microchannels, the cost of a single test can be very low. And the nano-restricted domain effect and co-calibrated probes can effectively eliminate the interference of complex samples such as blood and sputum [23,71]. Besides, its rapid and accurate detection properties enable rapid on-site quality control and monitoring. Wu's group developed a three-channel mCD-μPAD aptamer sensor and a portable detection device in collaboration with a smartphone. The fan-shaped microfluidic paper-based device integrates aptamers and fluorescent carbon dots for simultaneous detection of sulfonamides, chloramphenicol, and other contaminants in 15 min [72].

Incorporation with the hybridization chain reaction and multisite exonuclease III (Exo-III) cycling amplification, Li's group developed a highly sensitive and integrated biosensing platform for on-site bacterial detection (Fig. 3b) [69]. The system operates through target-initiated HCR assembly, generating DNA structures that facilitate Exo-III cleavage to release abundant amplicons. These products then migrate on an LFA strip, capturing DNA-conjugated CdTe/CdS nanoparticle probes to form a fluorescent test line, which is quantitatively measured by the portable fluorescence reader. Capable of simultaneously detecting various bacteria with low detection limits, this platform demonstrates notable advantages in isothermal operation, ease of use, and cost

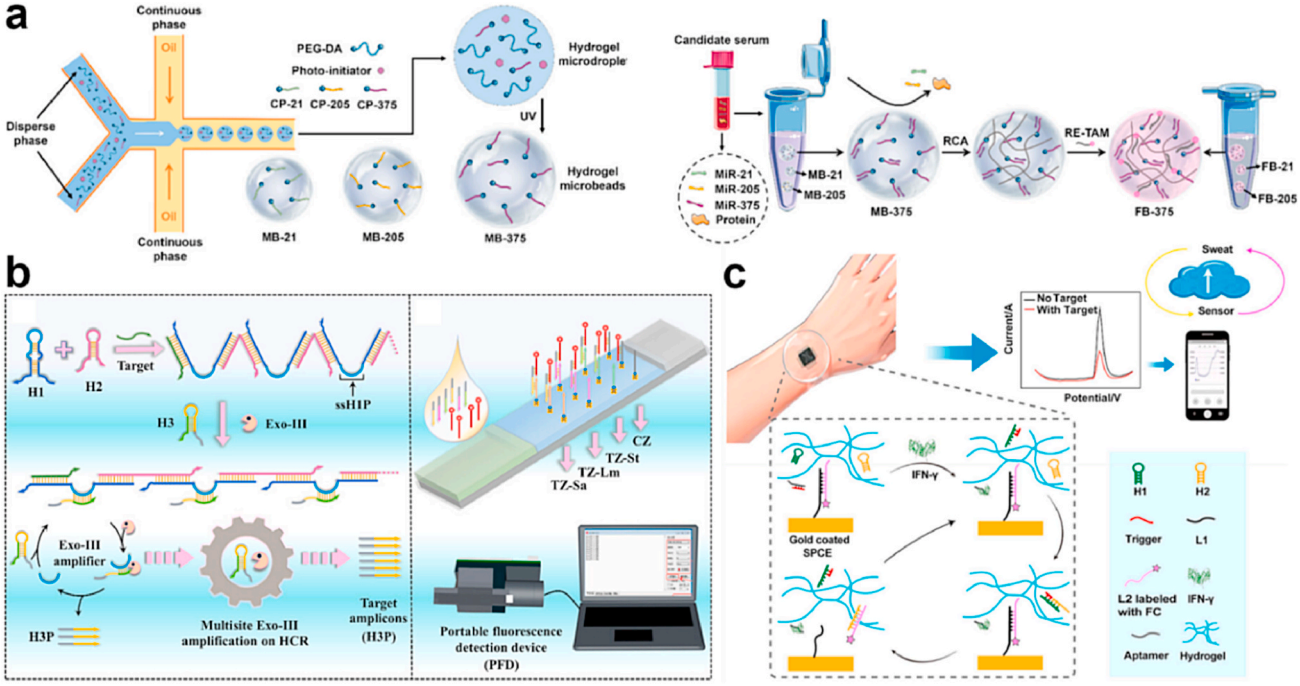


Fig. 3. Schematic Illustration of DNA nanotechnology based POCT devices: (a) hydrogel microbead system for cancer diagnosis [68], (b) the lateral flow assay based on HCR/Exo-III amplification strategy for on-site bacterial detection [69], (c) a wearable electrochemical sensor incorporated with DNA hydrogel for portable IFN-γ detection [70].

efficiency, highlighting its strong potential for multiplex nucleic acid testing in point-of-care applications.

3.1.3. Electrochemical devices

Electrochemical devices convert chemical signals into detectable electrical signals through the specific reaction of biomolecules with the electrode surface [26,73]. Its core strengths are divided into three main parts: ultra-high sensitivity, digitization and automation, simplicity and low cost [74]. Based on substrate or form factor, these devices can be classified into three main categories: traditional electrodes and screen-printed electrodes, paper-based electrochemical devices, and flexible/wearable electrochemical sensors.

Conventional rigid electrodes provide a stable platform for laboratory-based assay development and optimization. Fabricated from materials such as carbon, gold, or platinum, these electrodes offer excellent conductivity, reproducibility, and compatibility with various surface functionalization strategies for DNA probe immobilization. Further developed screen-printed electrodes significantly improve usability for POCT. Their standardized fabrication processes enable cost-effective production with consistent performance, providing the foundation for commercial portable detectors [75].

Flexible/wearable electrochemical sensors devices are designed for continuous, on-body monitoring, which integrate electrodes on flexible substrates such as biocompatible hydrogels [70], ensuring mechanical compliance and stable interfacing with the skin. These material choices bring key advantages such as enhanced wearer comfort, resistance to motion-induced signal fluctuation, and the ability of long-term real-time physiological or pharmaceutical monitoring.

Paper-based electrochemical devices represent a significant advancement in POCT by merging the benefits of low-cost substrate and electrochemical sensing, offering new material platforms for portable and on-site diagnostics. These devices utilize wax-printed hydrophobic channels and carbon electrodes, requiring no external power supply and costing less than $1 per assay [23,26]. Lyophilized reagents are pre-loaded on the chip and the user only needs to add a drop of sample to complete the assay within 15 min [23]. This integration of paper and electrochemistry exemplifies a powerful approach to developing accessible, user-friendly, and economically feasible POCT systems for widespread use in resource-limited settings.

3.2. Signal generation mechanisms

3.2.1. Electrochemical signals

Electrochemical detection represents one of the most widely adopted signal transduction mechanisms in DNA nanotechnology-based POCT devices, offering advantages such as high sensitivity, rapid response, and seamless integration with miniaturized electronics. By leveraging the unique programmability of DNA molecules, these platforms convert specific molecular recognition events into measurable electrical signals through strategies including redox label conjugation, DNA nanostructure-mediated electron transfer, and proton flow modulation.

The DNA nanopore-palladium electrode bioprotonic device developed by a team at the University of California enables dynamic monitoring of biomolecules (such as Streptavidin and the cardiac biomarker BNP) through proton flow modulation [75]. In our previous work, we developed a DNA nanotechnology-based wearable electrochemical sensor for portable IFN-γ detection in sweat (Fig. 3c) [70]. The platform incorporates a DNA hydrogel functionalized with aptamer probes for efficient sweat collection and specific target recognition, coupled with catalytic hairpin assembly for robust signal amplification. Ferrocene-labeled reporters captured on a flexible electrode enable highly sensitive electrochemical readout, which is wirelessly transmitted to a mobile application via a miniaturized potentiostat. This system highlights the potential of dynamic DNA nanostructures in enabling sensitive, portable, and intelligent POCT platforms for personalized health monitoring.

3.2.2. Optical signals

Optical detection represents one of the most versatile and widely adopted sensing modalities in POCT, prized for its high sensitivity, multiplexing capability, and adaptability to both qualitative and quantitative readouts. By leveraging the programmable recognition and signal amplification of DNA nanotechnology, optical POCT platforms translate specific molecular binding events into measurable changes in light properties.

(1) Fluorescence signals

Fluorescence analysis is widely valued for its high sensitivity and strong specificity; however, its reliance on bulky lasers and specialized detection equipment has historically hindered the development of portable sensing platforms. Fortunately, recent advances in smartphone software and hardware have effectively addressed this limitation. The built-in high-resolution cameras, sensitive optical sensors, and sophisticated mobile applications together enable miniaturized and cost-effective fluorescence detection without the need for conventional bulky instruments.

DNA nanoprobes release fluorescent signals after binding to the target, and mobile phone cameras with filters or micro-imaging cassettes capture the fluorescence intensity changes. Tan's group developed the CRISPR/Cas12a-G4 nuclease chemiluminescence platform captures the chemiluminescence signal by mobile phone and combines it with AI algorithms to achieve single-molecule-level detection [76]. The system utilizes a smartphone-based imaging module to quantitatively capture and analyze chemiluminescence signals triggered by Cas12a *trans*--cleavage of G4 DNAzyme. Capable of detecting both nucleic acid and non-nucleic acid targets with ultra-high sensitivity, this platform enables rapid, equipment-free field testing, making it a powerful tool for POCT and on-site analysis.

The development of novel fluorescent nanomaterials facilitates the creation of highly sensitive interfaces compatible with smartphone-based quantification. Xu's group developed a representative platform: an aptamer-functionalized DNA-silver nanocluster (DNA-AgNC) thin film for bacterial detection [77]. The sensing mechanism relies on target-induced modulation of the fluorescence emitted by the DNA-templated AgNCs. Specifically, aptamers against *Staphylococcus aureus* are conjugated to G-rich DNA sequences that host the fluorescent AgNCs. Upon bacterial binding, the conformational change or altered environment leads to a quantifiable change in fluorescence intensity. This solid-phase fluorescent film format is inherently suitable for integration with a smartphone-based reader: the film can be imaged by the phone's camera through an appropriate optical filter, and the fluorescence intensity can be digitally analyzed by a dedicated app to achieve quantitative detection.

(2) Colorimetric signals

Visual detection devices utilize color changes through colorimetric methods for rapid on-site detection, such as gold nanoparticle cluster capture for DNA detection. This method involves capturing multiple gold nanoparticle (AuNP) clusters on the surface of magnetic microspheres. When target DNA is present, a cascade hybridization reaction occurs, forming a “sandwich” structure, causing the solution to change from colorless to pink/red. Additionally, no instruments are required, making it suitable for rapid on-site pathogen screening [78]. Henry's group designed a paper-based peptide nucleic acid (PNA) sensors for detecting viruses/bacteria. When target DNA is present, PNA-DNA double strands form, causing electrostatic repulsion that disperses AgNPs, and the solution changes from an aggregated state (dark color) to a dispersed state (yellow) [79].

The integration of smartphones has enabled the development of all-in-one diagnostic systems that merge heating, incubation, detection, and readout into a single portable device. Unlike conventional isothermal

amplification methods that often rely on external heaters and incubators, Chen's group leverages the smartphone not only as an optical detector and data interpreter but also as a controllable heat source for incubation, developing a POCKET (point-of-care kit for the entire test) platform [80]. As demonstrated in the POCKET platform, such integration allows the entire testing process to be performed in a fully instrument-free, ultraportable system. By combining a smartphone-powered heater and foldable detection box with advanced nucleic acid amplification strategies such as iRPAS, the system achieves high sensitivity and specificity across diverse sample types while significantly reducing device size, cost, and operational complexity.

4. Application of DNA nanotechnology based POCT in drug analysis

4.1. Analysis of drug content and metabolites in biological samples

In the detection of medicinal components, the detection of small molecule drugs and their metabolites is crucial for drug efficacy evaluation [81,82]. DNA nanotechnology combines aptamer recognition with nanomachine signal amplification to solve the problem of insufficient sensitivity in traditional methods [83]. Integrating stimuli-responsive DNA hydrogels with plasmonic nanomaterials, a new paradigm of portable, instrument-free colorimetric assays has been developed that transcend the conventional limitations of sensitivity, selectivity and operational complexity. This advancement embodies the convergence of molecular programming and nanomaterial science, establishing a powerful and versatile platform for next-generation point-of-care diagnostics [84–86]. With the assistance of a microfluidic chip and smartphone-based image analysis software, Gao's group developed a portable and sensitive POCT platform for the on-site detection of melamine (MEL) (Fig. 4a) [87]. They replaced the DNAzyme cascade with a MEL-binding aptamer cross-linker, entrapping 15 nm gold nanoparticles (AuNPs) instead of enzymes, and embedded the entire sensing matrix within a gravity-driven polydimethylsiloxane microfluidic chip. Competitive binding of MEL with the aptamer collapses the hydrogel network to release AuNPs, and the visible color changes can be captured as images and quantitatively analyzed via grayscale measurement using dedicated software. This method enables portable and highly sensitive on-site detection of target analytes without requiring trained operators or large-scale instrumentation, demonstrating significant potential for applications in food safety, clinical testing, environmental monitoring, and related fields.

4.2. Release monitoring in drug delivery

DNA nanotechnology has emerged as a powerful platform for designing intelligent drug delivery systems due to its inherent programmability, biocompatibility, and responsive molecular recognition capabilities [90–92]. By integrating signaling elements, these systems.

not only facilitate efficient drug loading and targeted transport, but also enable real-time and in situ monitoring of release dynamics through sophisticated signal transduction mechanisms, allowing synchronized drug release and activation of reporting signals. Furthermore, coupling with amplification strategies enables ultrasensitive imaging and quantification of drug molecules even at low concentrations [93]. These advanced systems have shown promising potential for integration into POCT platforms, particularly for therapeutic drug monitoring and personalized medication management [94,95]. This synergy between dynamic DNA nanotechnology and miniaturized POCT devices paves the way for smart, connected drug delivery systems that support precision medicine and autonomous therapeutic regulation. This integration heralds a transformative shift towards more intelligent and responsive healthcare solutions, where the convergence of programmable molecular systems and portable diagnostics enables a new paradigm of dynamically adaptive treatment. It represents a significant step forward in the evolution of therapeutic strategies, moving from static

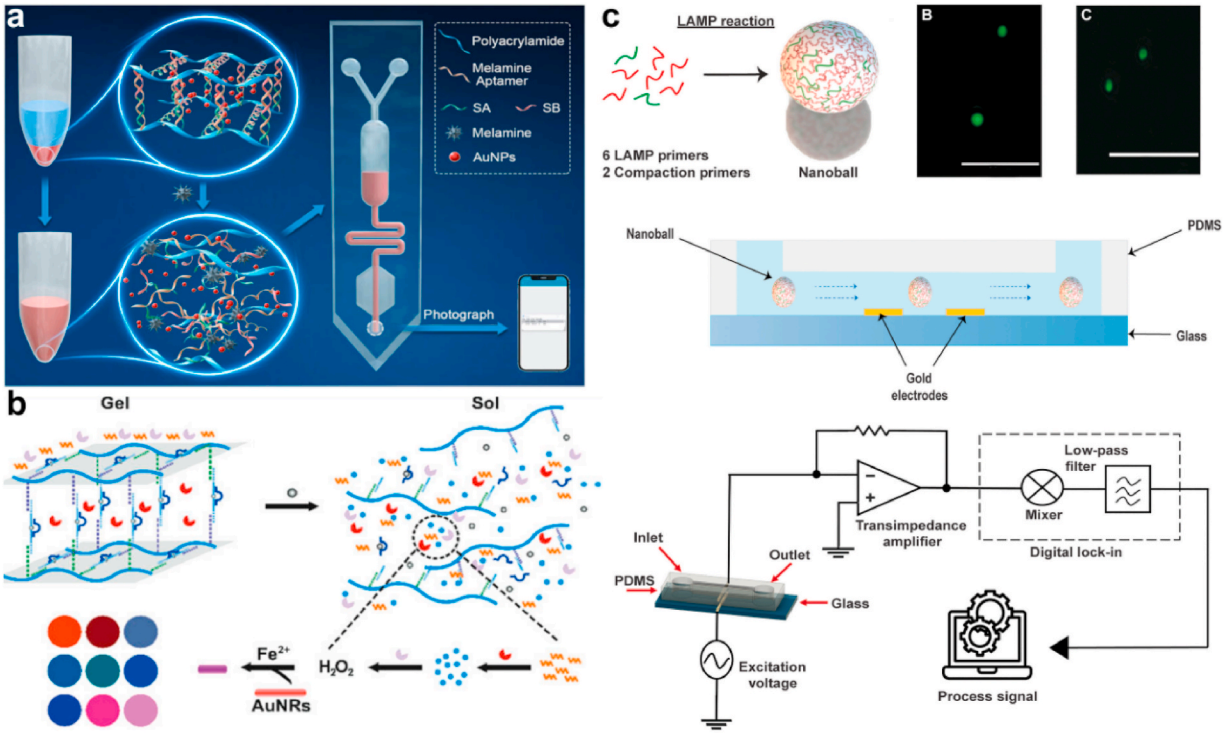


Fig. 4. Applications of DNA nanotechnology based POCT in pharmaceutical drug analysis: (a) stimuli-responsive DNA hydrogels for on-site detection of melamine [87], (b) hydrogel-AuNR system for visual detection of Pb^{2+} [88], (c) one-pot isothermal generation of DNA nanoballs for pathogens detection by electrical impedance [89].

interventions to context-aware, continuously optimized care pathways that align with the overarching vision of next-generation, patient-centric medicine [96–98].

Chen's group designed a stimulus-responsive tetrahedral DNA-RNA nanocage (TDRN) co-loaded with the chemotherapy drug doxorubicin (Dox) and P-glycoprotein siRNA [99]. By embedding RNA sequences via disulfide bonds, the drug and siRNA are synergistically released in the tumor microenvironment, significantly enhancing the therapeutic efficacy against drug-resistant tumors. The nanocage structure enhances serum stability and supports real-time monitoring of drug release kinetics. This technology enables co-delivery of DNA-RNA hybrid nanostructures, dynamically responding to glutathione (GSH) trigger-release, and is suitable for pharmacokinetic/pharmacodynamic analysis of drug-resistant tumors.

Yang's group proposed a drug release monitoring platform based on DNA-upconversion nanoparticle (UCNP) supramolecular assembly [100]. By assembling DNA aptamers with UCNPs at the interface and loading the anticancer drug mitoxantrone (MTX), the platform utilizes changes in the upconversion luminescence ratio to quantitatively measure drug accumulation and release rates at tumor sites in real time, enabling non-destructive in vivo pharmacokinetic tracking. The technical highlight lies in the integration of UCNP optical signals with DNA biological functions, where ratio imaging eliminates background interference, making it suitable for in situ pharmacokinetic analysis in subcutaneous tumor models.

4.3. Drug safety detection

In drug safety testing, DNA nanosensors are commonly used to detect heavy metal contamination in drug production, and they can detect trace heavy metal contamination in drug raw materials or production environment through self-assembled mesh structure and multiple signal amplification mechanisms [101–103]. This sophisticated approach leverages the inherent programmability and molecular recognition capabilities of nucleic acid architectures to create highly specific and responsive detection interfaces. The synergy between designed nanostructures and advanced signal transduction principles represents a significant advancement in analytical science, offering a pathway towards more reliable, efficient, and comprehensive quality control protocols within the pharmaceutical industry.

Yang's group architected a target-responsive hydrogel for the visible detection of Pb^{2+} (Fig. 4b) [88]. Upon Pb^{2+} introduction, the DNAzyme's catalytic motif is activated, executing a site-specific hydrolytic incision at the central ribonucleotide junction of the cross-linking substrate; this scission event undermines the network integrity, provoking a cooperative hydrogel collapse and the consequent liberation of the formerly immobilized glucoamylase (GA). Then the liberated GA fuels a Fenton-type generation of •OH radicals that anisotropically etch gold nanorods (AuNRs) in high-CTAB media, inducing a vivid chromatic sequence (orange → green → blue → purple → pink) discernible by the naked eye.

Liu's team developed a fluorescence/electrochemical sensor based on DNA hydrogel phase change, integrating rolled-cycle amplification (RCA) and hybridisation chain reaction (HCR) to achieve signal amplification, and combined with a microfluidic chip and smartphone image analysis to support real-time quantitative detection of heavy metals in the drug production site. DNA mesh nanosensors use double-stemmed ring DNA probes to self-assemble to form a three-dimensional mesh structure, and amplify the signal through chain substitution reaction, with a detection limit of uranium ions (UO_2^{2+}) as low as 2 pM [104]. DNA is used as a recognition probe, and combined with fluorescent labelling technology, it is possible to achieve the detection of lead (Pb^{2+}), cadmium (Cd^{2+}) and other heavy metals in the active state can be rapidly detected with a high sensitivity and an error of less than 10% from the traditional chemical extraction method. At the same time, DNA nanotechnology can also achieve intelligent multi-target detection, such as through molecular logic gate technology, heavy metal detection can be converted into binary encoded fluorescent signal output [105,106].

Pathogen detection is a vital component of drug safety assessment, and timely accurate identification of infectious agents is essential for preventing adverse drug interactions and ensuring therapeutic efficacy [107]. The application of DNA nanotechnology in pathogen detection has the unique advantages of high sensitivity, high specificity and programmability [108–112], and recent advances have been further driven by the integration of emerging technologies. Pelechano's group developed a “one-pot” isothermal amplification technique (RT-LAMP) for point-of-care nucleic acid testing, which can achieve label-free and highly sensitive detection of pathogens by self-assembling DNA nanospheres in combination with microfluidic impedance detection (Fig. 4c) [89]. By reprogramming RT-LAMP to autonomously form self-nucleating DNA nanoballs, the system eliminates complex preprocessing and reduces dependency on optical detection. The innovative use of impedance spikes generated as nanoballs pass through a microfluidic electrode pair allows quantitative and label-free detection of amplification products. Successfully validated with SARS-CoV-2, HIV, influenza, *Mycobacterium tuberculosis*, and β-lactamase genes, this method offers a versatile, low-cost, and equipment-minimized platform for multiplexed pathogen identification. It holds considerable promise for developing next-generation portable diagnostic devices suitable for resource-limited settings. And the DNA origami nanomachine designed by Wang's group distinguishes between thrombus and normal coagulation through the logic operation of thrombin concentration, and this principle can be extended to the dynamic identification of viral variants [113].

In bacterial detection, multiple nucleic acid detection and subtyping can be achieved by DNA nanotechnology, such as nanopore technology based on DNA dumbbell nanoswitches, which can recognize bacterial 16S rRNA fragments with single-base resolution, and achieve highly specific subtyping of *Escherichia coli* and Salmonella [114]. The DNA aptamer-modified nanoenzyme sensor has also been developed to detect bacterial toxins by modulating catalytic activity, with a high sensitivity [115].

5. Analysis of traditional Chinese medicine

The integrity and safety of Traditional Chinese Medicine (TCM) are paramount to its therapeutic efficacy and consumer health, necessitating robust methodologies for authenticating herbal species and detecting hazardous contaminants that may jeopardize product quality, including heavy metals, pesticide residues, and mycotoxins [116,117]. In response to these challenges, DNA nanotechnology-based point-of-care testing (POCT) has emerged as a transformative analytical platform, leveraging programmable nucleic acid assemblies and amplification strategies to enable highly sensitive, specific, and on-site visual identification of target analytes, thereby facilitating rapid quality control and safety assurance across TCM supply chains.

5.1. Authentication of TCM materials

The authentication of Traditional Chinese Medicine is of great importance to ensure both therapeutic efficacy and patient safety, driving an urgent need for rapid and reliable screening methodologies that can be deployed directly in market settings. In response to this demand, point-of-care testing (POCT) platforms leveraging DNA nanotechnology have emerged as a promising technical solution, enabling sensitive, specific, and on-site visual detection through programmable molecular designs and efficient signal amplification mechanisms.

In our previous work, a dual-signal amplification system for visual identification of ginseng was designed based on DNA cascade reactions (Fig. 5a) [118]. The miRNA specifically expressed in *Panax ginseng* activated DNAzyme released DNA fragments to trigger catalytic hairpin assembly (CHA) reaction for generating branched DNA junctions. These

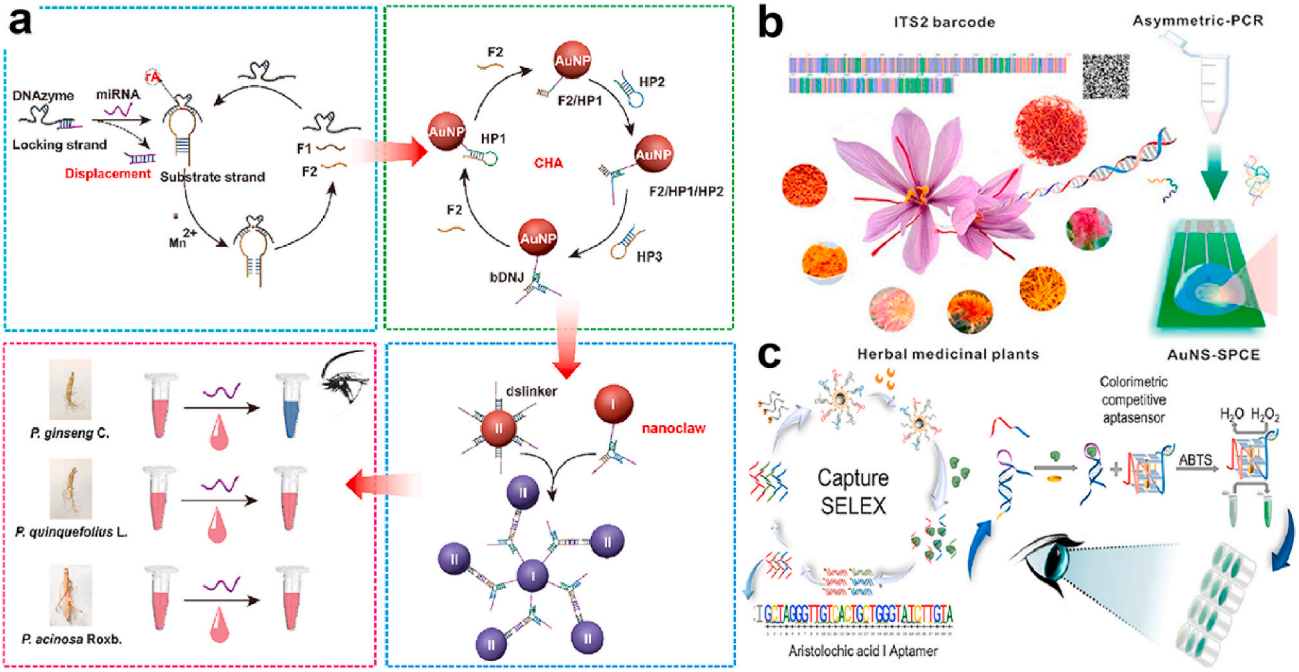


Fig. 5. Applications of DNA nanotechnology based POCT in traditional Chinese medicine analysis: (a) dual-signal amplification system for visual identification of ginseng [118], (b) high-curvature Au nanostructure array to distinguish closely related species [120], (c) a label-free colorimetric aptasensor for instrument-free detection of AAI [121].

junctions induce the aggregation of gold nanoparticles (AuNPs), resulting in a naked-eye-detectable color shift (red-to-blue). By integrating CHA and DNAzyme cascade amplification with AuNP colorimetry, the system achieves high sensitive and visible detection of specific miRNA in ginseng, providing a convenient and portable tool for on-site identification of adulterated herbs in TCM markets and pharmacies. We further integrated a triple signal amplification strategy for visual identification of ginseng and its processed products [119]. Combined with a smartphone-based software for portable quantitative analysis, this approach enables sensitive, on-site quality control in Traditional Chinese Medicine markets and regulatory settings.

Fan's group developed a homogeneous electrochemical DNA sensor based on tetraferrocene labeling and exonuclease III (Exo III) cyclic amplification for direct detection of specific DNA sequences [120]. They used Cordyceps sinensis genes as actual samples and validated the sensor's reliability through PCR product detection, precisely meeting.

The requirements for identifying the original species of traditional Chinese medicinal materials. The method can be extended to other easily confused herbal medicines, such as ginseng and *Fritillaria cirrhosa*, for DNA barcoding detection, addressing the challenge of authenticity verification.

Yang's team developed a high-curvature Au nanostructure array (HCAuNS) (Fig. 5b) [122]. Using lithography-free electrodeposition, 3D fractal Au nanostructures ("mushroom-like nanobranch arrays") were constructed on screen-printed carbon electrodes (SPCEs). This is used to distinguish between closely related species. For instance, the signals from saffron of different origins exhibit strong consistency, while the signal intensity from counterfeits (such as corn or safflower) is less than 20% of that from the authentic product, thus enabling precise differentiation. The nanobranches exhibit high curvature and large deflection angles, significantly enhancing probe accessibility. This design enables direct mid-hybridization with ITS2 DNA barcodes, bypassing complex sequencing. The technology serves as a portable field tool for TCM markets and customs, effectively addressing widespread adulteration issues.

The development of advanced nucleic acid-based biosensors holds significant potential for the on-site authentication of Traditional Chinese Medicine (TCM) materials. For instance, a tetrahedral DNA nanostructure-based fluorescent biosensor, coupled with hybridization chain reaction (HCR) amplification, has been engineered for the ultrasensitive and specific authentication of Fritillaria cirrhosaby targeting its unique DNA barcode, demonstrating a viable pathway for field-deployable discrimination of genuine herbs from adulterants [123]. Building on this foundational work, a broader and highly promising strategy involves the integration of catalytic hairpin assembly (CHA)--based DNA amplification circuits with nanoparticle-mediated signal outputs. This generalized approach leverages the inherent programmability and specificity of nucleic acid circuits to recognize unique genomic or molecular markers of authentic TCM materials. When further combined with portable or self-powered readout systems, such integrated platforms can enable the development of sensitive, instrument-free, point-of-care testing devices, thereby providing a powerful tool for effective and reliable authentication of TCM products.

5.2. *Safety assessment of TCM*

The assurance of safety in Traditional Chinese Medicine constitutes a critical priority, particularly in light of contamination risks posed by hazardous agents including toxic components, fungal toxins and heavy metals, which can compromise product integrity and public health. In this context, point-of-care testing (POCT) leveraging DNA nanotechnology has emerged as a powerful analytical tool, offering significant enhancements in detection sensitivity and specificity for the on-site monitoring of these contaminants, thereby reinforcing the overall framework of TCM safety assessment.

DNA nanoscale sensors can be used to construct biosensors based on DNA origami or aptamers, which amplify fluorescent/electrochemical signals to detect trace active components or toxins in traditional Chinese medicine. Yu's team developed a rapid, highly sensitive on-site detection method for screening the toxic component aristolochic acid I (AAI) in Chinese herbal medicines and plant products, addressing the limitations of traditional detection techniques (Fig. 5c) [121]. They employed the Capture-SELEX technology (a library immobilization-based selection strategy) to isolate an AAI-specific aptamer from a DNA library. Through

gel elution experiments and high-throughput sequencing (HTS) validation, they obtained an aptamer with high affinity and specificity. Additionally, they designed a label-free colorimetric sensor to enable visual identification of AAI-positive medicinal materials.

The application of DNA nanotechnology extends beyond clinical diagnostics to the field of Traditional Chinese Medicine (TCM) quality control. TCM, often derived from natural herbs, is susceptible to contamination by mycotoxins such as aflatoxin B1 (AFB1), a potent carcinogen. To address the need for highly sensitive and stable detection of AFB1 in complex herbal matrices, researchers have developed an electrochemical aptasensor based on a tetrahedral DNA nanostructure (TDN). In this system, a TDN scaffold was self-assembled and immobilized on a gold electrode surface. The TDN's rigid, three-dimensional structure provided a well-defined and stable platform for the immobilization of AFB1-specific aptamers. The key advantage of using TDN lies in its ability to precisely control the spatial orientation and density of the aptamers, preventing the steric hindrance and nonspecific adsorption often encountered in traditional single-stranded DNA probes. Upon binding to AFB1, the aptamer underwent a conformational change, leading to a measurable change in the electrochemical signal. This TDN-based aptasensor demonstrated exceptional performance, achieving an ultra-low detection limit and high specificity in detecting AFB1 in real TCM samples. The robust nature of the DNA nanostructure ensured the sensor's stability and reproducibility, making it a powerful tool for ensuring the safety and quality of herbal medicines [124].

The representative DNA nanotechnology-based POCT platforms discussed before, along with their key performance parameters, are comprehensively summarized in Table 1. As summarized in Table 1, the integration of DNA nanotechnology has led to the development of diverse POCT platforms with remarkable analytical performances. These systems demonstrate a wide range of detection capabilities. The selection of signal transduction mechanisms—including electrochemical, optical, and even logic-gated therapeutic activation—can be tailored to specific application requirements. Furthermore, the inherent programmability of DNA enables not only high specificity but also multiplexing capacity for simultaneous analysis of multiple targets. This versatility and performance underscore the transformative potential of DNA nanotechnology in advancing POCT for comprehensive pharmaceutical analysis, spanning from drug monitoring and safety assessment to the authentication and quality control of complex matrices like traditional Chinese medicines.

6. Challenges and prospects

6.1. Challenges

Despite the promising potential of DNA nanotechnology based POCT in pharmaceutical analysis, its practical application still faces multiple challenges, including structural instability, interference from complex sample matrices, and high production costs. Addressing these issues is critical for achieving reliable, scalable, and cost-effective point-of-care diagnostics.

6.1.1. On-site sample preparation

The integrated “sample-in-answer-out” POCT system necessitates the incorporation of on-site sample preparation into the miniaturized device, including cell lysis, nucleic acid or protein extraction and purification. This remains a significant bottleneck, particularly for the analysis of complex biological samples such as TCMs, which extracts present a uniquely challenging matrix due to the presence of diverse phytochemicals, polysaccharides, polyphenols, and pigments that can severely inhibit enzymatic amplification reactions and interfere with optical or electrochemical signals [65,66].

Therefore, overcoming the on-site sample preparation bottleneck is pivotal for future research of DNA nanotechnology-based POCT in pharmaceutical and TCM analysis. Promising strategies include the design of multifunctional solid-phase extraction materials compatible with portable platforms for the selective capture and purification of targets from complex herbal matrices. Furthermore, leveraging centrifugal microfluidic separation chip or capillary-driven paper-based separation systems can automate multi-step protocols without external pumps, which is especially valuable for processing viscous or particulate-rich TCM extracts. These devices bridge the gap between sample preparation and detection, enabling reliable on-site and analysis of complex pharmaceutical and herbal medicines directly at points of collection or distribution [54,56].

6.1.2. Balance between sensitivity and operational simplicity

Signal amplification strategies including DNA cascade reactions and nucleic acid amplification reactions could significantly enhance the sensitivity for target detection, however, these techniques typically necessitate precise thermal cycling and complex fluidic systems. This compromises the portability and operational simplicity required for on-site testing, while also prolonging the overall assay time. Conversely, amplification-free detection methods remain insufficient for detecting

Table 1
Quantitative performance of typical DNA nanotechnology based POCT methods.

Target	Signal type	LOD	Response time	Multiplexcapacity	Reference
microRNA-126	resonance Rayleigh scattering	0.16 fM	>3 h	Single-plex Detection	[32]
interferon-gamma (IFN-γ)	Fluorescence	Not reported	10 min	Single-plex Detection	[33]
ATP, IFN-γ	Fluorescence	Not reported	2-6 h	Multiplex Detection	[34]
PTK-7 & miRNA-21 (AND Logic Gate)	Fluorescence,ROS	Not reported	>4 h	Single-plex Detection	[43]
microRNA-21	Fluorescence,ROS	10 pM	>6 h	Single-plex Detection	[42]
Acetamiprid	Electrochemiluminescence	0.58 fM	>2.5 h	Single-plex Detection	[57]
miR-141	Fluorescence	145 fM	>1 h	Multiplex Detection	[58]
ATP		11 pM			
Insulin		240 pM			
microRNA-21 microRNA-205 microRNA-375	Fluorescence	0.2 fM	Several Hours	Multiplex Detection	[68]
		0.5 fM			
		0.1 fM			
16S rRNA	Fluorescence	0.35 fM	65 min	Multiplex Detection	[69]
interferon-gamma (IFN-γ)	Electrochemical	0.049 nM	30-60 min	Single-plex Detection	[70]
Melamine	Colorimetric	37 nM	60 min	Single-plex Detection	[87]
Pb^{2+}	Colorimetric	12.5 nM	2.5 h	Single-plex Detection	[88]
Cocaine		0.2 μM			
Pathogen Nucleic Acid	Electrochemical	10 target copies	<1 h	Single-plex Detection	[89]
miRNA	Colorimetric	165 fM	2 h	Single-plex Detection	[118]
ITS2 DNA Barcode Fragment	Electrochemical	0.18 fM	30-60 min	Single-plex Detection	[120]
Aristolochic Acid I	Colorimetric	225 nM	40 min	Single-plex Detection	[121]

low-abundance targets in clinical applications. This inherent trade-off constitutes a major barrier to the practical deployment of DNA nanotechnology-based POCT platforms. To address this challenge, recent research has focused on developing rapid, one-pot reaction systems that integrate isothermal amplification with signal readout in a closed format, thereby minimizing operational steps and contamination risks [125]. Besides, advanced physical and phase separation approaches might help reconcile the incompatibility between amplification enzymes and detection components within a single vessel. These emerging one-pot methodologies, combined with constant-temperature amplification techniques such as loop-mediated isothermal amplification (LAMP) [126], hold promise for reconciling the sensitivity-versus-simplicity dilemma.

6.1.3. Stability of DNA nanostructures

DNA nanostructures have some risk of degradation in biological environments and are susceptible to degradation by nucleases in complex biological environments, leading to functional failure, which is particularly critical for in vivo drug analysis and pharmacokinetic studies. For example, nucleases in the cytoplasm may disrupt the structural integrity of DNA nanocarriers, affecting drug delivery efficiency [127]. Currently, the risk of degradation can be addressed by chemical modifications or nano-restricted domain encapsulation, such as enhancing the resistance to enzymatic cleavage through phosphorothioate bonding [128] or locking nucleic acid (LNA) to improve stability in serum or cell lysates [129] or encapsulating DNA probes in DNA nanocages or liposomes to reduce enzyme exposure using physical barriers [130].

As bioactive molecules, DNA probes and nanostructures are inherently sensitive to environmental factors such as temperature fluctuations, pH variations, and ionic strength changes. The conformational integrity and target-binding activity of these structures can be compromised during storage, transportation, and on-site operation, posing a substantial hurdle for productization. Developing rigid architectures with higher thermal tolerance and lower ion dependence through optimized DNA sequence design would help enhance environmental adaptability and ensure superior performance [39]. Such strategies are essential for translating DNA nanotechnology from laboratory research into commercially viable POCT products.

6.1.4. Synthesis and manufacturing

The high cost of chemical synthesis of long-stranded DNA [131],has limited the popularity of POCT devices to a certain extent. Currently, cost reduction can be achieved through biosynthesis technology or standardized production. For example, phage amplification of DNA nanostructures can be used to reduce the cost [39]. Or the development of paper-based chips with injection molding or wax printing processes, the cost of a single detection can be very low [23,71]. Meanwhile, the preparation of 3D DNA nanostructures relies on precision annealing procedures, making it difficult to achieve high-throughput manufacturing. Some of the current technological breakthroughs include the use of centrifugal microfluidic chips for sample lysis, amplification and detection in one step to support batch production [132]. Alternatively, the amplification reagents can be freeze-dried in the microchip chamber to simplify operation and extend shelf life.

6.2. Outlook

DNA nanotechnology is poised to revolutionize pharmaceutical analysis and traditional Chinese medicine (TCM) quality control through intelligent, field-deployable platforms. Future advancements will focus on bridging cutting-edge nanodevices with practical applications in drug monitoring and TCM authentication, driven by three key directions.

6.2.1. AI-integrated TCM field identification

The integration of artificial intelligence (AI) is opening new frontiers for the application of point-of-care testing (POCT) in the field of Traditional Chinese Medicine (TCM) authentication. This integration spans multiple technical layers, from molecular-level DNA barcode analysis to macroscopic morphological and spectral feature recognition, enabled by sophisticated algorithms. Based on CRISPR-Cas systems combined with microfluidic chips or nanopore sequencers, the POCT (Point-of-Care Testing) platform generates vast amounts of sequence data or characteristic signals after on-site DNA extraction, amplification, and detection. Machine learning algorithms, such as Support Vector Machines (SVM) and Random Forests, alongside deep learning models like Convolutional Neural Networks (CNN) and Recurrent Neural Networks (RNN), are employed to process this data [133]. These methods enable rapid comparison, classification, and identification of specific DNA barcode sequences, achieving precise species identification and the detection of adulterated or counterfeit products. For example, CRISPR-coupled microfluidic chips and nanopore sequencers will enable on-site DNA barcode analysis for rapid species discrimination of high-value herbs, such as *Panax ginseng* vs. *P. quinquefolius*, resolving adulteration issues in supply chains [134]. Through AI-Vision Synergy, smartphone-based platforms can combine hyperspectral imaging with deep learning algorithms to correlate morphological features of TCM materials with chemical fingerprints. High-definition cameras or miniaturized hyperspectral imaging modules integrated into smartphones or portable devices can capture visual information of medicinal materials, including morphological features, color, texture, and internal microstructures, such as through portable microscopic imaging. Computer Vision and deep learning play a central role in processing this information. Well-trained Convolutional Neural Network (CNN) models, such as ResNet, VGG, or more lightweight architectures like MobileNet [135], can automatically extract distinguishing features directly from images, enabling automated authentication and geographical origin tracing. For analyzing 3D microstructures, point cloud processing networks can be employed to handle complex spatial features [136]. Following feature extraction, multivariate statistical analysis algorithms like Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA), and Partial Least Squares Discriminant Analysis (PLS-DA) are commonly used for dimensionality reduction and visualization [137]. These methods help differentiate medicinal material samples of various categories, such as authentic vs. counterfeit, different geographical origins and provide interpretability for the models. For example, convolutional neural networks (CNNs) trained on 3D micro-CT images of *Cordyceps sinensis* could automate authenticity assessment and origin tracing via cloud-based pattern recognition. DNA-encoded nano-tags loaded with encrypted geographical data will create tamper-proof “digital genotypes” for TCM, enabling blockchain-verified supply chain tracking from farm to clinic [138].

Portable near-infrared (NIR), Raman, or fluorescence spectrometers can be integrated with POCT devices to rapidly acquire chemical fingerprint spectra of medicinal materials [139]. Processing such complex spectral data requires robust pattern recognition capabilities. Deep learning models, such as 1D-CNNs and Long Short-Term Memory (LSTM) networks, are well-suited for learning features directly from raw spectral data. Meanwhile, chemometrics algorithms, including Support Vector Regression (SVR), Random Forest Regression (RFR), and Artificial Neural Networks (ANN), are widely used to establish quantitative or qualitative models that correlate spectral features with component content, quality grade, or authenticity of medicinal materials [140].

Future AI-integrated POCT TCM authentication systems will be multimodal, combining genomics, chemometrics, and morphometrics data. Advanced AI frameworks such as multimodal fusion learning and federated learning will play a crucial role in integrating information from diverse sensors and data sources, enabling more robust decision-making. Simultaneously, AI-generated “digital genotypes” or feature codes can be coupled with blockchain technology, leveraging consensus

algorithms like Proof of Work, Proof of Stake to ensure that supply chain data—from cultivation to clinical application—is immutable and traceable.

6.2.2. *Wearable dynamic drug analysis*

Wearable electrochemical patches integrated with DNAzyme-aptamer hybrids will continuously track drug metabolites in sweat/serum, with AI predicting dose adjustments via pharmacokinetic-pharmacodynamic (PK-PD) modeling to achieve Real-Time pharmacokinetic monitoring. "Lab-in-a-capsule" devices using pH-responsive DNA nanomachines will autonomously assess drug dissolution profiles and API stability in gastrointestinal conditions, transmitting data to regulatory cloud databases to achieve the purpose of quality control [141].

7. Summaries

DNA nanotechnology has become an important technological breakthrough in the field of POCT due to its programmability, high sensitivity and multifunctional integration capabilities. The development of multifunctional integrated POCT devices such as three-dimensional DNA nanoframes, paper-based devices, and CRISPR-driven detection systems has opened up more possibilities for POCT testing. Rolling Circle Amplification (RCA) and Hybridisation Chain Reaction (HCR), as well as logic gating design, give signal amplification and anti-interference capabilities, and enable precise control and automation of detection through microfluidic chips and smartphone-driven portable platforms. DNA nanotechnology is driving the development of POCT from a single test to a "test-treat-monitor" closed loop, and demonstrating unique advantages in sensitivity, portability and versatility. In the future, its cross-fertilization with AI, flexible electronics and synthetic biology will unlock more application scenarios, expanding from clinical diagnosis to home health, environmental monitoring and even industrial production quality control, and ultimately realizing "decentralized" and personalized management of medical testing.

CRediT authorship contribution statement

Yuyang Liu: Writing – original draft. **Chenxun Qiao:** Validation, Conceptualization. **Rui Bu:** Writing – original draft, Supervision. **Huangxian Ju:** Writing – review & editing, Supervision. **Peng Cao:** Funding acquisition, Conceptualization. **Yue Zhang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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

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Data availability

No data was used for the research described in this paper.

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