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Lateral flow assays: Progress and evolution of recent trends in point-of-care applications

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ABSTRACT

Paper based point-of-care (PoC) detection platforms applying lateral flow assays (LFAs) have gained paramount approval in the diagnostic domain as well as in environmental applications owing to their ease of utility, low cost, and rapid signal readout. It has centralized the aspect of self-evaluation exhibiting promising potential in the last global pandemic era of Covid-19 implementing rapid management of public health in remote areas. In this perspective, the present review is focused towards landscaping the current framework of LFAs along with integration of components and characteristics for improving the assay by pushing the detection limits. The review highlights the synergistic aspects of assay designing, sample enrichment strategies, novel nanomaterials-based signal transducers, and high-end analytical techniques that contribute significantly towards sensitivity and specificity enhancement. Various recent studies are discussed supporting the innovations in LFA systems that focus upon the accuracy and reliability of rapid PoC testing. The review also provides a comprehensive overview of all the possible difficulties in commercialization of LFAs subjecting its applicability to pathogen surveillance, water and food testing, disease diagnostics, as well as to agriculture and environmental issues.

List of Abbreviations

Word	Full Name
ALP	Alkaline Phosphatase
ATPS	Aqueous Two-Phase System
AIE-CDs	Aggregation-Induced Emission Carbon Dots
BSA	Bovine Serum Albumin
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CNTs	Carbon Nanotube
CAP	Chloramphenicol
CV	Cyclic Voltammetry
CQDs	Carbon Quantum Dots

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Word	Full Name
CRE	Carbapenem-Resistant Enterobacteriaceae
DNA	Deoxyribonucleic acid
DENV	Detecting Anti-Dengue Virus
DMSN	Dendritic Mesoporous Silica Nanoparticles
DPV	Differential Pulse Voltammetry
Eu-NPs	Europium Nanoparticle
EIS	Electrochemical Impedance Spectroscopy
FM	Fluorescent Microspheres
FAM	Carboxyfluoromescein
FQs	Fluoroquinolones
FITC	Fluorescein Isothiocyanate

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GNP	Gold Nanoparticle
GO	Graphene Oxide
GNSs	Gold Nanoshells
HRP	Horseradish Peroxidase
HCR	Hybridization Chain Reaction
ICP	Ion Concentration Polarization
IR	Infrared
ITO	Indium Tin Oxide
KPC	*Klebsiella pneumoniae* Carbapenemase
LOD	Limit Of Detection
LFA	Lateral Flow Assays
LAMP	Loop-Mediated Isothermal Amplification
LSPR	Localized Surface Plasmon Resonance
MNPs	Magnetic Nanoparticles
MET	Methamphetamine
Mag@QDs	Magnetic Quantum Dots
NASBA	Nucleic Acid Sequence-Based Amplification
NC	Nitrocellulose
NDM	New Delhi-metallo-β-lactamase
NPs	Nanoparticles
NIR	Near Infrared
NGAL	Neutrophil Gelatinase-Associated Lipocalin
POC	Point-of-care
PCR	Polymerase Chain Reaction
pLDH	Plasmodium Lactate Dehydrogenase
PEG	Polyethylene Glycol
PCR-LF	PCR Lateral Flow
QDs	Quantum Dots
qLOD	Quantitative Limit of Detection
QBs	Quantum Dot Nanobeads
RCA	Rolling Circle Amplification
RPA	Recombinase Polymerase Amplification
SDS	Sodium Dodecyl Sulphate
SERS	Surface Enhanced Raman Spectroscopy
Sas	Sulphonamides
SPEs	Screen-Printed Electrodes
SWV	Square Wave Voltammetry
TMB	3,3′,5,5′-Tetramethylbenzidine
TnI	Troponin I
TCs	Tetracyclines
TIF	Tissue Intestinal Fluid
TCA	Thermal Contrast Amplification
UCH-L1	Ubiquitin Carboxyl-Terminal Hydrolase-L1

1. Introduction

The LFAs are being diversified a lot in the last couple of decades in terms of sensitivity, variety of analytes, sample volume, processing time, analysis, etc. [1]. The detection is mostly based on a change in color and a very minimal dependency/requirement on the analytical instrumentation for result visualization. This made LFAs a popular choice in areas like pregnancy test, pathogen test in food/water/body fluid samples, detection of organ failure, etc. [2]. A typical outline of LFA consists of a top polymeric substance-based layer connected with a sample collecting pad that extends till the detection zone, where a specific analyte present in the sample can be bound and lead to color change. Currently, the membrane strips that are used as platforms for the detection systems are mainly made up of low-cost materials like nylon, nitrocellulose, polyethene, fused silica, etc. The detecting materials/analytes are attached in a dried form to the membrane and become active when interacting with fluids where specific reactions take place that result in color changes. Another variant to these LFA based devices includes a tube containing immobilized analytes where sample and strip are added [3].

Despite the continuous advancements in PoC systems, the LFAs suffer some limitations, like sensitivity, and reproducibility. This is sometimes due to a variable sample volume, blocking of pores, or an inactivation of antibody, etc. which impacts on the sensitivity and detectability of a target in the fluid [4]. All these limitations need to be addressed to meet the rising need to boost its usage in PoC detection systems. Many LFA based test kits have been designed, being pregnancy test and HIV test strips the most notable examples where the detection is based on simple on/off signals with nearly no processing time [5]. In fact, due to ease in its use and manufacture, every year more than 2 billion LFAs are produced with nearly 400 million malaria and HIV LFAs strips [6]. Since LFAs are optimum PoC systems (they are user friendly and do not require medical personnel for any sample collection as well as processing), the improvement of existing LFA systems is beneficial for society.

This review focuses upon the various aspects that are required to design a stable, sensitive and specific LFA for on-field detection. It focusses on the application of nanomaterial and analytical techniques for LFAs. Functionalization of nanomaterials also progressed in the miniaturization of laboratory separation procedures: thin-layer chromatography as well as the use of protein and nucleic acid specific analytes and labelling of analytes have also contributed to the advancements of LFAs and their specificity in diagnostics. Further the use of innovative nanomaterials, app connectivity in mobile phones, use of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based systems, and machine learning have extremely uplifted the performance of LFAs. For a fully functional LFA that has specificity and sensitivity, ceaseless efforts are required in optimizing the interactions to highly specific microscale level. Besides, a highly reproducible analytical method, capable of real-time analysis with sensitivity in heterogeneous samples also needs to be workable to deliver a field ready devise. The fixation of these loopholes at the very early stage of development help in reducing cost and efforts that could further be directed meaningfully for new design development. This review is a comprehensive compilation of LFAs, stating its origin and evolution to recent devices presenting aversatile. A versatile list of used analytes to increase the applicability of assay. Revolutionary and commendable achievements in the analytical methods that have also notably improved the sensitivity have been highlighted along with the current efforts towards the miniaturization of systems from micro to nanoscale, that helped in pushing the LFAs to new heights where new nanomaterials play a considerable role. These novel nano platforms in conjugation with analytical techniques have extended applicability of LFAs beyond biomedicine, and have been reviewed in the present article, aiming future LFAs technology in turning more user friendly, with high sensitivity and specificity. The review compiles from the literature a broad range of applications in diverse fields that reveal the wide scope of on-site detection studies. The review provides an overview of the present use and prospects of LFAs. Starting with an introduction to the fundamental aspects of LFAs, a fully description of the use of nanomaterials in LFA, as well as the comparison of various analytical methods are carried out, discussing about the pros and cons of their use. Finally, the review draws attention towards the applications of LFAs in various aspects and their future perspectives.

2. Assay design and advancement strategies

A universal LFA test card comprises of a thin nitrocellulose (NC) strip assembled with different components such as sample pad, absorbent pad, conjugate pad, and nitrocellulose membrane collectively combined on a plastic platform. A wide variety of biomolecules such as nucleic acids, proteins, and drug components, can be utilized as analytes for diagnostic applications [7]. Customarily, LFA functionality typically relies on the immobility of the conjugate biomaterials on the wet surface; all assembled onto the NC membrane strip and embedded into a plastic body, accompanied with the reagents and chemicals onto the strip. A schematic illustration of a generalized version of LFA is shown in Fig. 1 onto which a small amount (50 μl–80 μl) of sample is usually applied at the sample pad area. The sample can be a biological fluid, as mentioned in the figure, or any environmental sample such as pesticides, fungicides, ionic species, etc. The capillary action of the membrane makes the sample flow through the conjugate pad comprising the pre-incubated labelled conjugates. The biomolecular interaction resulting in appearance of an indicative visual line is achieved further,

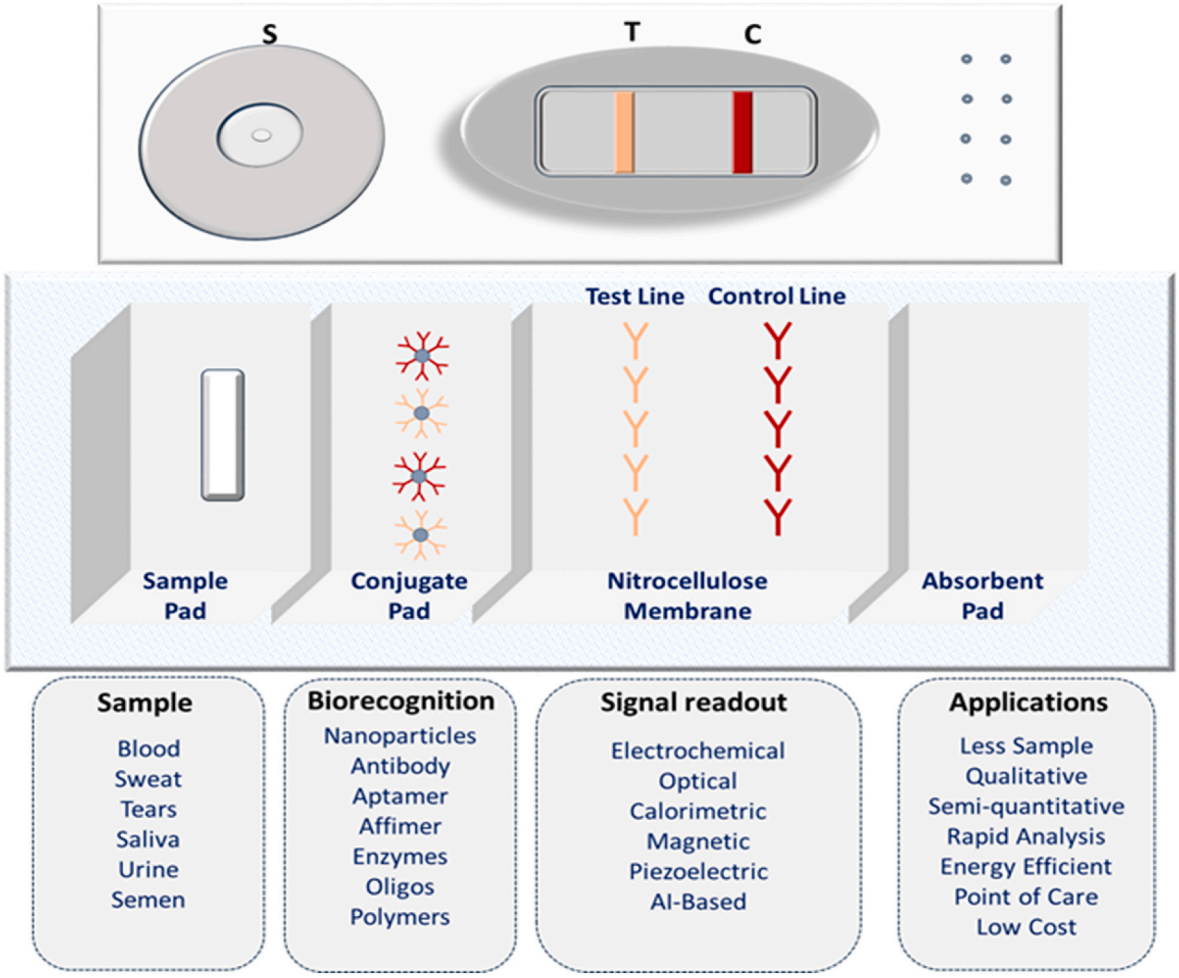

Fig. 1. Schematic design of LFA chips displaying its fundamental components such as sample pad, conjugate pad, absorbent pad; all fixed onto nitrocellulose membrane and the test line and control line demarcating the results. Sample pads can take up a wide variety of biological fluids such as blood, sweat, urine, etc. recognized by biorecognition elements found at the conjugate pad functionalized with nanomaterials, antibody, nucleic-acid, enzymes, etc. The signal result is determined by color, electrical, magnetic, or thermal output changes on the test and control line, dumping the excess fluid into an absorbent pad. The last column explores various features of LFA applications, such as being rapid, PoC, low-cost, or requiring fewer amounts of samples. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

venting out the excess liquid to an absorbent pad. The analyte is firstly recognized by the primary biomolecules that are usually gold nanoparticle (GNP) conjugates known as conjugate labels (protein/antibody/nucleic acid as described in Fig. 1). The resulting complex is then captured by secondary biomolecules and immobilized onto the membrane forming test and control lines.

The intensity of the resultant line signal which can be detected by color, electrochemical, thermal, or magnetic changes, is directly proportional to the dilution of the analyte that, in turn, depends on the amount of biomolecule labels on the test line [8]. The manufacturing of LFA on paper substrates has given mass-market appeal to its applicability. The porous matrices of paper strips enable the flow of the test solutions without any additional pumping instrumentation. Regardless of assorted properties, LFA limits itself to qualitative biosensing and analyte detection, thus, compromising with the sensitivity at low substrate concentration. Therefore, the current review summarizes fundamental aspects to be considered while designing paper-based assays for improving the sensitivity and efficacy of LFA, as illustrated in Fig. 2.

2.1. Sample enrichment strategies

Especially in clinical diagnostics, ultralow concentrations of analytes must be detected in samples such as serum, blood, saliva, or urine. As sensitivity is the prime concern for any LFA, various techniques are incorporated to work upon the sample concentration or purification of the target. To promote sensitivity in signal readout, it is vital to eliminate any interfering biomolecular components from the sample matrix to deliver accuracy in results. In this section, we throw light on some of the techniques used for sample enrichment such as filtration, magnetic separation, DNA amplification using PCR, increasing bioreceptor dilution, etc.

The conventional **filtration enrichment** is restricted to large sample volumes such as contaminated water evaluation for bacteria detection. Though effective, it comprises the incorporation of an external instrumentation which is a time-consuming process. If possible, this filtration step is beneficial in terms of enhancing sensitivity. In this context, a study reported an ICP (Ion Concentration Polarization) based preconcentrator onto the conjugate pad of LFA for β-hCG detection in pregnancy tests. The selective passage of ions under the effect of a simple 9 V portable battery through ion-exchange membranes enabled sample pre-concentration up to 15-fold [9]. The LOD could also be improved by one order of magnitude to 104 cells/mL for assessing water faecal contamination, as achieved by Beruga et al. by developing 0.25 μm pore sized filter along with peristaltic pump and microfluidic tubes to filter 300 mL water in 15 min [10].

Magnetic enrichment has always resulted in a potential methodology

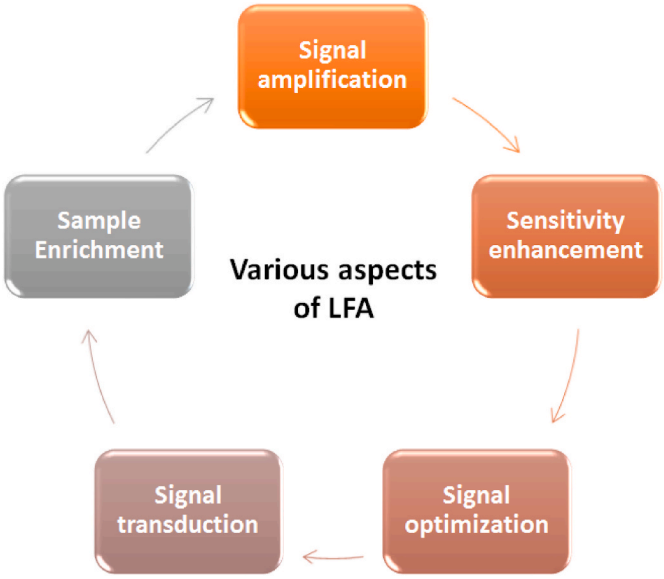

Fig. 2. Fundamental strategies to improve the efficacy of LFAs. The sample enrichment and preconcentration leading to signal amplification that in turn enhances the sensitivity of the assay and signal optimization employing diverse signal transducers such as label/non-label tags, nanomaterials, etc.

in terms of performance but uses multiple washing steps that are limiting its commercialization. Magnetic nanoparticles have been employed owing to their unique properties of high surface area, magnetism, and biocompatibility [11]. A strategy that combines nano-magnetic analyte tagging with radiofrequency sensing was investigated in a study that used differently sized iron-oxide nanoparticles. A typical example is Neutravidin that was capped onto these particles with biotin immobilized onto the NC membrane flowing along with analyte containing particles. The related supra-magnetic behaviour was studied by Salvador's group to successfully improve the assay sensitivity [12]. Another group also used supra-magnetic iron-oxide nanoparticles for detecting C-reactive protein delivering a 26-fold lower detection limit of 0.08 ng/mL, when compared to basic GNPs based amplification [13]. Antibody conjugated magnetic beads have also been used in magnetic field assisted preconcentration approach for detection of Troponin complex in less than 15 min [14–16].

2.2. Signal amplification strategies

LFAs have established its wide applicability in the field of diagnostics due to the significant advantages of immediate signal readout, affordable cost, stability, and selectivity, as well as ease of use at the point-of-care. Nevertheless, the limit of detection, which is a crucial key quantitative deliverable of LFAs comprising sensitivity of the test, should still be improved [17]. Since the discovery of first "over the counter" LFA pregnancy test kit by Margaret Crane in 1968, the use of GNPs as label tag has played the role of major signal developer and naked-eye output visualization identifier, as will be addressed more in detail in section 3.1 [18]. However, a low detection limit poses constraints to sensitivity and effective quantitative detection due to low signal intensity of GNPs portraying inhibition to critical diagnostic applications. This important issue is a matter of PoC terminology and rapid detection, compromising on the sensitivity issue of LFA. Therefore, various signal amplification strategies are employed by researchers relying on labelled and label-free moieties. Improvement in signal amplification approaches, which range from enzymatic catalysis to use of fluorescent probe, control of fluid flow, use of functionalized nanomaterial etc. have contributed to performance of LFA in diagnostics [19]. However, all these signal enhancement methods imply high chemical costs, additional external equipment, and multiple-step operations [20–23]. To reduce the elevated costs, various paper-based sample preconcentration methods have been developed in the last decade, such as isotachophoresis enabling concurrent antibody separation and concentration dependence upon electrophoretic mobility that produced a 400 times signal amplification [24]. An outlook on different label and label free signal enhancement techniques is given in the following sections.

a Label and label free signal enhancement techniques

The capillary action of the LFA strip for nanomaterials like GNPs, carbon nanomaterials, quantum dots, etc. conventionally used as colorimetric labels, control the LFA signal [25]. The properties of **colloidal gold** with easily controllable size, rapid synthesis, and biological compatibility have already proved its great potential in healthcare diagnostics [26,27]. Conventionally, commercial LFA test cards utilize the red color of low-cost GNPs or dyed beads that can be seen in the test region. This is responsible for the naked-eye optical signal detection, as it is causing the visible line development pertaining to positivity of the test [28]. This crucial attribute of gold colloid has led to the development, and successful mass production of user friendly LFA tests. The technique of using dual nanoparticles has on the other hand, significantly contributed to signal amplification in many LFAs as this increases the particle size causing an enhanced molar extinction coefficient that leads to improved sensitivity [25,29,30]. Choi et al. introduced the incorporation of two GNP antibody conjugates for signal amplification of LFA to detect the cardiac biomarker Troponin I with ultralow sensitivity of 0.01 ng/mL in just 10 min. The researchers played with the size of both GNP conjugates and achieved 100-fold higher sensitivity compared to the conventional Troponin I LFAs, even with serum samples of myocardial infarction patients [31]. The dual GNP methodology was also applied to melamine detection in milk samples screening and delivered a detection limit of 1.4 ppb as published by Zhong et al. in 2016 [32]. Apparently, the concept of using differently sized GNPs was also introduced for detection of bisphenol A known as Duo-LFS that rendered 10-fold improved sensitivity with a 0.076 ng/mL detection limit [33]. Another study reported by Zhu et al. for Hg^{2+} on-site detection was based on thymine–Hg^{2+} thymine, employing GNPs label tags. The assay delivered ultrasensitive 0.005 ppb LODs that was 40-fold improved compared to conventional LFAs [34]. The physicochemical properties of GNPs have been exploited for enhancing the sensitivity of LFAs even if the detection limit is lower by combining with an alternative nanomaterial, such as graphene-oxide (GO) [35], quantum dots (QD) [36], fluorescent tags [37,38], lanthanides [39], carbon dots [40,41], etc.

Apart from pure gold colloids, other variants for signal amplification rely on GNP enlargement by **silver staining** that reduces silver ion on the GNPs producing enhanced absorbance values for GNPs and intense coloration of the test lines [42]. Troponin I detection was performed using silver staining by integrating water-soluble hybrid nanofibers. When a Troponin I sample was added, subsequent release of silver ions from nanofibers produced a 10 times enhanced signal on the test line [43]. This strategy in a way amplifies the signal without compromising with the speed and elementary utility for the end user [15]. Another study based on detection of potato leafroll virus causing potato disease was reported incorporating sandwich complex of GNP labels with silver enhancement. They achieved a detection limit of 0.2 ng/mL in 15 min that was supposed to be 15 times more sensitive than conventional LFAs [44]. Additionally, studies using a competitive LFA show that silver staining signal enhancement strongly reduced the competitor amount and specific antibodies used to detect ochratoxin A, rendering 10-fold increased sensitivity to simple GNP based LFAs [45].

Furthermore, **enzymatic labels** have contributed primarily to widen the variety of bioassays and, simultaneously, nanocarrier enzymatic probes are generally exploited in LFA systems to improve the detection limits. Enzymatic labels such as Horseradish Peroxidase (HRP) and

Alkaline Phosphatase (ALP) have been used to amplify LFA signals by many researchers and albeit they are time consuming yet contribute towards high sensitivity [28]. Parolo et al. adopted basic GNP modified with HRP enzyme label in combination with TMB and achieved sensitivity up to one order of magnitude for detecting HIgG. This induced change in color was superior, when compared to unmodified GNPs based assays [46]. Another report employing a GNP-HRP conjugate for nucleic acid biosensing was developed by immobilizing thiolated deoxyribonucleic acid (DNA) and HRP on the GNP surface for improving sensitivity up to 1000 times with a 0.01 pM detection limit for targeting DNA [20]. Apart from this, many studies have used HRP labels in LFA for detection of influenza A and B viruses [47] Carbaryl and Endosulfan present in agricultural products [48] and *Listeria monocytogenes*, *Escherichia coli* O157:H7 as well as *Yersinia enterocolitica* [49]. Another crucial enzyme, applied by Panferov et al., was alkaline phosphatase that reduced 27 times the detection limit to 0.3 ng/mL, compared to conventional LFAs. They used two conjugates as GNP-monoclonal antibody against potato virus X and another antibody labelled with ALP against mouse IgG [50].

b Label free signal Enhancement.

Apart from label tags, other label-free methods were also adopted by researchers when sensitivity enhancement of LFAs was aimed. To achieve simplicity and low-cost accessibility of LFAs, the **dialysis method** has been integrated with LFA wherein samples are concentrated by removing small molecules from solutions. The potential hygroscopic property of polyethylene glycol (PEG) was exploited in a study as a good dialysate by concentrating the target sample. A combination of a semi-permeable membrane with PEG buffer and glass fibre was used and integrated in a 3-D printed lateral flow device for the concentration of the target along with its detection. Nucleic acid detection was then performed using HIV analytes as template with 10-fold signal amplification. As compared to available LFAs, this technique was more cost-effective and simpler, maintaining at the same time the sensitivity for point-of-care settings [19]. Moreover, other studies have reported integration of dialysis to microfluidic chips for concentrating the target samples such as HIV from whole blood and then attaining RT-PCR based detection [51]. Chiu et al. has demonstrated an Aqueous Two-Phase System (ATPS) implemented to LFAs with PEG for concentrating target biomarkers onto a 3D paper giving 10-fold improvement in detection of Transferrin [52]. Besides, ATPS with non-ionic Triton X-114 surfactant for biomarker concentration was adopted by Pereira et al. for detection of the malaria biomarker Plasmodium Lactate Dehydrogenase (PLDH) in serum [53].

3. LFAs and nanomaterials

Nanomaterials are a broad and dynamic class of materials with various morphologies and roles to play when integrated with any system. The association of nanomaterials with LFAs is old, but the relationship is evolving very rapidly. The few major materials sub-classes that are in use in LFAs are GNPs, magnetic nanoparticle, quantum dots, carbon nanotubes, etc. as listed in Fig. 3. Nanoparticles (NPs) are therefore the most diversified and indispensable nanomaterial subclass and are used for different reasons in LFAs. Quantum dots, magnetic NPs, etc. are some recent developments in this area exhibiting longer fluorescence, stability, and lower background signals, as compared to fluorescent dyes. Magnetic NPs can produce additional magnetic signals and it's an addon feature along with fluorescence.

3.1. Gold nanoparticles (GNPs)

These are the most impressive renaissance metallic nanoparticles with remarkable properties and thus applications. GNPs can be produced in a large variety of morphologies with different associated functional roles [54]. The electronic, physicochemical, optical, etc. properties of GNPs can be easily modified, and these changes extend their applicability to photodynamic therapy, gene and drug delivery, imaging, diagnosis and many more [55]. Interestingly, GNPs are the nanomaterials of choice for color based LFAs, typical size ranging from 20 nm to 40 nm is rose red, thus visible by naked eyes. In addition to nanoparticles, gold in other morphologies (stars, flowers, plates) in nanoscale is also finding use in LFAs. Moreover, number and size of GNPs in test zone of LFAs also impact on the sensitivity of the assay. Khlebstov et al. has shown that 16 nm GNPs at a concentration of 7×10^7 particles/mm^2, as well as 115 nm GNPs at a concentration of 1.5×10^5 particles/mm^2 depicted LOD in the range of ng/mL [56]. There are several "success stories" where GNPs were used in LFAs: In 2021, researchers developed gold nano star-based surface-enhanced Raman

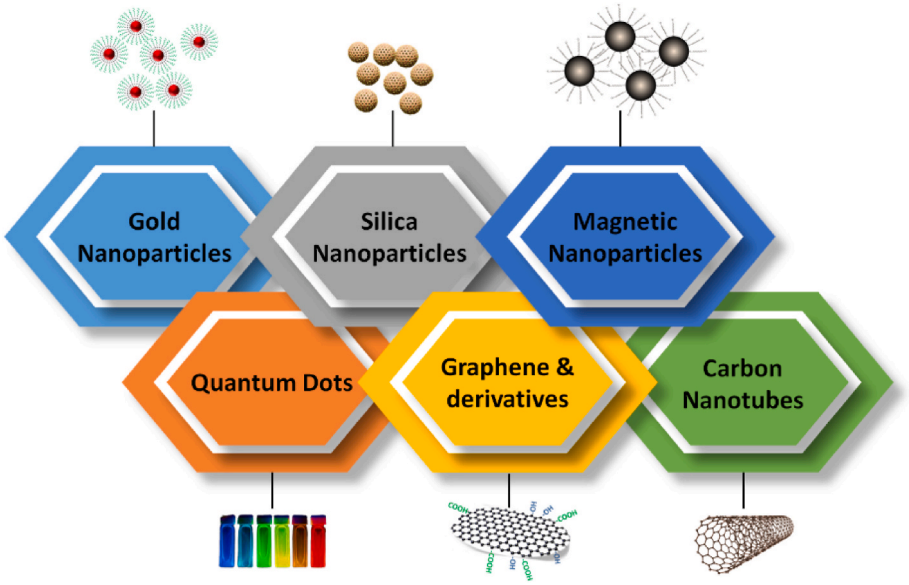

Fig. 3. Nanomaterials that are applied to design LFA, such as gold, silica and magnetic NPs, quantum dots, as well as carbon-based nanomaterials such as carbon nanotubes/carbon dots, graphene and its derivatives like graphene-oxide, reduced graphene-oxide, etc. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

scattering probe for detection of carcinogenic antigen to a detection limit of 1 ng/mL [57]. Since antibodies have extensive application in detecting antigens of an infection, GNPs loaded with TB antigen (ESAT-6, CFP-10) targeted antibodies were synthesized for development of a colorimetric-based TB antigens detecting LFAs. The LOD value for ESAT-6 conjugated GNPs was 0.0625 ng/mL with a processing time of 15 min [58]. Further, the strategy of doping fluorescent dyes in polymeric nanomaterial for immobilization, followed by antibody mixing also enhances the signal strength upon excitation. Doping of Cy5 into silica NPs has improved the detection of influenza antigen to nearly 8-fold [59].

3.2. Quantum dots (QDs)

QDs are nanoparticles derived from semiconductor material and have unique electronic and optical properties. Their optical properties were tuneable as they vary with size, because the decrease in size of semiconductor material results in quantum effects and this reduces the energy of electrons, modulating its interaction with the visible light [60], and bestow them to emit light of different colors in response to UV exposure [61]. These self-fluorescing NPs find application in a wide variety of fields including LFAs as they have overcome the weaknesses associated with fluorescent dyes, such as photobleaching, stokes shift, etc. The fluorescence signals of QDs have a nearly 10 to 20-fold longer lifetime, compared with fluorescent dyes [62,63]. Due to these outstanding properties, QDs have been recently exploited for the development of LFAs in view of the Covid-19 pandemic, like multiplex QD based LFAs for on-site, quick detection of different respiratory virus. These LFAs consist of 3-D CdSe@ZnS–COOH QDs adhered onto graphene-oxide nanosheets and the LOD of these LFA for human adeno, SARS-Cov-2 and influenza-A virus is 471 copies/mL, 8 pg/mL, and 488 copies/mL, respectively [64]. Another LFA for targeting the prostate-specific antigen (PSA) was designed using QDs embedded silica nanoparticles, being the LOD for PSA detection 0.138 ng/mL [65]. Besides, complexing/embedding QDs with other, QD-nanobeads derived LFAs, has also been developed for detection of *Clostridium difficile* -B toxin in faecal samples with a LOD of 0.297 ng/mL [66]. These kind of complexing/embedding QDs further improves the photo and chemical stability, hydrophilicity, signal intensity and, most important, environmental toxicity [67,68]. Besides embedding, development of magnetic QDs has further improved its features. Wang et al. has devised magnetic QDs in LFA for detection of botulinum neurotoxin type A as well as of staphylococcal enterotoxin B in food samples within just 30 min and a LOD of 2.52 pg/mL, and 2.86 pg/mL, respectively [69].

3.3. Magnetic nanoparticles (MNPs)

This is a special class of nanoparticles that are active under magnetic fields and are mostly derived from magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) that receive much attention in the biomedical and pharma field [70]. MNPs for the biomedical field must respond to minimum magnetic enrichments or high magnetic susceptibility and must lose their magnetic property when cutoff from a magnetic field [71]. For using a MNPs based LFA, a magnetic sensor (like a resonant coil magnetometer) is required to detect the magnetic signals with high sensitivity at both surface and within inner membranes [72]. The utilization of optical methods allows for the detection of magnetic nanoparticles at the test line in LFA. These nanoparticles have a molar absorption coefficient similar to that of colloidal gold within the visible spectrum. Consequently, they serve as colorimetric indicators, manifesting as a distinct dark brown hue against white nitrocellulose (NC) membranes. The optical density signal generated by magnetic nanoparticles is visible to the naked eye and can also be identified using optical commercial readers and smartphones. To boost sensitivity, aggregates of magnetic nanoparticles have been formed through controlled agglomeration with poly-L-lysine. A magnetic nanoparticle based LFA for the detection of nucleic acid to attomolar concentration was prepared by using antibodies conjugated MNPs. Moreover, a magnetic controller was also installed to control the movement of the magnetic probe achieving a LOD of 100 aM to 10 pM [73]. Another way of improving the LFA performance using MNPs is the pre-concentration of the target in complex matrixes (saliva, blood) using magnetic fields [74]. Sharma et al. designed a LFA for the detection of TnI/C (Troponin I/C), a cardiac marker, using MNPs conjugated with anti-Troponin-I antibodies where TnI specifically gets separated and concentrated on TnI-magnetic beads but allowing TnC to pass through the absorbent pad, achieving a sensitivity on pM level [14]. Integration of metals with MNPs is another way to create multifunctional nano-systems, as shown for a nanocomposite of gold impregnated MNPs for measuring temperature in hyperthermia treatment [75]. Altogether, the application and roles of MNPs have diversified in LFAs with improved sensitivity by combining it with other materials.

3.4. Carbon nanotubes (CNTs)

The advantages of PoC testing if combined with CNTs that exhibit high surface immobilization and dark coloration has also been studied largely [76]. The focus of public attention and interest since the discovery of CNTs by Iijima et al. is mainly attributed to its physicochemical properties aligning its utility for LFAs as well [77]. CNTs are large networks of hollow cylindrical hexagonal sp^2 hybridized carbon atoms forming a tubular arrangement of single wall CNTs and/or multiwall CNTs graphitic sheets. The black coloration and large surface area of CNTs, delivering higher binding sites for bioreceptors have contributed significantly to enhanced sensitivity for assay quantification. Though aqueous insolubility of CNTs pose limitations, various options of surface functionalization using surfactants have been incorporated to improve these solubility issues. A study reported by Sun et al. has presented surfactants that enhance solubility of CNTs and devised a LFA to quantify Methamphetamine (MET) 10 times higher sensitivity than conventional GNPs [78]. Another study reports DNA biosensor LFAs wherein CNTs have been used to increase the stability of triple helix DNA and vice–versa for identification of mismatched bases. This technique can even be used to differentiate between complementary DNA and one-base mismatched DNA, thus can be employed for detection of single-stranded DNA, better than basic CNT based LFA DNA biosensors with a LOD of 0.2 μM [79]. [80]. In fact, CNTs have been displayed as black tags for identification of antibodies in a much more sensitive way than ordinary GNPs tags for LFA [76].

3.5. Graphene

Graphene and its derivatives such as GO (graphene-oxide) attain a honeycomb arrangement of carbon atoms bearing hydrophilic hydroxyl and carboxyl groups making it an effective transducer for biosensing platforms [81,82]. LFA utilizes the property of large surface to volume ratio of GO due to its large heterogenous chemical structure that enables π-π stacking for bioreceptors moieties along with hydrogen bonding [83]. A recent report suggests the combination of nanomaterials with GO for multiplex LFA based screening of respiratory viruses. They used a multilayered 3-D film-like fluorescent tag generated via layering assembly of CdSe@ZnS–COOH quantum dots onto the GO surface. This multilayer promoted larger specific surface areas with high luminescence than spherical microspheres to simultaneously quantify influenza A virus, human adenovirus, and SARS-Cov-2 with ultralow detection limits and high accuracy. Wang et al. even validated the study in saliva samples of patients [74]. A recent study reports the layering of 80 ng GO onto the test zone of LFA strips for enhanced 2-fold increase in fluorescence-based targeting of ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1), a trauma brain injury biomarker. The assay was also validated in plasma samples of brain injury patients thus streamlining novel avenues in LFA diagnostics [84]. Apart from diagnostics, various

studies pertaining to the applicability of GO as bioconjugation molecule with antigen/antibodies have been performed to achieve higher sensitivity in sensing of food samples [85], bacteria [35], etc.

3.6. Silica nanoparticles (SNPs)

Silica nanoparticles (SNPs) represent a distinctive variety of inorganic nanoparticles with wide range of customization in terms of shape and surface properties [86]. SNPs are favoured in LFAs due to their chemical stability and high pore volume with adjustable size that serve as enrichment platform for label materials [87]. SNPs are compatible with almost all available signal formats ranging from colorimetric detection to SERS (Surface enhanced Raman spectroscopy). Recently, a chemiluminescence based LFA has been designed where dye-doped SNPs and TCPO (bis(2,4,6-trichlorophenyl) oxalate, H_2O_2 and imidazole) were used for the detection of staphylococcal enterotoxin C1 responsible for food poisoning. Another study developed QD-loaded SNPs for detection of prostate specific antigen (PSA) in blood with a LOD of 0.138 ng/mL and without any cross reactivity [88]. As an addition to the PSA detecting LFA, SNPs loaded with silica coated silver (SiO_2@Ag@SiO_2 NPs) was applied on LFAs where the LOD was improved to 1.1 ng/mL. Another report of SNP conjugated with QDs has been studied for detection of PSA showing a remarkable LOD of 0.138 ng/mL. A Ru(bpy)32^+ modified Mesoporous Silica Nanoparticles (MSN) has been developed as an electrochemiluminiscent probe for detection of troponin I in blood with a LOD of ≈0.81 pg/mL [89]. Indeed, the applications of SNPs are beyond and difficult to summarize here as they have application in detection of microbes both from diseased site as well as environment in water treatment and remediation investigations. To wrap up, the most captivating element lies in seamlessly blending a basic LFA with innovative yet accessible and economical nanomaterial-based methods. These fusion paves the way for the creation of highly promising advanced LFA devices [90].

4. LFAs and analytical techniques

The ease of portability as well as utility and, most importantly, the user-friendliness has given a mass-market appeal to LFAs. But as aforementioned, the limitations pertaining to sensitivity and accuracy have always faced challenges in routine applicability and complexity. To enhance the sensitivity, the integration of transducing technologies and chemicals has helped to improve and increase readout signals along with minimizing the false positives. The incorporation of various analytical techniques is depicted in the schematic diagram of Fig. 4 such as PCR, piezoelectric methods, SERS, fluorescence methods, electrochemical methods, smart-phones, infrared methods, etc. that have aided in extemporizing the accuracy and sensitivity of biosensing LFAs. The following sections will summarize some few examples along with the principles integrating these technologies that have given novel avenues to LFA biosensors, betting on the reliability of the technique at large. More significantly, the coherent consolidation of these transducing techniques has exhibited outstanding innovations in clinical diagnostics, food and water monitoring sectors and environmental testing [91].

4.1. Fluorescence detection lateral flow assay

Fluorescence is a type of photoluminescence caused by electrons that after being excited, almost immediately emit photons when released to

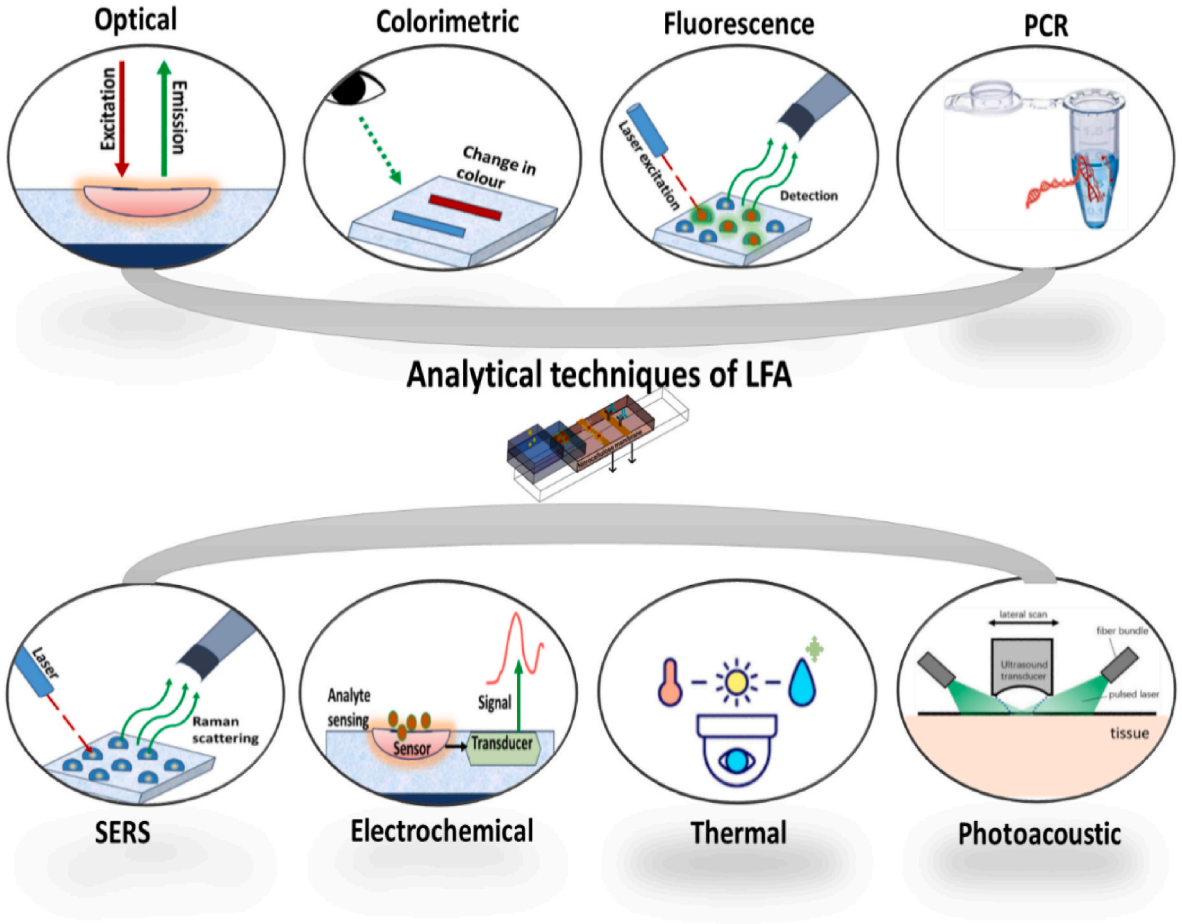

Fig. 4. Various analytical techniques for signal transduction of lateral-flow assays to enhance sensitivity of the detection using optical, electrochemical, Raman scattering, thermal, PCR based methodologies.

the ground state. These photons were first described by Stokes in 1852 and the so-called Stokes shift defines the difference between the photon energy that is released, and the one needed for excitation [92]. Generally, fluorescence instruments introduce either ultraviolet or visible light, typically from a photon source such as a laser, xenon lamp, or LEDs. The light is filtered by a monochromator, which selects a precise wavelength, often facilitated by a diffraction grating a component composed of closely spaced parallel lines on a glass or metal plate that separates the wavelength through light diffraction and interference, with each wavelength exiting at a distinct angle. Once the light is focused onto the sample at the chosen wavelength, the sample emits its own wavelength, which then travels to the detector. Laser Induced Fluorescence (LIF) represents an optical method of spectroscopy in which a sample undergoes stimulation through a laser, leading to the emission of fluorescence from the sample, which is then detected by a photodetector. LIF stands as a variant of fluorescence spectroscopy, distinct in its utilization of laser illumination instead of traditional lamp-based excitation. Fluorescence assays have wide applications ranging from lighting up fluorescent lamps to aiding in microbe detection, food adulteration, pesticide detection, bioimaging and biosensing [93]. Fluorescent materials used in biosensing application usually exist in nano dimensions and have the capabilities to generate analyte-specific response, enabling biosensors for multiplexing as well as for selective diagnostic. Currently, fluorescent based LFAs merge the specificity of immunoassays with the intense fluorescence of labels, enabling the accurate and quantitative identification of minute analytes. This analysis emphasizes different fluorophores utilized as reporters to design modern fluorescent based LFAs including fluorescent dyes, fluorescent microspheres, QDs, Europium nanoparticles, photonic nitrocellulose, carbon dots, etc. as shown in scheme in Fig. 5. The constraints associated with less sensitivity for conventionally LFA systems have been addressed by the addition of high surface area nano material employing fluorescent LFAs that provide an excellent LOD [94]. Hence, this kind of platforms are nowadays in demand for PoC screening with enhanced sensitivity, efficiency, cost-effectiveness, and rapid on-site applicability [66].

a Fluorescent dyes

Fluorescent dyes are well-suited for LFA based PoC technology platforms with sensitive detection. The fluorescent dye Cy5 has been one of the most widely used dyes for an efficient label in biological research areas of fluorescence imaging and LFA. Cy5 absorbs and emits light in the red range of wavelengths. Dyes doped with silica nanoparticles have also shown high sensitivity and photostability in an assay. Bamrungsap et al. have developed an LFA method based on fluorescence and Cy5-doped silica nanoparticles as labels to find the target influenza A nucleoprotein quickly and accurately [59]. When used with a portable strip reader under optimal conditions, the fluorescence based LFA can detect recombinant nucleoprotein targets down to 250 ng/mL with a sample amount of 100 μL in 30 min, without any interference from other proteins. This method was, compared to a commercial influenza flu shot, 8 times more sensitive than a test that used GNPs as signalling material. Apart from traditional fluorescent dyes, near infrared (NIR) dyes are also often used due to their high analytical sensitivity. Unlike GNPs, NIR dyes do not need to be professionally processed or changed beforehand, and they attach quickly to antigens and antibodies. Significantly, the sample matrix and tomographic materials do not exhibit fluorescence upon stimulation with NIR light. Moreover, a study by Chen et al. proposed a novel lateral flow model that uses a NIR fluorescent dye for detecting anti-dengue virus (DENV) IgG antibodies. IgG antibodies from goats were joined to DyLight-800 to mark it, and envelope

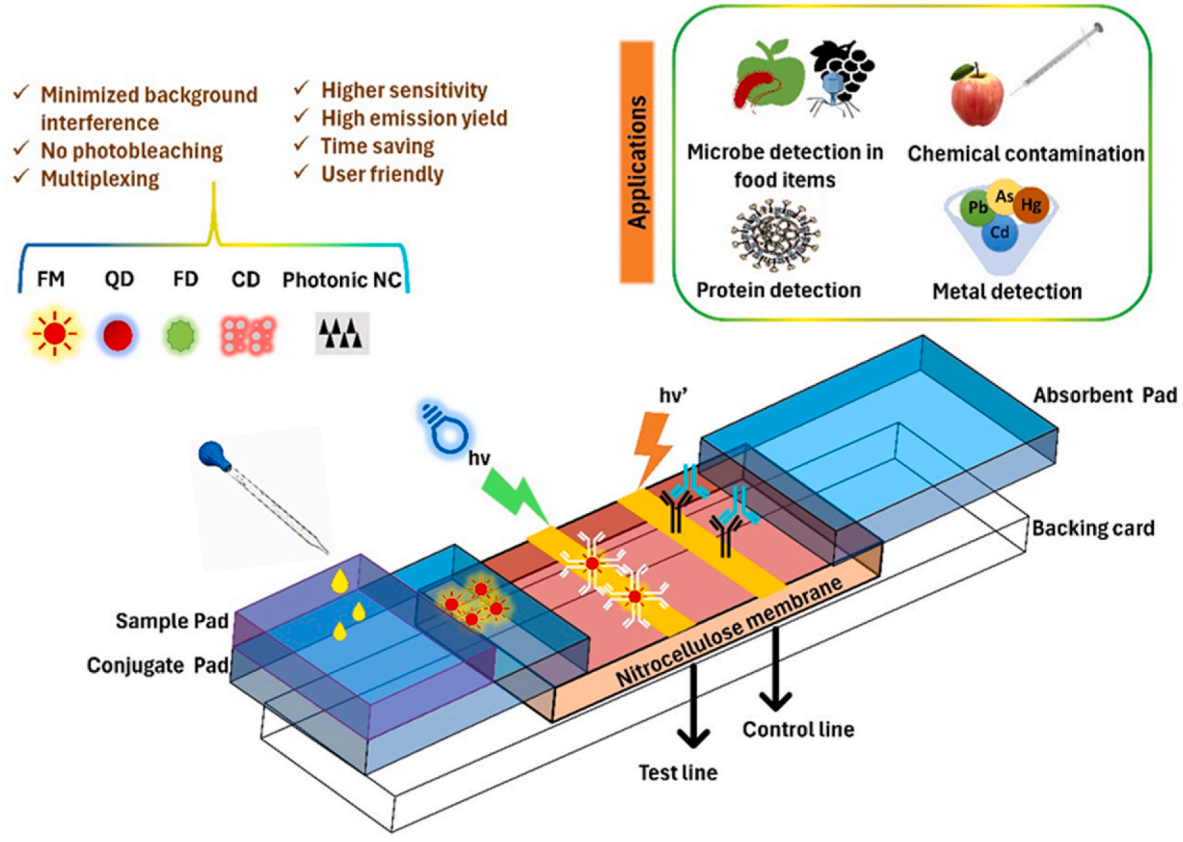

Fig.5. A schematic representation of nanomaterials (FM: Fluorescent microspheres, QD: Quantum dots, FD: Fluorescent dyes, CD: Carbon dots, Photonic NC: Photonic nitrocellulose) used in Fluorescence-based LFAs and their applications in food and healthcare industry.

protein-recombinant dengue type 1 was used as test line's capture protein. NIR-LFA allowed detection of DENV1 positives with a sensitivity of 95 % [94].

b Fluorescent microspheres (FMs)

Traditional fluorescent materials need a substantial concentration of target analytes to facilitate their detection, whereas FMs enable detection at significantly lower concentrations. FMs are well-suited for PoC testing due to their high detection capability and potential for commercialization. Wang et al. used FMs to develop an economical and sensitive lateral flow assay for targeting aflatoxin (AF) in distiller's grain samples. The 15-min test had a cut-off value of 25 μg/kg with a 3.4 μg/kg quantitative limit of detection (qLOD), yielding 95.2 %–113.0 % recoveries [95]. It turns out that the correlation coefficient is better than 0.99. Similarly, Cheng et al. developed an FM-poly-antibody probe--based LFA for rapid detection of casein by covalently conjugating carboxyl-modified FMs with antibodies. The assay produced a linear range 100 ng/mL to 10000 ng/mL with an LOD of 100 ng/mL. These FMs-LFA has lower LODs than colloidal gold LFAs that were also used to quantify casein [96]. Moreover, fluorescent microspheres are useful for medical imaging because they are non-toxic, non-biologically reactive and the Test and Control line fluorescence intensity can be measured via customized smartphone strip readers. This approach detected miRNA-21 and miRNA let-7a spiked in fake serum and yielded good recovery results, needing just 2 μL of sample volume to detect miRNA-21 with recoveries of 94.40 %–107.33 % and 85.00 %–106.83 %, respectively [97].

c Fluorescent Quantum dots

Quantum dots are also used as a fluorescent biomarker in LFA, due to their resistance to photodegradation and their exceptional optical characteristics. As a universal detection nanoprobe, Tu et al. utilized fluorescent and magnetic quantum dots in wheat germ agglutinin (WGA)-modified (Mag@QDs) to create a multiplex LFA that simultaneously detected *Salmonella typhimurium* and *Pseudomonas aeruginosa*. The LFA biosensor entraps two target bacteria using the tag of Mag@QDs-WGA, which consists of a Fe_3O_4 core of 200 nm diameter with multiple QD-formed shells, facilitating ultrasensitive detection via fluorescence and magnetic enrichment [98]. Similarly, a selective LFA for CAP detection that utilizes QBs as signal sources has been developed and the quantitative detection of target CAP was obtained by computing the difference of total colour (ΔE) values of test lines using test strip images where QB-based LFA (QBs-LFA) performed linear CAP detection from 0.1 ng/mL to 1.5 ng/mL. The LOD was 3.0 ng/mL that was lower in 50 and 66 times than the two colloidal gold kits (Shenzhen and Kang Testing Techn. Co., Ltd., and Guangdong Dayuan Oasis Food Safety Tech. Co., Ltd., China), respectively. CAP detection recoveries were 82.82 %–104.91 % at 0.1, 0.7, and 1.5 ng/mL spikes, respectively [99]. It is advantageous to embed many QDs within a single nanoparticle (NP), particularly to increase detection sensitivity and by fitting QDs onto pre-synthesized NPs or *in situ*, it is possible to enrich NPs with QDs [100]. Gao et al. reported quantum dots loaded DMSN labels that had 89.4 % fluorescence retention, compared to 65 % and 45.9 % in previous works on LFAs. Both thiol and amino-commodified DMSNs were synthesized where the adjustable densities of amino/thiol group affected the QD enrichment and fluorescence preservation. The naked eye detected ultra-sensitive serum amyloid A at 10 pg/mL that is 10 times more sensitive than reported studies [101].

d Europium nanoparticles (Eu-NPs)

Apart from quantum dots and fluorescent microspheres used in LFAs, Eu-NPs are also used to enhance sensitivity. Eu-NPs carriers enhance sensitivity by 100-fold compared to colloidal GNPs in LFAs [102] and have a long fluorescence lifetime for a particle size range of 75 nm–100 nm. Their high Stokes shift, which is generally over 200 nm, avoids scattered light from interfering with the measurement's excitation light. A study measured Neutrophil Gelatinase-Associated Lipocalin (NGAL) in urine using Eu-NPs as labels for FLAs that are driven by two monoclonal antibodies (MAbs): 2F4 and 1G1. Eu-NPs have a broad excitation band that increases its excitation probability and showed a sensitization for the detection of 0.36 and a detection range of NGAL in AKI of 1 ng/mL −3000 ng/mL. The intra-assay Cyclic Voltammetry (CV) was 2.57 %–4.98 % while the inter-assay CV was 4.11 %–7.83 % and there was a strong link between the analyser and the Eu-NPs-deployed LFA [103]. Similarly, an Eu-NP-established fluorescence assay (EuNPs-FA) was developed to detect antibiotic residues simultaneously, overcoming the single target detection and low sensitivity issues of already existing assay approaches. The EuNPs-FA utilized anti-tetracyclines (TCs), anti-sulphonamides (Sas), and anti-fluoroquinolones (FQs) monoclonal antibodies to detect (TCs), SAs, and FQs in 15 min with the qualitative cut-off values of 4.0 ng/mL for SAs, 2.4 ng/mL for FQs, and 3.2 ng/mL for TCs. These values were substantially lower than the food residue limit that range from 0.04 ng/mL to 4.40 ng/mL for SAs, 0.03 ng/mL to 5.14 ng/mL for FQs, and from 0.06 ng/mL to 6.85 ng/mL for TCs with linear correlation coefficients of more than 0.97. EuNPs-FA can detect all three antibiotics simultaneously due to disappearance of test line fluorescence intensity at standard doses of 2.4 ng/mL, 4.0 ng/mL, and 3.2 ng/mL [104].

e Carbon Dots (CDs)

Aggregation-Induced Emission Carbon Dots (AIE-CDs) exhibit intense red emission at high concentrations that have been employed to create a new LFA technology for SARS-Cov-2-specific IgG and IgM detection. In traditional fluorescence assays the ratios of test line to the control line are linearly related to the concentrations of the molecules and new LFA AIE-CDs fluorescent labels methods were developed to improve the LODs [40]. Nitrogen-doped CQDs that were hydrothermally synthesized from citric acid and polyethyleneimine, have been used in a fluorescent immunosensor for aflatoxin M1 (AFM1) analysis. After immobilizing the anti-AFM1 antibody on amine functionalized CQDs and the CQDs/Ab, the probe was used to develop AFM1 assays showing that increasing AFM1 concentrations suppressed the CQDs/Ab solution fluorescence. These fluorescent nano-sensor had a low limit of detection as 0.07 ng/mL in standard buffer providing great sensitivity for AFM1 in the range of 0.2 ng/mL to 0.8 ng/mL under optimized conditions [105].

f Photonic Nitrocellulose

Since the 1960s, one-dimensional and two-dimensional porous NC materials have been used to effectively immobilize probe biomolecules for a wide range of bioassays, such as blotting, flow-through tests, and LFAs. Micro-/nanopore photonic NC has been developed as a potential 3D material for LFAs providing a consistent substrate for quantitative bioassays with greatly improved fluorescence signals for biomarker detection. Dong et al. developed 3-D NC microneedles to detect TNF-α in mouse tissue intestinal fluid (TIF) in a minimally invasive manner. The polymer was strong and biocompatible enough to penetrate mouse skin and catch TNF-α in TIF on the microneedle surface, where highly organized photonic surface structures enhance Fluorescein Isothiocyanate (FITC) antibody fluorescence for precise TNF-α detection [106]. Despite a wide variety of fluorescent labels, the method suffers with specificity and sensitivity issues as known for several commercial kits where GNPs are in use. Furthermore, there are chances of false positive results with fluorescent tags and top of all is the cost.

4.2. Electrochemical LFAs (EC LFAs)

Electrochemical signalling is a fascinating integration for LFAs since

it is inexpensive, highly sensitive, and easy to use. Electrochemical-LFAs (EC-LFAs) also have the advantage of offering a wide detection range, excellent repeatability, and the ability to do measurements in real time. It is possible to get both good analytical outcomes and miniaturization at an affordable cost, not only due to well established electrochemical electrode mass production processes but also due to the inexpensive required instrumentation. The lack of interference from sample matrices is another important characteristic of electrochemical analysis providing enormous benefits compared to optical detection techniques [107,108]. In the meantime, the use of disposable electrodes based on indium tin oxide (ITO), Screen Printed Electrodes (SPEs), including Gold SPEs (SPGEs) has advanced LFA-based electrochemical sensing, for single portable "use-and-throw" devices [109]. Using 3D architecture of electrochemical transducers in LFAs is better than using other types because they allow better interactions between the analyte's surface and the transducer by letting sample liquid flow through them. The greater electroactive surface area may also increase the sensor's dynamic range [110]. The possibility of label-free detection is an additional fascinating benefit of electrochemical detection with applicability in diverse fields as depicted in the schematic of Fig. 6.

a Methods of signal generation in EC-LFAs.

The three most frequently used techniques for signal generation in EC-LFAs are impedimetry, amperometry and voltammetry. To identify a signal, redox indicators are usually needed for approaches based on voltammetry and amperometry. The frequently and widely used methods of investigating electrochemical reactions at an electrode include CV, Differential Pulse Voltammetry (DPV), Square Wave Voltammetry (SWV), etc. being SWV the latest and most advanced version of voltammetry, which uses potential pulses having a constant amplitude and a staircase potential function. An alternative method of measuring DC voltage is electrochemical impedance spectroscopy (EIS). It has been used in LFA to analyse the impedance as a function of the applied AC potential frequency [111,112].

b Advancements of EC-LFA

Using CV and EIS, Deenin's et al. recent EC-LFA study on the detection of Covid-19 achieved a LOD of 2.98 pg/mL with a good response time. A screen-printed electrode was inserted into the core of a lateral flow device to create an electrochemical test strip (E-test strip), aiming to capitalize the exceptional binding affinity of the SARS-Cov-2 antigen with ACE2 [113]. Human inflammation is indicated by the C-reactive protein, which can be detected using EC-LFA. In a study using linear sweep voltammetry (LSV), Petruzzi et al. reported achieving 3

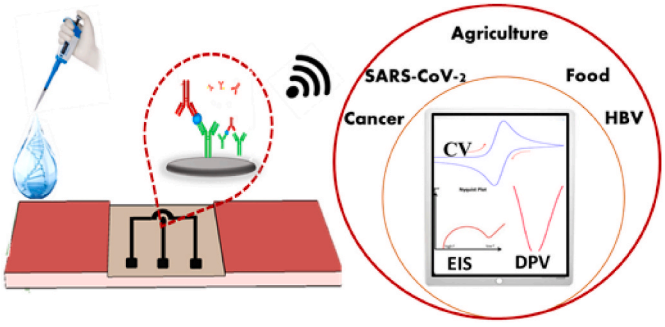

Fig. 6. A schematic figure displaying electrochemical sensing methodology EC-LFAs with the electrode that can be screen-printed, exploiting the basic antigen-antibody interaction. The EC-LFA signal generation by Differential Pulse Voltammetry (DPV), Cyclic voltammetry (CV), Electrochemical Impedance Spectroscopy (EIS), etc. that has its applicability to detect a wide variety of targets in the fields of human health, agriculture, food monitoring, etc.

ng/mL and 25 ng/mL detection limits in buffer and filtered saliva, respectively with multiplexing of the electrochemical lateral flow device [112]. Srisomwat et al. recently published a study on the use of EC-LFA for the detection of the hepatitis B virus (HBV) and demonstrated an automated DPV paper-based EC-LFA that has a short response time (7 min) and a good LOD (7.23 pM). Without needing any amplification procedure, this sensor identified HBV DNA in patient serum with high effectiveness [114]. Moreover, electrochemical methods can be used on label-based (enzymes, nanoparticles, etc.), or label-free platforms. Various studies have been conducted on EC-LFAs using stripping voltammetry and electrochemical analysis in lateral flow devices with lower detection limits and wider linearity ranges [115], using chronoamperometry (CA) [116], chronocoulometry (CC) [117], CV [118] and EIS [111]. Table 1 summarize some of the studies for electrochemical sensing.

4.3. SERS

Strip-based testing through LFAs is a convenient, easy to use, affordable and efficient procedure that can also be used in conjunction with advanced characterization techniques, like SERS. SERS is a vibrational spectroscopy method that improves low Raman scattering signals when using gold and silver NPs that interact with the Raman excitation laser and produce an optical phenomenon named Localized Surface Plasmon Resonance (LSPR). With the benefits of speed and volume testing, SERS and LFA together may prove to be the ideal combination for accurate and dependable testing. The test zone that may be a spot or line are examined using a Raman spectrometer at the proper laser excitation to interact with the NPs. To depict the construction and operation of traditional LFAs, SERS-based LFAs, and the integrated SERS approach with LFAs, may lead to increased biomolecule sensitivity with low detection limits.

The SERS-based LFAs have huge commercialization potential as handheld Raman spectrophotometers are available that made the use of SERS in detection beyond laboratory facility. These Raman spectrometers are affordable as well as easy to handle with no requirement of installation and can be carried anywhere easily. Raman is a non-invasive spectroscopy tool where scattering of light is detected. The light scatter when it interacts with molecules and may follow Rayleigh scattering, stokes or anti-stoke Raman scattering. Exchange of energy the interacting photons and molecules is the basis of Raman scattering as this results in transition of energy state of the molecule. The Raman spectra provides both structural and qualitative information about the material [122].

SERS-LFA biosensors have been developed, using the catalytic hairpin assembly (CHA) amplification strategy to screen the biomarker of miR-106b and miR-196b for lung cancer detection. The LFA assay was developed with target miRNAs, and biotin molecules modified palladium (Pd)–gold core–shell nanorods (Pd-AuNRs). The test lines (T1 line and T2 line) contain Pd-AuNRs generated "hot spots", achieving

Table 1
List of some recent studies showing the use of electrochemical LFAs employed for detection of various disease biomarkers in diagnostics applications with ultra-low detection limits.

Analyte	Electrode type	Technique	LOD	Ref.
PSA	SPE	Square wave voltammetry	0.02 ng/Ml	[119]
Dengue NS1 protein	SPGE	Cyclic voltammetry	50 ng/mL	[120]
Troponin 1	ITO	Cyclic voltammetry	0.1 pg/mL	[117]
Cardiac Troponin T	SPE	Cyclic voltammetry	0.15 ng/mL	[118]
f-PSA	SPE	Amperometry	0.1 ng/mL	[121]

detection limits down to aM level, with high selectivity, uniformity, and reproducibility [123]. Another recent report presented a high sensitivity SERS-LFA performed multiplexed detection of anti-SARS-Cov-2 IgM/IgG. A Raman reporter dye was synthesized by coating Ag shell on SiO_2 core (SiO_2@Ag) exhibiting monodispersed nature. Anti-human IgM and IgG were used for immobilization onto test lines of strips with SiO_2@Ag-spike and protein-anti-SARS-Cov-2 IgM/IgG immunocomplexes. A portable Raman instrument was applied to analysis target IgM and IgG, and enhancement of signal was 800 times better than standard GNP based LFAs [124]. Similarly, for Covid-19 detection SERS-LFAs were used to alter the traditional colloidal gold nano particles for human IgM and IgG detection. The LOD for this assay was of 1 ng/mL to 0.1 ng/mL which is 100 times lower compared with commercial LFA testing kits [125]. With the aim to overcome the weak sensitivity and limitations of LFA strips that are colorimetric, one of those dual-mode SERS-LFA strips accurately diagnoses the SARS-Cov-2 and influenza A virus. The reproducibility of SERS detection enhanced by taking average of multiple signals on control and test lines achieved an estimated LOD of around 5.2 PFU/mL and 23 HAU/mL, respectively, which is 10 and 40 times more sensitive than the gold standard ELISA measurement signals [126]. A recent study by Li et al. introduced a multiplex SERS –immunochromatography (ICA) employing a graphene oxide-based film-like magnetic tag (GFe–DAu–D/M) to efficiently capture and detect various bacteria in intricate samples. The 2D GFe–DAu–D/M tag, possessing universal bacterial capture capabilities consisting one layer of small Fe_3O_4 nanoparticles and two layers of 30 nm GNPs onto monolayer GO nanosheets. Assay facilitated swift enrichment of various bacteria enabling quantitative analysis of target bacteria on test lines via specific antibodies. This innovative technology allows for direct and simultaneous detection of three significant pathogens (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium*) with detection limits reaching as low as 10 cells/mL [127]. One of the reported studies describes the design of a film-like dual-mode nano label that generates co-enhanced colorimetric-fluorescence signals by loading multiple QDs with molybdenum disulfide (MoS_2) nanosheets. The specificity of the LFA system was significantly enhanced by constantly coating three layers of red and green QDs onto the surface of MoS_2, thereby suppressing the inner filter effect of 2D nanomaterials. In combination of dual-mode LFA a simultaneous detection of two pesticides (clothianidin, carbendazim) and two veterinary medications (kanamycin, chloramphenicol) in complex food sample was performed. The methodology has LOD of 0.1 ng/mL and fluorescence signal sensing with 46-fold improvement in sensitivity. The presented dual-fluorescence platform has excellent application prospects for the point-of-care assessment of small-molecule [128].

Magnetic SERS approach: Since the discovery of magnetic SERS tags, they have also been explored for sensitive detection and as a core shell of nanoparticle used as SERS tag. These nanomaterials usually consist of Fe_3O_4@Ag and Fe_3O_4@Au, core shells where the core is iron nanoparticle covered with Au or Ag. In this approach an external magnetic field is applied to separate tags with great magnetic responsiveness in complicated samples, allowing to efficiently remove impurity interference from the samples and ease off the substantial loss of by traditional dilution techniques. Ag-coated Fe_3O_4 was introduced in LFA as a magnetic SERS tag by Wang et al. to enhance SERS signals for virus detection on the test strips. The rapid identification through enriching the target virus by loading Raman reporter molecules and particular recognition antibodies, led to detection limits of 50 PFU/mL and 10 PFU/mL, for the H1N1 virus and human adenovirus (HAdV), respectively. This approach is easy to use, saves a significant amount of time, and requires no sample preparation step. The methodology offers a novel idea for the precise recognition of pathogenic microorganisms in biological samples. Since then, there has been a continuous progress in LFA magnetic tags-based detection approaches [129]. Liu et al. have prepared Fe_3O_4@Au MNPs with rich internal hot spots, excellent magnetic responsiveness, and good dispersion for the analysis of dual biomarkers, such as SAA and CRP. The detection limits are 0.1 ng/mL and 0.01 ng/mL, which are 100 and 1000 times higher than those of standard AuNP-LFA strips that use the same antibody, respectively. Compared with previous SERS tags, the magnetic core-based SERS NPs can load numerous Raman reporter molecules, actively capture the target analyte, and have higher stability, indicating its important role in clinical and field detection [130]. Recently, LFA strips with dual 5, 5′-dithiobis-(2-nitrobenzoic acid) (DTNB)–fixed satellite Fe_3O_4@Au (Mag@Au) SERS tags with nanogap have been reported for diagnosis of two SARS-CoV-2 functional proteins. The Mag@Au nanoparticles, of 238 nm with core of Fe_3O_4 and gold shell, are designed to effectively enrich the target protein in complex samples, which enhances the SERS signal of the LFA strip, and allows for quantitative SERS detection. In this approach, both spike and nucleocapsid proteins quantified simultaneously with LODs of 23 pg/mL and 2 pg/mL, respectively. Such type of system has the potential to have a great impact on future *in situ* respiratory virus disease detection [131]. Nevertheless, the tiny specific surface area, low immunobinding effectiveness, poor fluidity on the strip, and difficulties in precisely creating nanogaps on the nanostructure continue to be limitations of the existing magnetic SERS tags. The use of magnetic nanoparticles in SERS-LFA is severely restricted by these flaws, and new materials are desperately needed to address these issues.

4.4. Thermal Contrast Amplification (TCA)

An alternative approach to optical LFA sensing is the Thermal Contrast Amplification (TCA) that was acquainted in the LFA biosensing research for signal transduction. TCA relies upon the changes in temperature when metallic nanoparticles on the test line are irradiated using a near IR laser and monitored with an IR camera. The metallic NPs on the test lines convert the light to heat by tweaking the laser beam within the wavelength range of the LSPR peak of the NPs. The combination of high-resolution IR cameras (0.1 °C) with signal transduction serves as signal enhancer that promote a precise quantification of analytes [132]. A recent study demonstrated 8 pg/mL sensitive detection of human immunodeficiency virus (HIV) p24 protein spiked in human serum using TCA employing different sized GNPs for optimizing TCA based LFA designs, as well as different laser emission wavelengths for signal transduction [133]. Moreover, TCA has been studied for improving detection limits by 10 to 20-fold for silica-core gold nanoshells (GNSs) loaded onto NC membranes of LFAs. A high laser power leading to 57-fold amplified sensitivity was also reported using transparent glass coverslip substrate for microfluidics assays [134]. This results in a 5-fold and 12-fold decrease in detection limit for conduction and radiation based thermal sensing modes as compared to traditional visual readouts [135] and HCG biomarker quantification delivering 2.8 mIU/mL detection limits.

4.5. Polymerase Chain Reaction based FLA (PCR-FLA)

Although the Polymerase Chain Reaction (PCR) has become a fundamental part of clinical and diagnostic analysis to detect a large variety of targets with high sensitivity, it has the drawback of being time consuming because conventional PCR findings must be visualized using agarose gel electrophoresis, taking the entire detection process to one to two days. Therefore, a DNA-immuno-biosensor test in conjunction with PCR-LFA has been developed to get around these limitations [136]. As shown in Fig. 7, PCR amplified products are tested using LFA strips in clinical and environmental samples to diagnose diseases early.

This combination reduces labour costs and equipment complexity while being quick and cost-effective. It is based on paper deployed biosensing for PoC screening [137]. It has also been used to identify pathogenic microorganisms, mycotoxins, cancer, and infectious diseases. The Covid-19 epidemic has shown that large-scale testing with lateral flow tests (LFTs) is feasible and acceptable for early disease

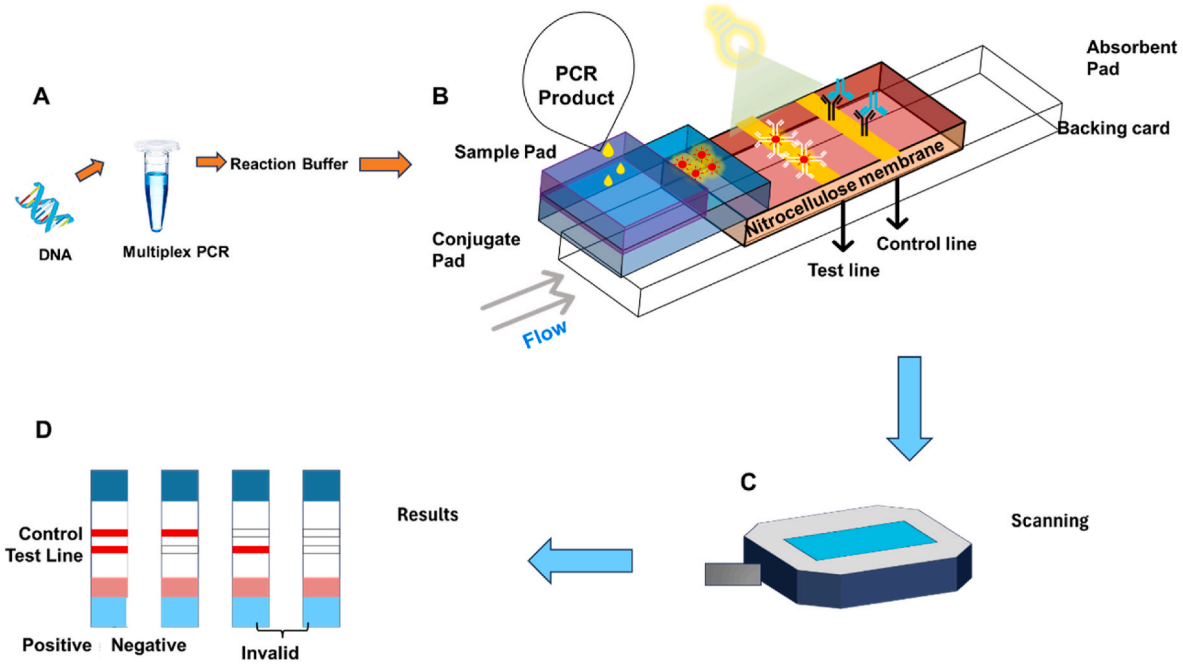

Fig. 7. A schematic representation of a PCR-FLA (A) Sample and reaction buffer preparation (B) layout of PCR-LFA (C) scanning of the sample using test strip (D) and typical results: If both the test line and the control line turn red, the result is positive. If only the control line turns red, the result is negative, and without any red control line, the result is invalid. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

diagnosis as a quick, inexpensive technique that can be combined with PCR results. Lateral flow strips are used to locate the amplicon, and PCR is used to copy the species-specific target DNA sequence. Primers with biotin and 6-carboxyfluoromescein (6-FAM) linked to their 5′ end were used by Banger et al. to create a PCR-LFA. Based on the concentration of genomic DNA, a sensitive test was created to identify the Cya gene, which is present on the Bacillus anthracis pXO1 plasmid [138]. The detection of diseases in Atlantic white prawn, (*Litopenaeus setiferus*) samples. Through the combination of a typical LFAs and a compact PCR device, the food industry can also reliably and economically perform DNA-based technique for the on-site identification of *Litopenaeus setiferus* samples [139]. This method is used in paper-based PoC testing biosensors for detecting RNA dependent RNA polymerase that enables the detection of target analytes within minutes and does not necessitate the operation of a costly and sophisticated instrumentation by a trained individual. As an initial iteration of PCR, water bath PCR was used to eliminate the temperature fluctuations and efficiently attain the optimal temperature for conducting thermal cycles [139]. Paper based analytical LFAs and PCRs are therefore also used in nucleic acid testing, including food safety analysis, medical diagnostics, and environmental monitoring. Nucleic acid can be tested using two LFA methods such as the direct detection of DNA using capture and labelled reporter oligonucleotide probes or detecting DNA labelled with hapten along with reporter labelled antibodies or streptavidin. Using tailed primers to create duplex amplicons with single-stranded DNA tails, the first recombinase polymerase amplification-nucleic acid LFA has been presented where DNA tails allow fast hybridization with a GNP labelled reporter probe and an immobilized capture probe, reducing test time and cost [140].

In addition to the advancement of single-target LFAs, the feasibility of employing sensors with the capability to detect multiple analytes has been studied simultaneously. Multiplex PCR and LFD assays were designed to detect pathogenic *Vibrio parahaemolyticus* and multiplex PCR amplification was performed with biotin, Dig-conjugated primers targeting thermolabile hemolysin (THL), and thermostable direct hemolysin (TDH) genes. The optimization and evaluation of the method was achieved by using agarose gel electrophoresis and universal lateral flow dipsticks [136]. Multiplex lateral flow PCR was used to detect pathogenic bacterial species in swab and blood samples showing that the broth enrichment-multiplex method of lateral flow immunochromatography can rapidly identify the carbapenemase-producing organism (CPO), which is an important intestinal carrier for preventing and controlling infections in rectal swabs [141]. Similarly, Lai et al. developed multiplex lateral flow strips that use asymmetric PCR, barcoded capture probes, and streptavidin-coated GNPs for simultaneous and visual detection of *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi-metallo-β-lactamase (NDM) genes in Carbapenem-resistant Enterobacteriaceae (CRE) strains. Multiplex carbapenemase gene detection in a one-pot assay technique was possible with DNA barcode capture probes on test and control lines. Nucleic acid probe-based approaches are cheaper than antibody based lateral flow immunochromatographic tests, easier to prepare, and more sensitive due to the amplification strategy [142]. In conclusion, detection apparatus such as fluorescence detectors, transilluminators, and electrophoresis apparatus are rendered superfluous by this multiplexing.

4.6. Nanozymes

Over the past few years, nanozymes have garnered extensive usage in biocatalysis, bioassays, and nanobiomedicine due to their durability and affordability. Nanoparticles have been identified to exhibit catalytic capabilities similar to enzymes like oxidase, catalase, and peroxidase, earning them the name "Nanozymes". Various kinds of nanoparticles (including iron, gold, platinum, nickel-palladium, etc.) have been harnessed for their Nanozyme properties in the creation of colorimetric biosensors [143]. Presently, nanomaterials have showcased enzyme-like behaviour, particularly in oxidoreductase and hydrolase functions. Nanozymes, mimicking oxidoreductase activities such as catalase and peroxidase, have therefore found widespread application in biosensors. Although nanozymes may not match the specificity of natural enzymes, their superior stability positions them as noteworthy substitutes in crafting the next generation of wearable biosensors. Much like traditional enzymatic techniques, a nanozyme facilitates a specific reaction, such as the oxidation of a chemical species using H_2O_2 in the case of peroxidase nanozymes. For sensing applications, a colored chemical

species like tetramethyl benzidine (TMB) is employed, and alterations in the reaction color (i.e. absorbance spectra) in the presence of the analyte are observed. The analyte has the potential to interact with either the nanozyme or the elements of the catalyzed reaction, thereby influencing the reaction kinetics [144]. An intriguing illustration of nanozyme-based assays involves GNP based colorimetric assays where GNPs act similarly to peroxidase enzymes, HRP, catalyzing the conversion of TMB into colored products. Han et al. reported concave palladium-platinum (Pd–Pt) nanoparticles as nanozyme probe based LFA utilizing sandwich format for both qualitative and quantitative detection of *Escherichia coli* O157. Enhancing the sensitivity of the LFA involves the application of the TMB substrate onto the test line, where the nanozyme accumulates in the presence of analytes. The assay exhibited a sensitivity of 9.0×10^2 CFU/mL in milk, surpassing that of traditional colloidal gold-based LFAs by a remarkable 111-fold [145]. Another study introduced a new magnetic LFA utilizing iron oxide decorated with platinum probes (Fe_3O_4@Pt) for the dual-mode detection of gastrin-17 (G-17), a crucial biomarker for early diagnosis of gastric cancer with probe material possessing both magnetic properties and peroxidase activity. The peroxidase activity enhances the intensity of brownish coloring of the Fe_3O_4@Pt probes on the test strip, achieving LOD of 10 pg/mL observable with the naked eye. The magnetic property facilitates easy sample separation and enrichment with the signals being quantitatively analysed using magnetic readers. The linear detection range using the magnetic signal spans from 10 pg/mL to 2200 pg/mL, with a calculated limit of detection as low as 3.365 pg/mL [146].

5. Applications of LFAs

LFAs have represented the most diversified and versatile applications in a wide range of disciplines in point-of-care detection strategies. They have deeply penetrated the commercial marketplace owing to their end-user easy-to-use device platforms with rapid output of results. They have remarkably outstretched and paved their reach to clinical diagnostics for high performance testing, food inspection for detecting harmful food-borne pathogens and adulterants, veterinary applications for diagnosing animal health, and environmental surveillance for detecting pollutants/contaminants in water, soil, air, etc., as well as plant diseases. A schematic listing has been well illustrated in Fig. 8. Various applications and detection techniques applied on LFA are also summarized in Table 2, at the end of this section.

5.1. LFAs for monitoring food samples

The awareness about food safety has increased among public in the past several years due to outbreaks in food-borne diseases caused by pathogens including bacteria, viruses, fungi and parasites comprising various identified food borne pathogens. The most common food-borne pathogens that cause food-borne disease outbreaks are as follows: *Listeria monocytogenes*, Vibrio sp., *Staphylococcus aureus*, *Escherichia coli* O157:H7, *Campylobacter jejuni*, *Salmonella enterica*, *Bacillus cereus*, *Clostridium perfringens*, and shiga toxin-producing E. coli. In the year 2014, several foodborne disease outbreaks spanning multiple states were reported. In the US, these outbreaks included *E. coli* connected to ground beef and clover sprouts, L. monocytogenes tied to caramel apples, soy sprouts, and cheese, and Salmonella linked to bean sprouts, nut butter, poultry, and cheese (Centers for Disease Control and Prevention, 2015). The World Health Organization (WHO) has provided an estimated number of nearly 23 million foodborne illnesses and 5000 deaths each year in Europe that are caused by these pathogens [147]. The routine detection procedures involve conventional culturing procedures, immunological testing methods of ELISA procedures and latex agglutination tests, plate counting, PCR based techniques and micro array procedures that are time exhaustive procedures, with cumbersome, required skilled manpower, sophisticated instrumentation, and cost intensive chemicals that restrict the follow up of testing procedures.

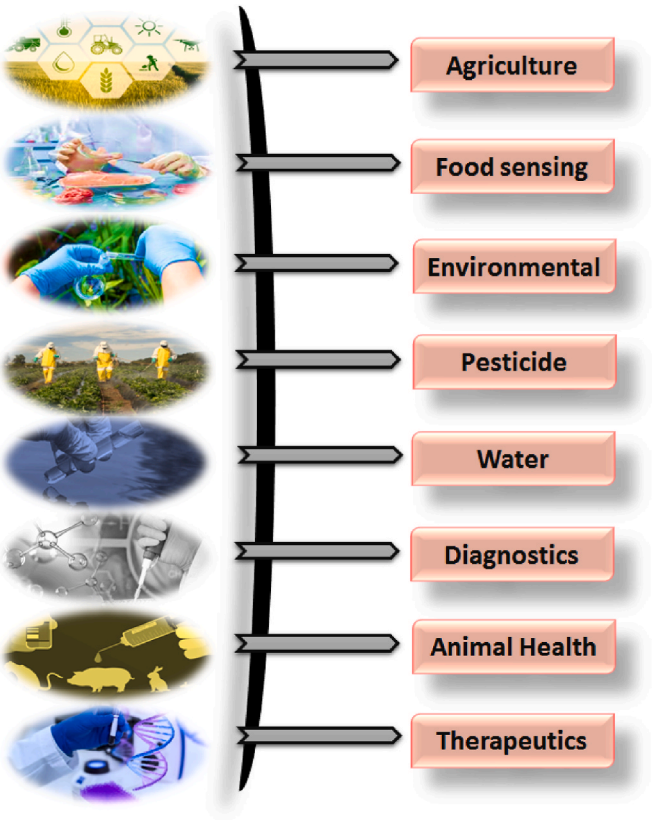

Fig. 8. A schematic tree diagram displaying applications of LFAs in food biosensing, medical diagnostics, pathogen sensing in water, agricultural pesticide biosensing, environmental sensing of ionic species, etc., animal health and therapeutics.

Therefore, the need for a rapid on-site detection assay which can be easily carried out by a non-skilled person that does not require additional instrumentation following complex procedures was suggested. When compared to some laboratory tests, LFAs have demonstrated tremendous potential for the quick identification of foodborne pathogens and offer several advantages, including cost-effectiveness, portability, convenience of use, quick results, and dependability. Owing to these benefits, LFAs are now widely used as quick tests for identifying a variety of food pollutants, including poisons, germs, viruses, and pesticides [148].

Kim et al. used the sandwich assay design, with GNPs as labelling tags in conjunction with antibodies that target the recognition elements, to build a strip-based sensor for the detection of *E. coli* O157: H7 [148]. To develop color-labelled probes, GNPs were conjugated with monoclonal antibodies against *E. coli* O157:H7 and the conjugation pad was utilized to set the antibodies with color labels, that were subsequently dried. The conjugates and the *E. coli* O157:H7 cells interacted as the liquid passed the conjugation pad and toward the NC membrane and the conjugates of GNPs and *E. coli* antibodies engaged with the capture antibodies creating a sandwich-like structure at the test zone. GNP conjugates interacted with the secondary antibodies in the control zone to create another sandwich-like configuration. Consequently, two red zones were displayed by positive samples in the sandwich assay and just one by negative samples. The color intensity of the test zone increased as the number of *E. coli* cells in the sample grew, exhibiting a positive connection. Additionally, Bruno et al. used DNA aptamers to create sandwich design LFAs for *L. monocytogenes*, *E. coli,* and *S. enterica*. Typical LFAs use conjugates of colloidal gold particles to produce visual signals, like the colloidal GNP-monoclonal antibody conjugate used by Wiriyachaiporn et al. as signal probes for the detection of *S. aureus* [59].

Table 2
List of various analytical techniques applied on LFAs for biosensing application.

Nanomaterial	Analytical technique	Principle of detection	Sample content	Limit of detection	Application/detection target	Ref.
Optical sensing on LFA						
GNP	Optical	Streptavidin-biotin amplification system with recombinase polymerase	Circulating non-coding RNA	19.41 CFU/mLl	*Salmonella enteritidis* detection	[193]
Magnetic Beads	Optical	Magnetic bead-based Immuno-CRISPR assay (ImmunoMag-CRISPR)	Whole blood	18 pg/mLfor CXCL9	Urinary biomarkers CXCL9 and CXCL10	[194]
GNP	Optical	Immuno-chromatographic assay from single piece of cellulose paper	Human plasma samples	4 ng/mL	*Plasmodium falciparum* histidine-rich protein 2 (PfHRP2), malaria biomarker	[195]
GNP	Optical	qLiNE (quick light normalization exam) transforms ubiquitous smartphones into a robust LFA reader	Saliva	0.16 ng/mL	Salivary cortisol (CTS), stress hormone	[196]
GNP	Optical	Frequency-based lock-in amplification	Slimming food	(1.0–1.2) μg/g	Furosemide in slimming health foods	[197]
GNP	Optical	LFA with smartphone camera and a dark readout box fabricated by 3D printing	Tear	14.12 pg/mL	Brain-derived neurotrophic factor (BDNF) glaucoma biomarker	[198]
GNP	Optical	GNP based assay with handheld scanning reader	Maize	4.92 ng/mL	Atrazine (ATZ) in maize	[199]
AGNP	Optical	Anti-profenofos polyclonal antibody conjugated AgNP	Liquid vegetables	0.01 ppm	Profenofos pesticide residue in vegetables	[200]
SERS sensing on LFA						
GNP@AGNPS	SERS	Core-shell GNP@AgNPs with embedded reporter molecules	Corn samples	3.6 μg/kg	Zearalenone mycotoxin contamination in corn	[201]
AU@SIO_2 SERS NANOTAG	SERS	4-mercaptobenzoic acid (4-MBA), and 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) encoded silica-encapsulated gold nanotags	Corn, rice, and wheat	0.24 pg/mL for AFB1 and 0.37 pg/mL for OTA	Aflatoxin B1 (AFB1) and Ochratoxin A (OTA) Mycotoxin contamination	[202]
GNP	SERS	5,5′-dithiobis-2-nitrobenzoic acid tagged GNP	Serum	0.14 pg/mL	Proteinic stroke biomarker S100-β	[203]
GNP@AGNP	SERS	DTNB or MBA labelled GNP@AgNP conjugated with anti-tetracycline monoclonal antibody or anti-penicillin receptor	Milk	0.015 ng/mL, tetracycline and 0.010 ng/mL for penicillin	Antibiotics- tetracycline and penicillin detection in milk	[204]
GNP@AGNP	SERS	Anti-E. coli O157:H7 monoclonal antibody on gold-silver core-shell nanostructures loaded DTNB	Milk, beef, etc.	69.4 CFU/mL	*Escherichia coli* O157:H7 (*E. coli* O157:H7) in food	[205]
GNP@AGNPs	SERS	Au@AgNPs encapsulated in 4-MBA conjugated with antibodies receptors	Environment water and Agriproducts	8.6 pg/mL for IMI, 97.4 pg/mLfor PYR and 8.9 pg/mL for AFB1,	Imidacloprid (IMI), Pyraclostrobin (PYR) and Aflatoxin B1 (AFB1) in water and agricultural products	[206]
Electrochemical Sensing on LFA						
Ferrocene carboxylic acid conjugated electroactive species	Electrochemical	Screen-printed electrode inside a lateral-flow device	Binding of THC to the cannabinoid type 2 (CB2) receptor	1.30 ng/mL	Δ9 tetrahydrocannabinol (THC) and cannabidiol (CBD)	[207]
Ferrocene tag integrated lfa	Electrochemical	Differential pulse voltammetry operated on a smartphone-based device with an electrochemical readout	Anti- LipL32 in human sera	8.53 pg/mL	LipL32 outer membrane protein of pathogenic Leptospira species,	[208]
Ferrocene cyanide with GNP	Electrochemical	nanocatalytic redox cycling	Serum or Saliva	12 pM	Insulin detection	[209]
AgNPs	Electrochemical	ocFlow magnetic microbead (MμB)-based metallo-immunoassays	Serum	750 pM NT-proBNP and 10 pM MC	Model composite (MC)and Heart failure marker NT-proBNP	[210]
Mesoporous Core-shell palladium@platium NP	Electrochemical	Nanomaterial-enhanced multiplex electrochemical immunosensing (NEMEIS)	Spiked samples with atrazine and acetochlor	0.24 ppb atrazine and 3.2 ppb acetochlor	Herbicides-atrazine and acetochlor	[211]
LFA with electrochemical sensor	Electrochemical	Reactivation of the phosphorylated AChE exploited to measure total amount of AChE	*In vitro* red blood cells	0.02 nM ache enzyme	Organophosphorus (OP) pesticides and nerve agents	[212]

(*continued on next page*)

Table 2 (*continued*)

Nanomaterial	Analytical technique	Principle of detection	Sample content	Limit of detection	Application/detection target	Ref.
FLUORESCENCE SENSING ON LFA						
Antibody-conjugated fluorescent gold nanorods	Fluorescence	Plasmonic fluor, as a bimodal colorimetric and fluorescent reporter in LFAs	Human serum samples and nasopharyngeal samples	IL-6 (LOD 93 fg/mL), SARS-CoV-2 S1 antibodies (LOD 185 pg/mL) and SARS-CoV-2 antigen nucleocapsid protein (LOD 212 pg/mL)	Interleukin-6 and nucleocapsid protein of SARS-CoV-2	[213]
Quantum Dot Nanobeads	Fluorescence	Simultaneous detection of four respiratory viruses by fluorescent lateral flow strips in a multi-channel test cartridge	Clinical samples	Sars-cov-2 antigen (0.01 ng/mL), iav antigen (0.05 ng/mL), ibv antigen (0.31 ng/mL), and adv antigen (0.40 ng/mL)	Sars-cov-2 antigen, iav antigen, ibv antigen, and adv antigen	[214]
Integrated microfluidic immunoassay chip	Fluorescence	Vacuum-driven microfluidic chip	Human serum samples	10.35 ng/mL	Anti-SARS-CoV-2 spike protein monoclonal antibody	[215]
Fluorescence LFIA	Fluorescence	FinecareTM	Plasma from 150 reverse trancriptase–PCR (RT-PCR)-confirmed positive individuals and 100 prepandemic samples were tested	Clinical study-92 % sensitivity and 100 % specificity	Total binding antibody units (BAUs) (BAU/mL) against SARS-CoV-2 spike protein receptor-binding domain	[216]
Silica Nanoparticles	Fluorescence	Cy5-loaded SNP conjugated to monoclonal antibodies	Detection shown in viral transport media as specimen matrices	0.55 μg per test	Influenza B virus protein	[217]

While colloidal GNPs are the most widely used labelling materials, their sensitivity is not sufficient to fulfil the requirements of food safety regulations. To overcome this limitation, researchers have investigated a variety of labelling materials, including carbon nanoparticles, magnetic nanoparticles, chemiluminescent tags, gold, or silver enhancement, and fluorescent tags. For the sake of food safety, numerous studies have published LFAs based on QDs for the diagnosis of *L. monocytogenes* [149], pesticide metabolites [150], antibiotics [151], and chloramphenicol [152]. Taranova et al. in 2015 used different-color emission QDs demonstrating qualitative and quantitative analysis capability of the LFAs. A super-paramagnetic lateral-flow immunological method was created by Wang et al., in 2013 to recognize *Bacillus anthracis* spores using a sandwich assay design with a portable magnetic assay reader to evaluate the magnetic signal from the super-paramagnetic nano beads [153].

Furthermore, the commercial processed and packed food products can nowadays also be contaminated with microbial toxins [4]. LFAs have been appropriately developed for detection of these contaminants or pathogens derived toxins (mycotoxins and phytotoxin) in food products [4,107,154–156]. Mycotoxins are hazardous byproducts of fungal metabolism that can infect a variety of food products, such as cereals, almonds, and dehydrated fruits. Similarly, phycotoxin is another toxic compound that can contaminate food and is harmful to human health. Commercially available LFAs for mycotoxins in food have been validated for several mycotoxins, including aflatoxins (AFTs), ochratoxins, and deoxynivalenol [107]. The sensitivity and specificity of the assays are determined by the quality of the antibodies and the design of the test strip like an immunochromatographic assay developed to detect AFT B1 [157]. Usually, AFT is divided into four categories: B1, B2, G1, and G2. In this assay, gold-labelled polyclonal antibodies and AFT B1-BSA were used as detector and capture reagents against AFT B1, respectively. A membrane-based lateral-flow immune-dipstick assay was developed by Tang et al. [158] for the fast screening of aflatoxin B2 (AFT B2) in food samples. Another toxin that can contaminate food is phytocotoxin, which can be detected quantitatively in water via LFA using fluorescent labels, sulforhodamine B, encased in quantum dots for phycotoxins to detect microcystin [159,160]. Using colloidal gold in a wheat sample, two more harmful compounds have also been identified: deoxynivalenol (DON) and zearalenone (ZEA) [65]. The used test strips demonstrated good qualitative DON and ZEA detection and have the potential to be a dependable, quick, and affordable on-site analytical screening method. Wheat, corn, and feedstock were screened using a colloidal gold lateral flow strip to simultaneously identify fumonisin B1 and mycotoxins. The outcomes agreed with both ELISA and LC-MS results.

The most potent neurotoxins produced by the anaerobic *Clostridium botulinum* are called botulinum neurotoxins that result in death and paralysis by preventing the release of acetylcholine [161]. LFAs were developed to identify and differentiate between the harmful Botulinum A and B, which are to blame for 80 % of diseases brought on by milk and apple juice. Recently, an LFA based on GNPs and aptamers was used to detect *Salmonella enteritidis*, and it could even detect low colony forming units (CFU) [7,162]. Although, LFA are a useful tool for the rapid and simple detection of mycotoxins in food samples and can provide valuable information for food safety and quality control, monitoring mycotoxins in food and feed may necessitate a variety of approaches across the entire production chain, and the LFAs should be vigorous and flexible sufficient to guarantee a valid analysis in all these scenarios [163,164]. The characteristics of the target analyte and the associated matrix may necessitate the use of an organic solvent during the extraction process. Nevertheless, antibodies and LFA components, particularly NC membranes are hazardous to organic solvents. As a result, establishing an optimal solvent system for both, analyte solubility and operation method can be demanding during an assay [165]. There are often situations when an extra dilution step in an appropriate buffer is needed to create a suitable medium for a more effective analyte detection. Altogether, NPs and QD based detection of food microbes is best of monitoring food safety, but the method suffer specificity issue due to which one LFA is not applicable to wide food variety. Monitoring of toxins and other contaminants in food is more preferred with broad applicability. In toxin monitoring, antibody based LFA are advantageous with better solvents and membrane systems.

One of the recent research studies of a competitive LFA for penicillin on-site detection, is created considering several parameters including the conjugation concentration of antibody, the conjugate concentration of Pen-BSA, the membrane's pore size, and the blocking buffer. To examine the color strength, different amounts of penicillin (1 pM–1 mM) were applied to the sample pad. The LOD for penicillin obtained from the LFA was 10 nM, which agreed with the LOD determined using the colorimeter program "ColorGrab." Furthermore, LFA was verified using

food samples that had been spiked with milk, beef, and eggs, and it also shown negligible cross-reactivity with other β-lactam antibiotics. Therefore, LFAs can be effectively used for the POC detection of penicillin in food samples on a broad scale (Fig. 9a) [166]. The SERS-LFA guarantees food safety against *E. coli* O157:H7 using gold-silver core--shell nanostructures loaded with two-layer Raman reporter molecules of 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) presented in Fig. 9a. For a constant and quantitative analysis of bacterial detection, regression models based on machine learning were applied to the Raman signal intensity at 1335 cm^{-1} on the test line of SERS-LFA strips. The Raman signal intensity of DTNB was 6.94 × 10^1 CFU/mL, which was roughly four orders of magnitude lower than the visual limits and the concentration of the spiked food samples was 10 CFU/mL. The presented SERS-LFA shows considerable promise as an effective instrument for *E. Coli* O157:H7 point-of-care testing [167].

5.2. LFA for environmental monitoring

Global environmental pollution has emerged as a critical concern and various pollutants and contaminants infiltrate the environment through anthropogenic activities such as industrial processes, agriculture, and daily life, as well as through naturally occurring events [164]. Monitoring pollutants enables the identification of the spatial distribution of contaminants, aiding in the assessment of which sites are at risk. Peak concentrations are usually attained when measurements are conducted at the waste point, and data are typically on average concentrations in environmental media. A continuous, on spot and real-time monitoring of pollutants in the environment is required and for this LFAs stand out as unique solution that are quick, easily operable even by non-skilled individuals, and do not necessitate extensive testing procedures or instrumentation.

Over a 10-year span, LFAs have been developed for the detection of heavy metals (37 %), with pesticides (14 %) as the subsequent area of focus. Algae (11 %), pathogens (10 %), toxins (8 %), drugs (6 %), and other compounds (14 %) constitute the remaining portion of application of LFAs in environmental monitoring. Lead (Pb) detection in contaminated water was swiftly and selectively achieved through LFAs using an oligocytosine chain as a receptor for the complexes that were created using this approach, which also employed phenylboronic acid as a chelating agent. It was possible to detect Pb at concentrations as low as 0.05 ng/mL by establishing a sandwich configuration involving Pb (II), oligocytosine GNP conjugates, and bovine serum albumin phenylboronic acid conjugates [168]. A Cd-EDTA-BSA-GNP-based LFA was employed for the detection of Cd^{2+} ions in tap and drinking waters, yielding a detection limit of 0.1 ppb. This achievement surpassed the performance of any paper-based metal sensors to date. Recently, bisphenol A (BPA), a chemical pollutant widely used in industry as a manufacturing component of polycarbonate bottles, has been placed on a watchlist for further scrutiny due to its detrimental effects on the endocrine glands. To address this concern, a straightforward and swift detection method based on LFAs has been developed. This method exhibits superior sensitivity when compared to gas chromatography (GC) and liquid chromatography (LC)-mass spectrometry (MS). Additionally, the approach offers benefits such as a brief analysis time, one-step detection, and on-the-spot testing [162]. In another study an ultrasensitive and multiplexed immunochromatographic strip (ICS) was created using multilayered fluorescent nanofilm-guided signal amplification. A flexible 3-D nanofilms developed through layer-by-layer assembly of three layers of small QDs onto two-dimensional GO nanosheets by electrostatic adsorption was formed and then modified antibodies were incorporated as fluorescent tags in the ICS target detection. A rapid and sensitive detection in real samples/environmental samples (meat

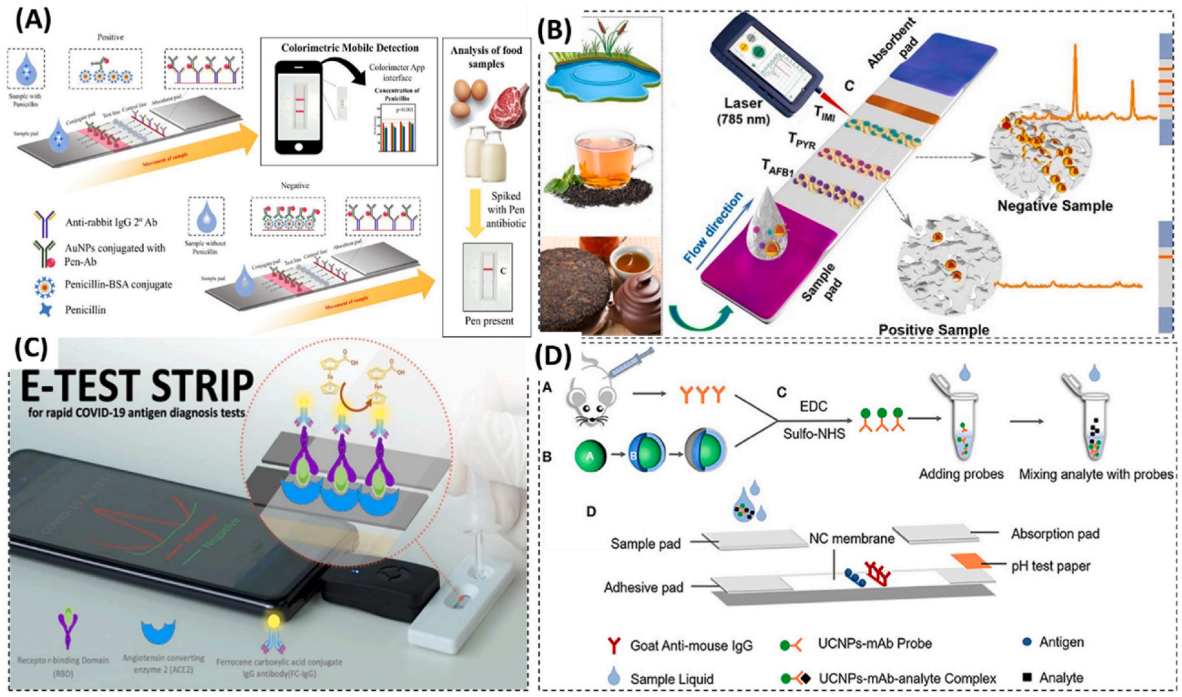

Fig. 9. Some examples of LFA used in different domains. (a) Competitive LFA for the recognition of penicillin in food samples, Copyright Permission taken from Ref. [166]. (b) SERS with LFA technique allowing simultaneous identification of imidacloprid (IMI), pyraclostrobin (PYR), and aflatoxin B1 (AFB1) using a single test strip. SERS nanotags were immobilized conjugated with antibodies on three separate test lines of strips to enhance Raman signal Copyright Permission taken from Ref. [170]. (c) SARS-CoV-2 screening for sensitive COVID-19 diagnosis using ferrocene carboxylic acid-SARS-CoV-2 antibody (Fc-IgG) as probe to capture antigens forming an immunocomplex. The ACE2 receptor, immobilized on the electrode, captures this immunocomplex, and resulting electrochemical signal is detected using smartphone Copyright Permission taken from Ref. [113]. (d) Advanced competitive UCNP-LFA for quick and precise quantitative assessment of three pesticides with exceptional sensitivity. Additionally, the ability to tolerate interference from different agricultural matrices, allow to efficiently screen for these pesticides in food samples within just 40 min Copyright Permission taken from Ref. [187].

extract, water etc.) was performed with a short testing time (15 min), good stability, and high reproducibility (RSD <8.71 %). The presented approach of utilizing GO–MQD–ICS shows a potential to satisfy the needs of practical, on-site detection of small-molecule pollution [169]. In one of the research approaches researchers used a SERS-LFA detection approach with excellent sensitivity and multiplex analysis of aflatoxin B1 (AFB1), pyraclostrobin (PYR), and imidacloprid (IMI) at a single assay strip as presented in Fig. 9b. Antibody-conjugated SERS nanotags were immobilized on three test lines of the strips using the immune-specific interaction between antigen and antibodies. The approach shows the higher sensitivity than the colorimetric signals LOD for IMI, PYR, and AFB1 were 8.6 pg/mL, 97.4 pg/mL, and 8.9 pg/mL respectively. Notably, it shows potential in identifying various pesticides and mycotoxins in agricultural and environmental samples [170].

5.3. LFAs for disease diagnostics

The majority of the LFAs are found in test kits for both human and animal diagnostics. Urine samples are often tested for the presence of human chorionic gonadotropin using the most used FLA, which is sometimes referred to as the pregnancy test. These days, LFA-based devices can be thought of as effective PoC testing application alternatives in the virus detection that are able to identify in 5–30 min several analytes (such as proteins, amplicons, nucleic acids, and haptens) from a wide range of biological samples (such as urine, plasma, nasopharyngeal swabs, spit, serum, sweat, and faeces) [4,7,163]. The lateral flow tests have a high sensitivity for detecting human immunodeficiency virus (HIV-1 & HIV-2), as well as hepatitis B and C viruses [171]. In Covid-19 cases, while LFAs cannot directly identify SARS-Cov-2 in an infected individual, they can be a valuable tool in analysing an individual's immune response behaviour and helping to fight the global Covid-19 epidemic. However, in lateral flow Covid-19 neutralizing antibody test, the level of neutralizing antibody against SARS-Cov-2 in plasma, serum and whole blood samples are detected in a semi-quantitative manner [172,173] and to establish an isothermal and non-enzymatic signal amplification system, a LFA strip-based device was developed for enhancing SARS-Cov-2 signal amplification and enabling sensitive RNA detection within a 90-min diagnostic process. In another study, Grant et al. [174] utilized commercially accessible SARS-Cov-2 Abs for creating a half-strip LFA (an LFA with no sample or conjugate pads but sample and conjugates premixed in an additional container) measured with an optical reader. Furthermore, multivalent GNPs stabilized in polymer and containing derivatives of sialic acid that can bind to SARS-Cov-2 spike proteins were used to construct an LFA detection device [175]. Several other techniques such as LAMP, CRISPR-Cas13a, PCR, RT-RPA, etc., were used to amplify virus nucleic acids and employed LFA for visualization [176,177]. The recently devised Bio-SCAN, platform, characterized by high sensitivity, cost-effectiveness, and user-friendly features, uses commercially available streptavidin-biotin-based LFA strips to detect a one-step FAM-labelled amplicon created by RT-RPA for target sequence, that requires only a single guide RNA and recombinant biotin-labelled nuclease Cas9 (bio-dCas9) [156]. This novel COVID-19 diagnosis tool that is extremely selective, sensitive, and quantitatively connected with a smartphone was developed in combination with screen-printed electrodes electrochemical detection and antigen test kits. The exceptional binding affinity of SARS-CoV-2 antigen to ACE2 was utilized to produce an electrochemical test strip (as presented in Fig. 9c) with a signal intensity that is proportional to the concentration of SARS-CoV-2 antigen (LOD = 2.98 pg/mL in less than 12 min). The results show consistency with the obtained results from RT-PCR [113].

LFAs were also developed for cardiac disorders; cardiovascular diseases (CVDs) that encompass a range of heart-related disorders, including ischemic heart disease, heart failure, stroke, cerebrovascular diseases, thrombosis, arrhythmia, and cardiomyopathies [178]. However, there are currently insufficient products on the market for the diagnostic measurement of N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), a cardiac biomarker for acute heart failure [179]. Additional research validated the potential application of QDs linked to antibodies associated with CVDs as a viable method for assessing the risk of human cardiovascular conditions [180,181]. A combined venture between SCIENION (Berlin, Germany) and the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (North Rhine-Westphalia, Germany) has demonstrated the integration of LFAs into cancer diagnosis. The goal of this partnership is to develop an LFA for bladder cancer [182]. A SERS-based multiplexed LFA was reported, which adopts the dual signal amplification strategy of multiple effective hotspots and magnetic enrichment to support simultaneous and sensitive detection. To this aim, a multilayered magnetic-core dual-shell nanoparticles with controllably small nanogaps was created through layer-by-layer (LBL) assembly of two Au@Ag satellite layers onto superparamagnetic Fe_3O_4 cores, using polyethyleneimine. These multifunctional tags were then conjugated with particular antibodies in the LFA system to enable quick capture, separation, and quantitative analysis. To identify four targets simultaneously with extreme sensitivity on two test lines, two Raman reporters were modified and placed in internal nanogaps on the surface. This made the construction and signal reading of SERS-LFA much easier, with LODs as low as pg/mL. The developed assay could quickly identify multiple targets and drug residues in 35 min. This developed methodology outperformed conventional colloidal gold immunochromatography in terms of stability, throughput, and sensitivity (up to 400 times), indicating its enormous potential for use in point-of-care diagnostics [183].

5.4. LFA for agriculture application

LFA has been efficiently used to detect various pesticides such as insecticides, fungicides, and herbicides in agriculture land and agricultural produce [184,185]. Globally, the use of pesticides has increased significantly due to the expanding agricultural sector; the top five countries using pesticides are China, the US, Thailand, Argentina, and Brazil [110,185]. To improve agricultural productivity and food security, the Bio-SCAN system has recently been developed as a PoC testing platform for agriculture, enabling plant gene editing, crop breeding, transgenic detection, and early molecular diagnosis of phytopathogens [165]. An immunochromatographic test using LFAs based on QDs identifies the organophosphate pesticide metabolite (3,5,6-trichloropyridinol) quickly, and accurately with nanogram resolution. Similarly, CdSe/ZnS (core/shell) QDs were used to visually identify benzothiostrobin residues quantitatively in strawberries [150,186] and broad-spectrum monoclonal antibody labelled LFAs, with up-converting nanoparticles (UCNPs) were able to identify various residues of three organophosphate pesticides in food samples [165,187]. Using horseradish peroxidase (HRP) and GNP as tracers, LFA concurrently detected also endosulfan and carbaryl in food samples [48]. To achieve quantitative pesticide residue detection, methyl parathion and imidacloprid haptens were labelled using HRP and ALP as chemiluminescent probes. This resulted in the creation of recombinant peptidomimetic-nano luciferase tracers for the development of assays using nanoluciferase (NanoLuc), which achieved high precision for the detection of imidaclothiz in agricultural samples [188,189]. Pt–Ni(OH) 2-D nanosheets with peroxidase-like properties were used in a bidirectional LFA for enhanced detection of fenpropathrin and acetochlor [190]. Additionally, organophosphate pesticides were detected using disposable screen-printed CNT electrodes by measuring acetylcholinesterase (AChe) [191]. Although, LFA strips are promising, a lot more development is needed before these devices can be widely used for pesticide detection in environmental samples. Problems like low repeatability and sensitivity to elevated analyte concentrations are commonly brought up by researchers. Moreover, the majority of LFA devices only offer results that are semi-quantitative or qualitative. The need for multiplex detection devices presents another difficulty because different pesticides are

usually applied to the same crop and leave diverse environmental residues [192]. A quick and accurate lateral flow immunochromatographic method for the multi-residue detection of pesticides was designed integrating a unique fluorescent labelled monoclonal antibody as presented in Fig. 9d. The assay allowed for sensitive detection with a range of 0.98 ng/mL to 250 ng/mL and at 500 ng/mL, with no cross-reactivity detected. The detection of food samples also involved the study of matrix interference caused by different agricultural products, thus needing the development of a screening method for quickly identifying the multiple pesticides in food samples strip test [187].

6. Future direction and challenges of LFAs

Over the past three decades, LFAs have been thoroughly studied and produced on a commercial scale. These portable, quick, and affordable devices have enabled to diagnose track illnesses in real time. Diagnostic approaches could be revolutionized worldwide, and, due to the straightforward, inexpensive related technology, they received attention in point-of-care and laboratory-based molecular diagnostics. The combination with standard technologies, like electrochemical sensing, SERS, fluorescence detection, and the use of nanoparticles, improved the sensitivity and specificity of LFAs, facilitating multiplexing with higher limits of detection and rapid diagnostic. Further advancement in LFAs may be introduced in the market with the next generation of chips combined with DNA amplification and detection, as well as using new technologies like CRISPR and nano or quantum materials to improve the sensitivity of the LFAs. Despite the numerous advantages of LFAs the problems of low repeatability and need of high analyte concentration, as well as the fact that they only provide qualitative or quantitative data, have not yet been solved. Unfortunately, LFA technology still needs for furthermore refinement and testing to reach for good commercialization of diagnostic kits, and there are also concerns about their proper disposal in the environment, as they may contain heavy metals, nanoparticles, quantum dots, and fluorescent labels, thus be environmentally hazardous when used extensively. It is urged by the community to apply proper regulations and guidelines during the disposal of such kits. The development of quick and accurate analytical methods for various applications with LFAs is the demand of the time. The future direction of LFAs as PoC, needs to overcome the hurdles of sample preparation and progress toward quantitative and multiplexed detection. So far with our understanding, we like to point out on strategies like.

(i) using novel markers and signal amplification tools to achieve higher limit of detection,
(ii) developing new recognition elements (aptamers/MIPs - Molecularly imprinted polymer) for specificity improvement,
(iii) using multiplexed detection approaches,
(iv) applying artificial intelligence along with analytical techniques, and
(v) integrating multistep process to one step (collection, processing, and detection).

Furthermore, LFAs multiplexing is a relatively young field that is now generating a lot of interest in the medical community. To distinguish diseases at PoC level, multiplexed sensing should clearly be the focus of future research in LFA based diagnostic kits. LFA's top two concerns are assay imprecision and product stability. There is a genuine assurance that concerns about product stability are typically restricted to the biologicals in the assay system when one can rely on tried-and-true production procedures, particularly assembling LFA, within a controlled environment in terms of both temperature and relative humidity. The market for LFA Testing Solutions has obstacles despite a growth trajectory, because the demand for constant test sensitivity and specificity improvement to satisfy the strict regulatory criteria is one major difficulty. For LFA developers, achieving great sensitivity without sacrificing specificity is still a technical challenge. Furthermore, competitiveness is heightened by market fragmentation and the presence of multiple players, making it difficult for businesses to distinguish their offerings, and forge a significant market position. Moreover, the substantial upfront costs associated with research and development, along with the need for regulatory clearance, create an obstacle to the entry of new firms and, hence, restrict market accessibility.

CRediT authorship contribution statement

Saloni Kakkar: Writing – original draft, Conceptualization. **Payal Gupta:** Writing – original draft, Data curation. **Shiv Pratap Singh Yadav:** Writing – original draft, Visualization. **Divakar Raj:** Writing – original draft, Methodology. **Garima Singh:** Writing – original draft, Visualization. **Sakshi Chauhan:** Writing – origina. **Manoj Kumar Mishra:** Writing – original draft. **Elena Martín-Ortega:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Stefano Chiussi:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Krishna Kant:** Writing – review & editing, Writing – original draft, Validation, Supervision.

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.

Data availability

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

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