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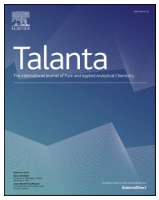

Contribution of magnetic particles in molecular diagnosis of human viruses

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ABSTRACT

Viral diseases are the primary source of death, making a worldwide influence on healthcare, social, and economic development. Thus, diagnosis is the vital approach to the main aim of virus control and elimination. On the other hand, the prompt advancement of nanotechnology in the field of medicine possesses the probability of being beneficial to diagnose infections normally in labs as well as specifically. Nanoparticles are efficiently in use to make novel strategies because of permitting analysis at cellular in addition to the molecular scale. Henceforth, they assist towards pronounced progress concerning molecular analysis at the nanoscale. In recent times, magnetic nanoparticles conjugated through covalent bonds to bioanalytes for instance peptides, antibodies, nucleic acids, plus proteins are established like nanoprobes aimed at molecular recognition. These modified magnetic nanoparticles could offer a simple fast approach for extraction, purification, enrichment/concentration, besides viruses' recognition precisely also specifically. In consideration of the above, herein insight and outlook into the limitations of conventional methods and numerous roles played by magnetic nanoparticles to extract, purify, concentrate, and additionally in developing a diagnostic regime for viral outbreaks to combat viruses especially the ongoing novel coronavirus (COVID-19).

1. Introduction

Far-reaching pandemics of infections have been relatively rare all over history, but once they occur they can be alarming. These infections influence a large number of populations and cause millions of deaths every day. Even with the development of diagnosis and treatment by medicine, these epidemics are nature's mode of evoking us that despite our hard work; nature can never be controlled by us.

Viruses are one of the main sources of infection and global death, mostly due to the growth of impervious strains of viruses and the contrary side effects related to sustained usage that leads to reducing the significance of operative antiviral treatments [1]. Humans have been combating these viruses since earlier our species had even progressed into its modern form. Thanks to immunization platforms, specific ailments that are caused to kill countless and gradually inactivate others have been eliminated. Still, certain lethal viruses around the world present a severe hazard to community health because of not having consistent sources to fight them. Inhibition of the spreading of the virus requires quick and accurate diagnosis and appropriate management of the contagious agents. Many specific diagnostic techniques are available for the extraction and detection of different deadly viruses (Table 1). In this situation, nanotechnology proposes an adaptable and reliable platform to detect diseases caused by viruses. Different carriers having nanoscale size (e.g., solid lipid nanoparticles, liposomes, inorganic nanoparticles, polymeric nanoparticles, and more) have appeared as a novel "antiviral agents" because of their exclusive chemical and physical characteristics [2]. Additionally, the surface modification of nanoparticles widens their applications and unlocks their innovative potentials for adapting them to attain a future objective.

Multidisciplinary investigations have been done for the progress of unconventional approaches to improve antiviral diagnostics and therapeutics, in which nanotechnologists play a vital role and shoulder their social accountability. As one of the game-changers of the previous era, amongst numerous science and technology fields, nanotechnology offers inventive ways to solve a broad range of difficulties and problems concerning inhibition, identification, and detection of viruses. Moreover, the efficiency of orthodox therapies is gradually vanishing away due to the increase in resistance against the virus, which could be

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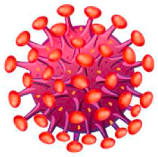
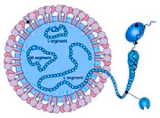
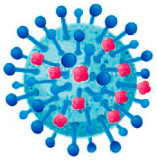
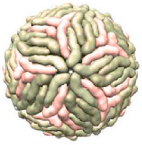
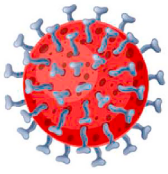
Table 1
List of some deadly viruses in human history and conventional systems used for their detection.

Type of virus	Average fatality rate	Conventional detection system	Ref
Marburg virus (MARV) 	23%–90%.	Polymerase chain reaction (PCR) and enzyme-linked immunosorbent assays (ELISA)	[3]
Ebola virus (EBOV) 	25%–90%	Reverse transcription Polymerase chain reaction (PCR)	[4, 5]
Human immunodeficiency virus (HIV) 	30%	Polymerase chain reaction (PCR) and enzyme-linked immunosorbent assays (ELISA	[6, 7]
Hantavirus (HPS) 	36%	Serology, reverse transcription Polymerase chain reaction (PCR	[8, 9]
Influenza virus (A, B, Spanish flu) 	40%	Serology, rapid antigen testing, reverse transcription-polymerase chain reaction (RT-PCR), immunofluorescence assays, and rapid molecular assays.	[10]
Dengue virus 	2%–20%	Serological testing, and RNA amplification using reverse transcriptase PCR	[11]
Coronaviruses (SARS-CoV) 	–	Reverse transcriptase PCR	–

positive because of the enhanced variation in peripheral protein sequence leading to new viral strain [12]. Furthermore, nanotechnology manipulates nanoparticles for viral extraction and detection generally, focused on most typical and fatal viruses, namely influenza, hepatitis, HIV, and ebola counting the ongoing novel coronavirus COVID-19 [13]. Through nanotechnology; viruses can be identified or deactivated by the labeling of viruses with nanoparticles, constraining the duplication of the virus on entry in a host cell, or through blocking viral proteins present on the virus surface as shown in Fig. 1. Subsequently fabricating a targeted nano-system is also beneficial for the elimination of the spreading of viral infection. The detection systems combined with nanoparticles delivered various valuable tools that can be practical for

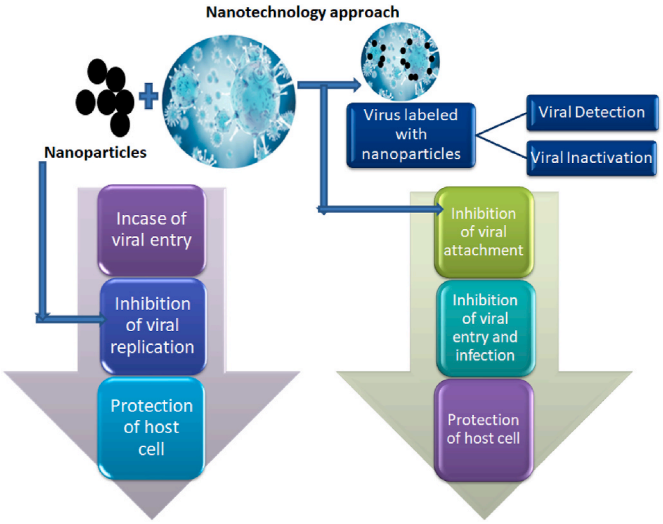


Fig. 1. Prospects of nanotechnology for prohibiting the spread of viral infection.

the revealing of pathogenic viral agents for diagnosis purposes. It comprises, though not restricted to, the handling and valuation of nanoparticles, reducing systems dimensions and platforms to utilize nanoscale properties accessible from interfaces between viruses and surfaces.

The current review focuses on the progressive as well as continuing strategies established on magnetic nanoparticles for the specific and non-specific diagnosis including extraction, purification, enrichment, and detection of viruses for combatting fatal infections. Non-specific methods target all types of DNA or RNA regardless of their sequences, while the specific method can target specific sequences of DNA or RNA. The specific method is more appropriate for diagnostic systems as an assay for a specific pathogen. Specific nucleic acid diagnosis is significant where the isolation of a specific sequence of DNA or RNA is preferred. We first discuss limitations regarding conventional techniques along with the contribution of different nanoparticles for virus detection and later move towards prominence concerning the employment of magnetic nanoparticles (MNPs) for point-of-care (POC) testing for nucleic acid extraction, enrichment, and detection.

2. Limitations of conventional systems

Different analytical assays for separation, extraction, recognition, and observing of virus infections have been developed and are extensively used in repetitive and routine diagnostics applications. Specifically, the separation and recognition of afresh evolving contagious diseases is challenging and thought-provoking. In view of unmet requirements and population expansion, the improvement of nontoxic and active antiviral drugs is a challenging task. Additionally, viruses that are transmitted through travel like dengue viruses, HIV (human immunodeficiency virus), chikungunya viruses, influenza viruses, and HPV (human papillomavirus), or others require diagnostic in addition to therapeutic procedures that inhibit their growth and spread. Several aspects are required to stop the epidemic spread of a newfangled virus. A well-founded investigation system and detailed information of the noticed variations assist in revealing the danger of an imminent disease and permitting suitable actions to be taken in a period, such as quarantine and invention of a vaccine.

In day-to-day practice, equally molecular biological techniques and quick antigen tests are used, both having their usual pros and cons. In numerous examinations, RT-PCR (real-time polymerase chain reaction) has been established for the most profound and sensitive process in influenza diagnostics. Nevertheless, the better practical exertion, the

greater expenses, and a lengthier hands-on time can be disadvantageous in comparison to the rapid antigen test. Approximations of the sensitivity of diagnostic rapid tests differ importantly in the range between 20% and 90% [14]. Yet, the patient's choice significantly affects the perceived positive and negative prognostic standards. Even better-quality antigen tests produce a sensitivity of only 79.9% when matched to the PCR test, which decays to 67.3% with time. The quick test can therefore be utilized as a bedside test that delivers the first outcome in minutes with higher diagnostic sensitivity in comparison to PCR [15]. Innovation with better-quality potential in the analytical system for viruses is desirable for medical healthcare from diagnostics to therapeutics.

Traditional methods including serologic test, PCR (polymerase chain reaction), and ELISA (enzyme-linked immunosorbent assays) have not rather been complex, however have been lengthy, inefficient, depending on resources, and have restrictions. In Table 2, few methods for amplification of nucleic acid are presently accessible aimed to diagnose contaminations inside laboratory, caused by viruses globally, along with benefits as well as restrictions of them are précised. Therefore, requirement of an accurate and specific system for detection is tremendously growing. To attain this objective, distinctive configurations and approaches have been made to develop a responsive and reliable virus sensor using nanoparticles.

RT-PCR has been accepted as an exclusive as well as a reliable test for analyzing and measuring dissimilar RNA within laboratories and medical diagnosis because of eminent precision in the amplification of RNA. Following the existence of coronavirus, many procedures aided RT-PCR to recognize this deadly virus [23,24]. RT-PCR aided practices have been broadly practiced in COVID-19 detection because of their suitability and accuracy in viral detection and epidemic control but are also persistently delayed because of long procedures as well as labor constraints. Refined extraction and estimation of nucleic acids through complex samples are the foremost necessity to analyze in RT-PCR [25]. Lower-grade efficacy regarding removal might affect unsuccessful signs via amplification and therefore leads to the wrong diagnosis. Orthodox practices for binding of nucleic acids involve several long steps, also subjected towards impurities [26]. To manage and regulate the spontaneous coronavirus increase, conservative methods consumed a lot of manpower as well as greater cross-infections threat. For that reason, fast, convenient, and self-propelled techniques for nucleic acid extraction are enormously essential for detecting coronavirus, but also additional diseases as well.

Table 2
Benefits along with shortcomings regarding various traditional systems employed for diagnosis.

Method of Detection	Benefits	Shortcomings	Ref
Real-time PCR/RT-qPCR	Extremely specific and precise, Genotyping, Bolted tube process lowers the risk of cross-contamination, Fast, not demanding, Complex recognition, Estimation of viral load quantitatively	Needs costly lab apparatus in addition to incandescent probe, Fabrication of TaqMan probes involves nearly whole data regarding the sequence of target nucleic acid, Susceptible towards inhibitors	[16, 17]
ELISA-Enzyme-linked immunosorbent assays	Simple, safe, specific, efficient, and eco-friendly, cheap and sensitive process, Immediate investigation possible devoid of complex pre-treatment of a sample, radioactive substances as well as a large quantity of organic solvent, Required reagents are not costly	Laborious besides costly, Require refined methods along with rich culture medium, Probability of wrong results due to inadequate blockage of restrained antigen, Instability of antibody, Require transport as well as storage at low temperature	[18, 19]
LAMP-Loop-Mediated Isothermal Amplification	Very sensitive, Simple to perform, No need of costly heat cycler, Rapid (results in <1 h), Quantitative, Genotyping, Easy to detect even with the naked eye, Comparatively unaffected by inhibitors that exist in a sample	Requirement of six primers, High risk of carryover contamination, Limitation for multiplexing, Using a naked eye to detect only is not sufficient because it varies according to color perception by an observer	[16, 20]
Serologic tests	Health workers can use directly, Produce instant results, Improved diagnostic sensitivity as well as the positive detection rate	Weak antibody response, Limited specificity of the antigens, Requires skilled technicians, time-consuming, Costly	[21, 22]

Marketable kits and methods, although expensive, are simple to use and typically yield better RNA quality. The accessibility of commercially registered chemical components is also extremely affected due to the interruption of the worldwide supply network as a result of the viral epidemic. Extraordinary price in addition to short accessibility regarding these components execute restricted way towards testing capabilities in both wealthy and unfortunate countries and have contrary side effects associated with extra health problems [27]. Thus, there is pronounced motivation to advance substitute systems or devices that only need nearby, available, and economical chemicals, but also are easy to execute, and competing the depiction of commercially available kits. Above and beyond easing supply deficiency, the unusual means should preferably eradicate the hazard of controlling live viruses, so dropping the severe biological safety necessities upon analysis suitability [28]. Any technique of extraction depending on self-building of RNA satisfying the above-stated standards may escalate abilities for testing in scientific practices, nonurban healthcare services, academia labs, as well as field analysis locations [29]. To address these shortcomings, nanoparticle aided extraction and detection methods are expedient, uncomplicated, and friendly with self-propelled practices [30].

3. Non-magnetic nanoparticles in viral diagnosis

Nanotechnology can be generally defined as the strategy and usage of numerous nanomaterials and devices for various applications including analysis, handling, regulating, and inhibition of diseases [31, 32]. Many nanomaterials shown in Fig. 2, have been utilized for extraction and detection of viruses comprising MNPs (magnetic nanoparticles), QDs (quantum dots), SiNWs (silicon nanowires), VLPs (virus-like particles), graphene, inorganic nanoparticles, liposomes, nanoparticles of self-assembled protein, polymers, and metal, silica nanospheres, CNTs (carbon nanotubes), nanostructured surfaces and films [33–35].

The employment of nanoparticles aims to take benefits of nanocarriers, eluding their limits. Their appealing properties, such as bioavailability, optimum tunable size, charge, shape, biodegradability, high SRP (surface plasmon resonance), photon exchange, superparamagnetism, luminescence, biocompatibility, immunocompatibility, and tolerability offers an unusual methodology for viral detection. Also, they can easily be ornamented/attached/bonded to different linkers, functional groups, biomolecules, as well as several additional nanomaterials, having the ability to diagnose and treat simultaneously [36]. Nano-based detection along with extraction has benefits over outdated methods to permit easy, speedy, highly sensitive, and label-free detection of viruses leading to a positive influence on public health. This innovative methodology will advance the improvement of regulatory systemization in addition to POC (point-of-care) nanodiagnostic in clinical practice. The nanoparticles usage in such technologies is interesting to recognize, neutralize, and interrupt these pathogens afore they enter into the body. These nanomaterials could be synthesized or acquired from biological sources [37].

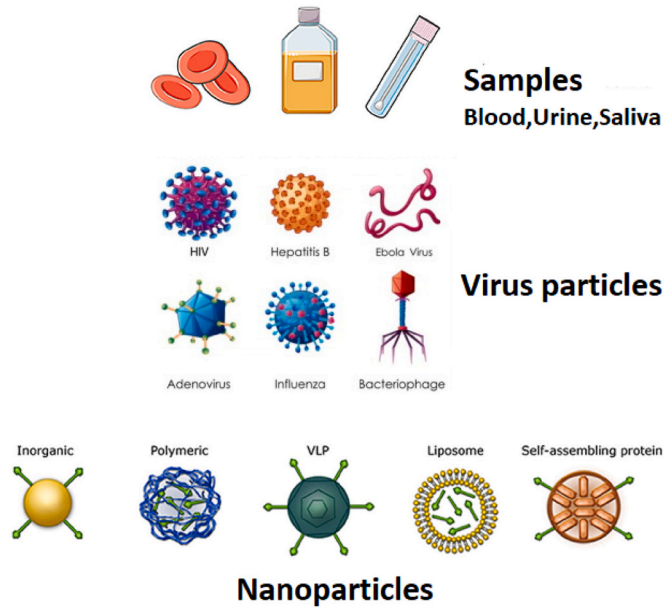


Fig. 2. Schematic view of some nano-magnetic nanoparticles employed to detect various viruses in biological samples (reproduced and modified figure according to Refs. [33–35]).

Continuous efforts have been made for refining the physicochemical characteristics of nanoparticles by surface modifications. Synthetic nano-based formulations played a remarkable role in the diagnosis as a lot of detection systems, based on nanoparticles, show improved well-being and efficiency over conventional methods. These nanoparticles have assemblies that resemble pathogens of nanoscale size and stimulate the progression of the human immunity system. Developments of novel nanosystems based on the similarity between synthetic nanoparticles and viruses provide a way out towards persistent and evolving human infections [38]. Presently, miscellaneous nanoparticles are being exploited for virus detection because of their exceptional properties by different tools, summarized in Table 3.

Nanoparticles propose various prospects in the field of molecular diagnosis. Yet, despite these involvements, it is extremely thought-provoking to securely transform nanoparticles from laboratory invention to clinic. Nanoparticles are very useful for biomedical applications; however, have some bottlenecks which should be addressed to assist their extensive employment in the comprehensive healthcare system. Despite many advantages, they have a contrary side which is the agglomeration or sedimentation of nanoparticles, which optimizes their usage against *in vitro* viral diagnosis. This problem can be overcome only through proper surface functionalization. Nanoparticles are being employed because of their exceptional as well as novel properties, but researchers across the world have comprehended the importance of stable nanoparticles to develop consistent *in vitro* biocompatibility models [55].

An additional concern is the absence of reliable procedures aimed at the biological and physicochemical characterization of nanoparticles [56]. It is supposed that the physiochemical characteristics of nanoparticles for instance composition, size, shape, charge, crystallinity, solubility, surface area, in addition to surface derivatives for functionalization are risk factors to cause potential toxicity. Nanoparticles are not themselves a threat. There are only a few aspects that make them risky, specifically their mobility and enhanced reactivity. The ability to extensively produce nanoparticles is another difficulty that is to be overcome for the wider commercialization of nano-based formulations [25]. Consequently, we should give other perceptions to enhance and upgrade processes and advance more in the transformation of bench-top research to clinical practice.

Another challenge is to understand the genomic and proteomic structure of viruses for their real-time diagnosis. A substantial rate of mutation and consequential genetic multiplicity is also a foremost problem for diagnosis. Viruses do not have adequate targets, hence investigations about the weak points of the virus and susceptibilities of infected cells will allow designing particular ligands that can be used to functionalize nanoparticles to target the virus [57]. Moreover, each virus reacts differently from one host to another. Hence, extending the spectrum for nanoparticle-based viral diagnosis is still very challenging. Prominently, with this high rate of virus diffusion, there is a critical requirement to develop a safe and quick method to extract and detect viruses at a reasonable cost. Another challenge is the safety of the workplace using nanoparticles. Health hazards of functionalized nanoparticles should be properly estimated, comprising their fabrication, storing, delivery, applications, possible abuse, and discard.

Applications of nanoparticles enhance the sensitivity, speed, and

Table 3
Different non-magnetic nanoparticles and their properties used in the detection of viruses.

Nanoparticles	Properties	Detection technique, system	Type of virus	Detection level	Limit of detection	Ref
Quantum Dots (QDs)	The broad range of absorption, extended fluorescence lifetime complex staining, photoluminescence, and photobleaching resistant	Dual-stain imaging technique, a system based on QDs-DNA and FRET	Human Immunodeficiency Virus (HIV), Hepatitis B Virus	fg/pM	17.02 fg/mL	[39,40]
Carbon Nanomaterials (Carbon nanotubes, Silica nanoparticles)	High sensitivity and selectivity due to their high surface area.	Electrochemical or Optical-based detection systems	Hepatitis B Virus, Papillomavirus	fM/pM	3.4 PFU/mL, 8.6 pM	[41–44]
Silver Nanoparticles	Fluorescent characteristics	Optical-based detection system	Human Immunodeficiency Virus and Hepatitis B Virus	pM/nM	4–8 nM	[45–47]
Aluminum, Copper, and Zinc Nanoparticles	Nanoporous morphology, catalytic properties	Optical, Electrochemical-based detection system	Dengue virus	pM/nM	7 pM, 10^5–10^7 copies mL−17.4 μM,	[48–51]
Gold Nanoparticles	Optical and electrical properties	Fluorometric, surface-enhanced Raman scattering (SERS), light-scattering, colorimetric, and electrochemical techniques	Rift Valley Fever Virus, Hantaan Virus, SARS (Severe Acute Respiratory Syndrome), HEV (Hepatitis E Virus), DENV (Dengue Virus), HPV (Human Papilloma Virus), IAV (Influenza A Virus)	pM/nM	10- 10^2 copies/mL	[39, 52–54]

reliability of, as well as provide more effective options for viral diagnosis; therefore, there is an opportunity that, with more research, it will revolutionize the fight against ongoing COVID-19. Still, numerous aspects need to be considered and a thorough study concerning nanotoxicity should be made for safety and reliability; the requirement for vigorous scale-up synthesis; the biological reactions for nanoparticles containing exposure levels, systemic accumulation, tissue and organ distributions of test living subjects; the possible toxicity of the nanoparticles in the short and long term [58].

4. Contribution of magnetic nanoparticles (MNPs) in the diagnosis of viruses

Innumerable inorganic nanoparticles, such as gold, silver, iron oxide, etc., have found their usage in nucleic acid extraction, purification, and detection. Among these, magnetic nanoparticles are extensively consumed for such applications attributed to the high ratio of surface area to volume, excellent dispersion, and extraordinary rate of their bonding to recognition constituents. Their ability to control accumulation magnetically, superparamagnetic behavior, inexpensive preparation, quick isolation inside buffer solutions, along with detection of the signal makes purification, pre-concentration, and separation regarding nucleic acids quick and specific [59,60]. MNPs are being used by researchers to immobilize proteins, antibodies, enzymes, and more bioactive substances for speedy and effectual biomolecules separation utilized for targeting [61]. In complex samples, biomarkers can be enriched and preconcentrated, separating interfering matrices, and enhancing the sensitivity and specificity of testing. *In vitro* MNPs based extraction and detection contribute significantly towards a diagnosis of diseases rapidly at the initial stages, consequently helping inhibition, controlling, as well as diagnosis [62]. MNPs have been of great interest to researchers because of their tunability in morphology, surface coating, functionalization, and due to their exceptional properties that have been displayed in Fig. 3. They play an important role in real-time detection systems if combined with a fluorescent or chemiluminescent probe. It is possible to attach an extensive variety of groups for functionalization to magnetic nanoparticles for increasing their chemical functionality, constancy, wettability, as well as bonding adaptability aimed at a large number of applications. The extraction and detection of nucleic acid present in a sample depend on the affinity of nucleic acids to the coating or functional moiety present on the surface of MNPs. It can be specific or non-specific.

Functionalization and surface coating by oxiranes, carboxylic acids, amines, in addition to aldehydes are generally employed for immobilization of enzymes, proteins, nucleic acids (RNA and DNA), plus bioanalytes onto the surface of nanoparticles covalently [63]. They possess both magnetic particles and nanoparticles characteristics so can easily be manipulated by external magnetic fields. MNPs reduce the time of relaxation of protons regarding water molecules, as a result, contrast is generated that has also been utilized to detect viruses [64]. On account of biocompatibility, exceptional dispersion properties as well as suitable chemical functionality aimed at fixation, it is possible to employ magnetic nanoparticles bonded to different elements for recognition to captivate biomolecules, to isolate support magnetically from the mixture of reaction, and also as compact adsorbent [65].

MNPs accumulation and dispersability could easily be regulated by applying a magnetic field externally. Nonmagnetic particles bonded to MNPs remain suspended in solution uniformly when there is no field. On application of magnetic field; these particles get isolated. Active molecules for instance bio-adsorbents and functional ligands bonded with MNPs possibly are attached with particular biomolecules, for instance, proteins, DNA, and enzymes, and could be partitioned via a magnetic field which is applied externally. The aforementioned technique offers exceptional specificity, fast isolation as well as significant reproducibility that paved the way for a scientific revolution in biological research [66]. Finite-size, surface coating, and magnetic properties have a substantial impact on viral diagnosis. Nanoparticle size shows the possibility of nanoparticle interaction with the outer environment [67]. As the size of MNPs decreases, there is a greater probability that atoms confined inside the nanoparticle will become surface atoms and with a higher percentage of surface atoms. Magnetic properties of MNPs also decrease with that reduces their efficiency for detection [68]. The

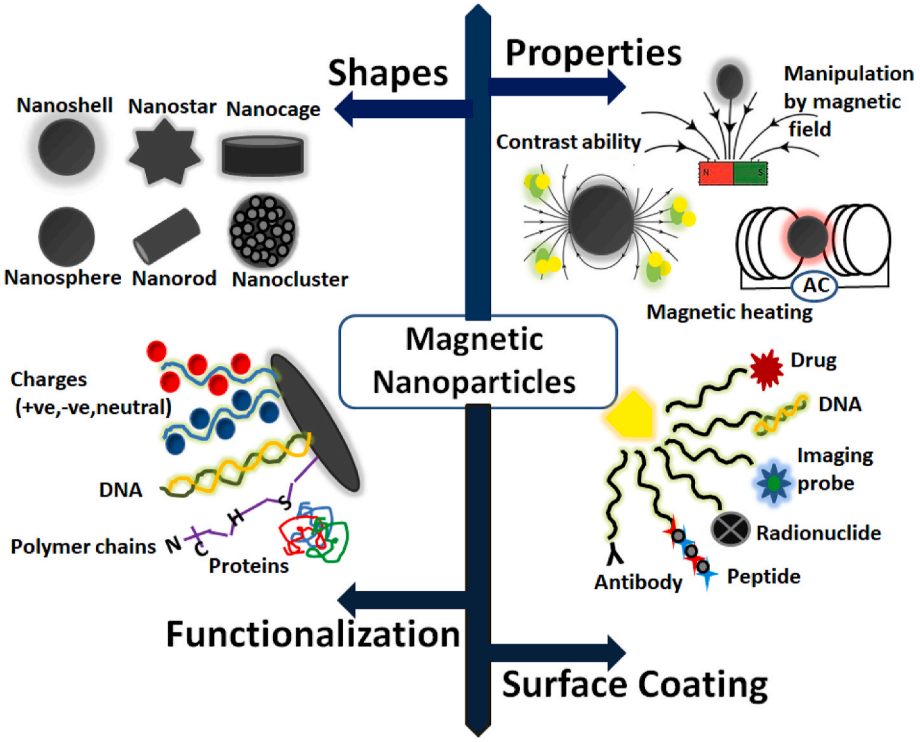


Fig. 3. Morphology, functionalization, surface coating, and properties of MNPs.

instability of magnetic nanomaterials makes it important to develop approaches to stabilize MNPs against degradation and enhance biocompatibility. Such strategies frequently include modification of the surface with an organic layer or inorganic layer [69]. The surface functionalization of MNPs governs the binding efficacy of nucleic acids. Different materials or polymers have been used to modify the surface of MNPs for instance silica, dextran, polystyrene, or poly (vinyl alcohol) (PVA), polyethylene glycol (PEG) to maintain their stability and enhance their performance for diagnosis [70]. The coating of MNPs reduces the risk of opsonization and also their neutral pH excludes the functional group's conjugation.

Hence, synthetic polymers, for instance, PAA (poly (acrylic acid)) are favored for their capability to bind to biological macromolecules, such as nucleic acids [69] Suitable surface coating of MNPs is necessary, which not only gives colloidal stability to the nanoparticles but also maximizes the possibilities for use in various other applications. The colloidal stability of MNPs under physiological conditions, for instance, at pH~7.4, in blood, in physiological salts, and protein concentration is the minimum requirement for biomedical applications [71]. Therefore, the agglomeration of MNPs has to be stopped via a surface coating, either during or after synthesis. The molecules or functional groups bonded covalently can more improve colloidal stability than adsorbed ones. An optimized coating on MNPs surface is required to interact with nucleic acids. The coating layer of core-shell nanosystems provides optimum hydrophobicity/hydrophilicity in a given medium and active sites for anchoring bio-functions [71]. Some properties of magnetic nanoparticles including their size and composition used in viral diagnosis have been summarized in Table 4.

Considering the significant potential regarding MNPs for viral diagnosis, we described extraction, purification, concentration, and detection of nucleic acid employing MNPs in the following sections.

4.1. Extraction and purification of nucleic acid

One elementary constituent of life is "nucleic acid" which is tremendously vital for physiological processes taking place inside the body. They primarily transfer, in addition to retaining, genomic information that assisted in detecting mutation in genes linked to some specific health situations. Its isolation and decontamination are significant in molecular biology. Isolation of RNA and DNA is a phase before diverse biochemical and diagnostic processes like replicating, recognition, intensification, hybridization, sequencing, and DNA production [79]. The extraction of nucleic acid by traditional methods was lengthy and laborious. It contains a multiplex procedure of removal and centrifugation that is severely controlled by low clarity and small yields of the separating samples [79]. Early nucleic acid extraction and purification are significant for inhibiting, treating, as well as recognizing the disease. In the previous era, MNPs have been used to extract nucleic acids that are present in the lysed samples by their adsorption on MNPs because of the existence of modified functional moieties on MNPs surface [80]. Extraction and purification based on MNPs are free of centrifugation and have been recognized as easy, simple, controllable plus attuned with mechanization as well as scaled-up procedure [81,82].

The modified MNPs adsorb and separate the nucleic acid quickly from contaminated lysis solution employing an externally applied magnetic field. Afterwards, nucleic acids are further separated from the functionalized MNPs by the desorption route in the eluent utilizing this methodology. This system is although much smoother and faster than orthodox techniques, still, it is multi-step, which is inadequate for applied detection [83].

Techniques based on MNPs have established significant concern due to their expedient manipulation, low cost, and easiness of automation. Various aspects comprising lysis and washing solutions (buffers, MNPs, ethanol) would affect nucleic acid production. The mean RNA and DNA yield attained through 1 mL of Hep G2 having approximately 10^6 cells have ranged in between 9.7 and 14.7 μg at A260/A280. Simultaneous extraction of RNA or DNA from cancer cells consuming silica-coated MNPs was appropriate for future acts for instance, such as PCR as well as RT-PCR [84]. Immobilization of nucleic acid via SPRI (Solid-phase reversible immobilization) onto MNPs proposes an elegant alternate for approaches based on centrifugation or else columns [85]. During drying, it is feasible to reversibly bind MNPs inside the sample with nucleic acids. These nucleic acids are promptly isolated from contaminations by the magnetic field, and as a result, purified nucleic acids with a dissimilar ionic strength are freed from MNPs via eluting buffer after several fast washing steps as shown in Fig. 4 [86]. SPRI permits exhaustive washing steps for eradicating inhibitors in reactions taking place in molecular biology in addition to producing next-generation sequencing and better-quality RNA for PCR. Extraction of RNA based on MNPs has been integrally accessible, extensible, as well as responsive towards mechanization following no centrifugation besides the usage of low-cost materials. Though considerably quicker besides easier when compared to procedures based on spin column, still further, such approaches to extract comprise of manifold treating phases including lysis, bonding, rinsing, plus elution, that enhances operative complications in real-time clinical diagnosis.

Table 4
Characteristics of few magnetic nanoparticles used in viral diagnosis.

Particles characteristics	Size (nm)	Composition	Sensitivity	Ref
Cross-Linked Iron oxide	30	5 nm core with 10 nm dextran coating	Low nM~pM, 50 viruses/ 100 μL	[72]
Iron Oxide	19.5		<1 nM	[73]
Cubic FeCo nanoparticles	12.8	1.5 nm oxidized shell	2×10^6 nucleic acids	[74]
Antiferromagnetic nanoparticles	100	Multilayers of the ferromagnetic, interlayer of nonmagnetic material	10 pM	[75]
γF_2O_3	324 ± 7	poly (styrene/ acrylamide)	2×10^{-2} viruses/mL	[76]
$Fe_3O_4@SiO_2$	–	APTES (3-aminopropyl) triethoxysilane) and SA (succinic anhydride) multilayer coating	4.42×10^{-14} g/mL	[77, 78]

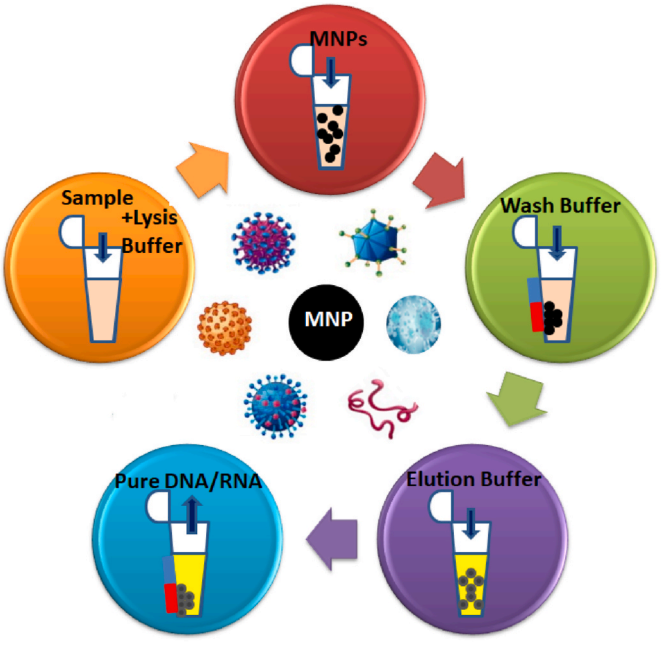


Fig. 4. Schematic procedure for nucleic acid purification by means of MNPs.

Another favorable methodology was developed to isolate RNA of viruses out of contaminated samples of MAVRICS (magnetic-nanoparticle-aided viral RNA isolation from contagious samples). The method consumes accessible reactants, with effortless assemblage within fundamentally established labs. This strategy allows nontoxic, inexpensive, and operative RNA extraction out of diagnostic or green specimens. The aforementioned method opposes kits that are commercially available for detecting influenza, SARS-CoV-2, as well as RSV (respiratory syncytial virus). As this approach is centrifugation-free, therefore continuing and future research will be majored in self-regulating high-throughput of RNA extraction by liquid-handling robots. To put it concisely, MAVRICS has a great potential to develop a qualifying methodology for prevalent community analysis and wastewater management in the present-day and future epidemics [87]. An automatic rapid nucleic acid extractor was developed using MNPs for processing 16 samples instantaneously. This system is simple and friendly to operate and completes the process of nucleic acid extraction in 30 min. The yield and purification of 16 samples from one hepatic cellular cancer (HCC) sample propose that the developed system is stable and reliable [88].

Nucleic acids separation by magnetic nanoparticles revealed several benefits over the challenging methods, consenting to segregate nucleic acids directly from non-prepared samples, with culture media, water, physiological liquids, as well as blood, etc. Practically, sample volumes offer no limitations on this technique and can be taken comparatively selectively and effortlessly even from viscous complex utilizing the capability to alter the magnetic characteristics of nanoparticles [89].

4.2. Enrichment/concentration of target substance

Viruses pose a continuous danger for health globally. Therefore, enriching target analytes rapidly has been critical and essential that are present in low concentrations in complex matrixes to detect the viruses. A methodology was proposed that integrates MRS (magnetic relaxation switching) with MS (magnetic separation) to detect pathogens in single step along with extreme reproducibility and sensitiveness. In this method, magnetic field with strength 0.01 T was applied that part out large MNPs with diameter of 250 nm from small MNPs having diameter of 30 nm. T2 (transverse relaxation time) of molecules of water surrounded by small MNPs was used to read signals in such assays as shown in Fig. 5. The proposed approach assimilates enrichment, extraction, also detection of target analyte in a single step. The whole process of immunoassay was finished within 30 min. It showed improved reproducibility, good sensitiveness, as well as appropriate procedure, consequently offers platform towards POC investigation in comparison to tradition sensors [64].

HAV (Hepatitis A virus) remains primary source that results in hepatitis. Approaches for recognizing HAV are very inadequate. To attain this objective, protamine (P) was bonded to MNPs surface possessing diameter of 20–30 nm covalently followed by chemical reaction that was carried out in three steps. When utilized to concentrate HAV out of milk (40 mL), PMNPs (50 μl) were introduced in sample. After 20 min gentle rotation, there was a capturing of PMNPs by a magnet continued for 30 min. PMNPs that were seized were rinsed by buffer solution of glycine (NaCl-0.14 M, glycine-0.05 M, Tween 20–0.2% (v/v)) at pH of 9. Extraction of HAV-RNA was performed utilizing "QIAamp MinElute Virus Spin Kit" followed by its measurement via simultaneous RT-PCR. This technique presented LOD (limit of detection) equals to 8.3 × 100 PFU (Plaque forming units) regarding HAV present inside milk. This entire process designed for concentration possibly was accomplished within 50 min. This established system has been affordable as well as simple to recognize [90]. Carboxylated MNPs have also been used for immobilization of target; HBsAg (hepatitis B surface antigen) aimed at quick separation magnetically. The selected aptamers were used to develop a chemiluminescence aptasensor based on magnetic separation and immunoassay to detect HBsAg from pure protein or actual serum samples with LOD of 0.1 ng/mL, considerably less than LOD measured by an ELISA (0.5 ng/mL). The concentration of HBsAg is directly proportional to chemiluminescent intensity with range starting from 1 ng/mL to 200 ng/mL [91]. SDA (strand displacement amplification) in combination with magnetic nanoparticles and electrochemiluminescent (ECL) nanospheres (EN), "enrichment−stowage−cycle" approach has been suggested for developing biosensor based on electrochemiluminescence to recognize DNA of HIV. H1-MNP (H1-Capture hairpin DNA) conjugates efficiently enrich as well as isolates DNA out of composite matrix straightly, shortening operational period along with procedure. This process enhanced ECL signals close by 11.3 fold. The signals were more amplified by SDA nearly 3.77-fold. MNPs

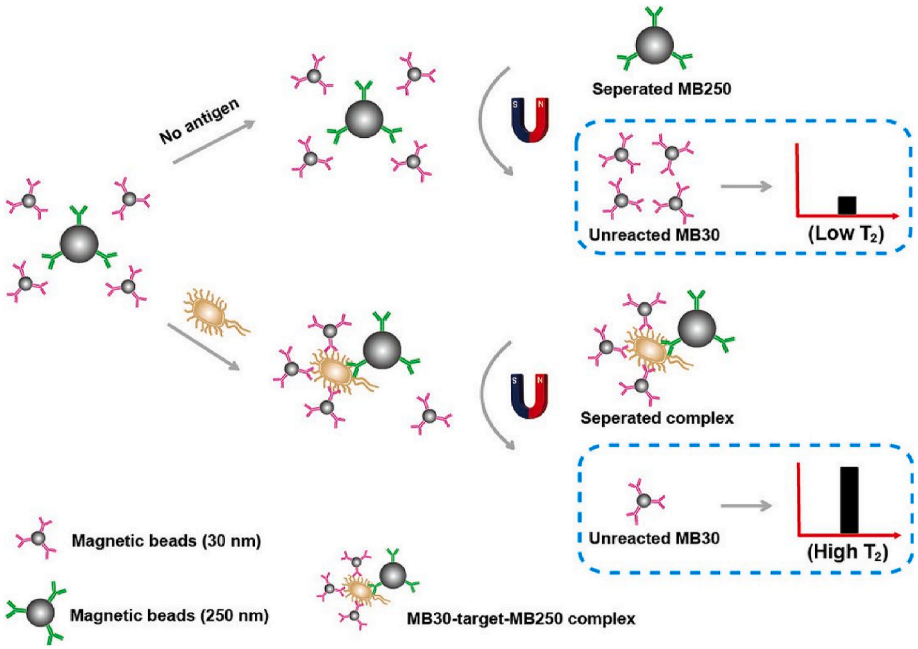


Fig. 8. Process of extracting viral RNA through lysis, binding, washing and elution of samples by means of functionalized nanoparticles of Zinc ferrite (reproduced and modified figure according to Ref. [101]).

incorporation boosted specificness for detection as well as constancy, driving the above-mentioned scheme suitable for real-world utilizations. Efficacious recognition regarding HIV-DNA inside composite samples, for instance in milk, FBS (fetal bovine serum), urine, plus blood) showed its probability for diagnosis on time as well as precise quantification of biomarkers present in actual samples with low concentration [92]. Enriching concerning target compounds, impurities exclusion, in addition to decontamination of recognized analytes offers pronounced accuracy along with opportuneness intended for future research.

Magnetic nanoparticles have also been used for detaching or else separating particles of virus, as an alternative of extraction viral nucleic acid. Enriched particles of virus intensely bounded with MNPs due to the presence of functionalized receptors designed for targeting. Virus particles gained magnetic property after bonding to SPIONs (superparamagnetic iron oxide nanoparticles). Afterwards, virus get detached taking advantage of these SPIONs using magnet coupled with cell-reliant tittering analysis, qRT-PCR (quantitative reverse transcription-polymerase chain reaction) test, in addition, immunochromatographic test strips. Biomimicry of SPIONs enriches virus inside samples to improve virus detection as revealed in Fig. 6 [93].

4.3. Detection of nucleic acid

Effectual RT-PCR analysis necessitates quantifiable nucleic acid removal out of different specimens that maintain extraordinary pureness. Lower efficiency for extraction and quality possibly will have variation in inhibitors of PCR that generates poor signals, resulting in incorrect negative outcomes due to unreliable readouts in the time of amplification. Accordingly, speedy, suitable, and mechanized nucleic acid extraction systems are extremely required for observing and avoidance of infectious diseases [94].

A fast and precise detection technique was developed to investigate RSV and ADV types of respiratory viruses coming out of identical testing analytes. It was comprised of twofold steps: co-extraction of DNA along with RNA taken out of mucus, followed by complicated RT-PCR. The instantaneous nucleic acid co-extraction process established on MNPs and the viral DNA and RNA amplification from mucus technologically advanced a complex RT-qPCR mode. This MNPs-based technique presented improved co-extraction effectiveness regarding DNA as well as RNA, in addition to an evaluation in distinct clinical samples. The time requisite was shortened, and the approach simplified preparation of a sample aimed at PCR analysis i.e. entire preparation of sample besides separation of nucleic acid possibly completed within 30 min. MNPs utilization in addition to prevention concerning centrifugation formed the basis of computerized co-extraction of nucleic acids including RNA as well as DNA. An easy method along with the prevention of using organic solvents and also having displeasing smells mark it appealing to be used for repetitive analytical labs, particularly to detect pathogens responsible for respiratory diseases through complex RT-qPCR. Whereas it indicates initial exploration, more research on clinical specimens is requisite eventually [95].

Silica-coated MNPs are broadly used to extract out of different biological specimens. A vigorous and innovative Fe_3O_4@Silica (silica-coated magnetite particles) was employed to extract RNA from samples of serum obtained from the ZIKA virus. After the synthesis of MNPs, these nanoparticles are functionalized by silica through TEOS (tetraethoxysilane) hydrolysis in a basic medium. By purely dispersing agglomerates of magnetic particles in a solution of GdnHCl (guanidinium chloride), the surface of particles coated with silica was able to bind RNA. Efficacy of extracting RNA had been assessed through removing RNA out of serum taken from ZIKA virus, further monitored via PCR. In addition to the elimination of inhibitors of PCR, statistics specify outstanding recapture of target nucleic acid (RNA). A developed system of silica functionalized MNPs offers economic, operative, and equipped for a scale-up method whose execution is comparable to profitable substitutes to prepare samples regarding DNA along with RNA. The budget required for medical examinations is possibly reduced by hundred times employing practically accessible MNPs conjugated with prepared material aimed at extraction of the virus [30].

A different system for immediate detection of many viruses was suggested. This scheme has verified high efficacy and appropriateness for handling clinical test specimens. In addition, a magnetic isolation method was accustomed through the trial, which started through the extraction of a nucleic acid towards chemiluminescence recognition. On account of the mentioned positive and active adoption of the MNPs, this evaluation can be adapted into an automatic setup for the real-time revealing of numerous infections that will additionally decrease the cost of detection per pathogen. The manipulation of MNPs functionalized with silica for extracting nucleic acid and MNPs functionalized with carboxylic groups in chemiluminescence transformed the scheme to an automatic system to scale-up high throughput strategies. The above-mentioned analysis also provided an alternate way to examine clinical samples in blood screening components [77]. Single-step complex RT-PCR had been conducted for intensifying nucleic acids extracted from the virus. Diverse probes stabilized by amino groups to capture target sequences regarding HCV, HBV, as well as, HIV had been distinctly bound to MNPs surface functionalized by carboxylic groups as shown in Fig. 7. Incubation of these probes functionalized MNPs with RT-PCR products labeled with biotin inside alternating tubes assist in detaining particular sequences of HCV, HBV, else HIV. SA-AP (Streptavidin-modified alkaline phosphatase) gets attached to biotin. Lastly, CL (chemiluminescence) had been measured after addition of AMPPD (3-(2′-spiroadamantane)-4-methoxy-4-(3′-phosphoryloxy)phenyl-1, 2-dioxetane) [77].

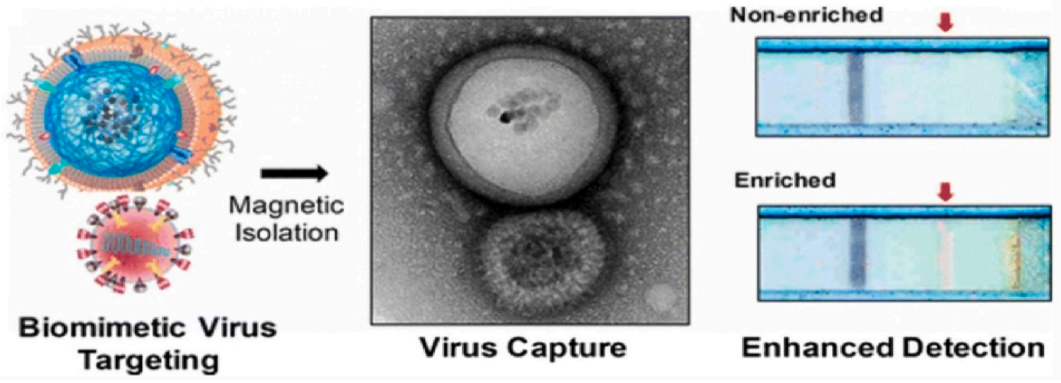


Fig. 5. Representation of MS-MRS sensor. Magnetic beads of 250 and 30 nm diameter precisely grab as well as enrich target analyte forming 'MB250-target-MB30′ sandwich conjugate. Afterwards separation by magnet, T2 signal generated by water molecules surrounding MB30, which are not being reacted, was employed as the readout (reproduced and modified figure according to Ref. [64]).

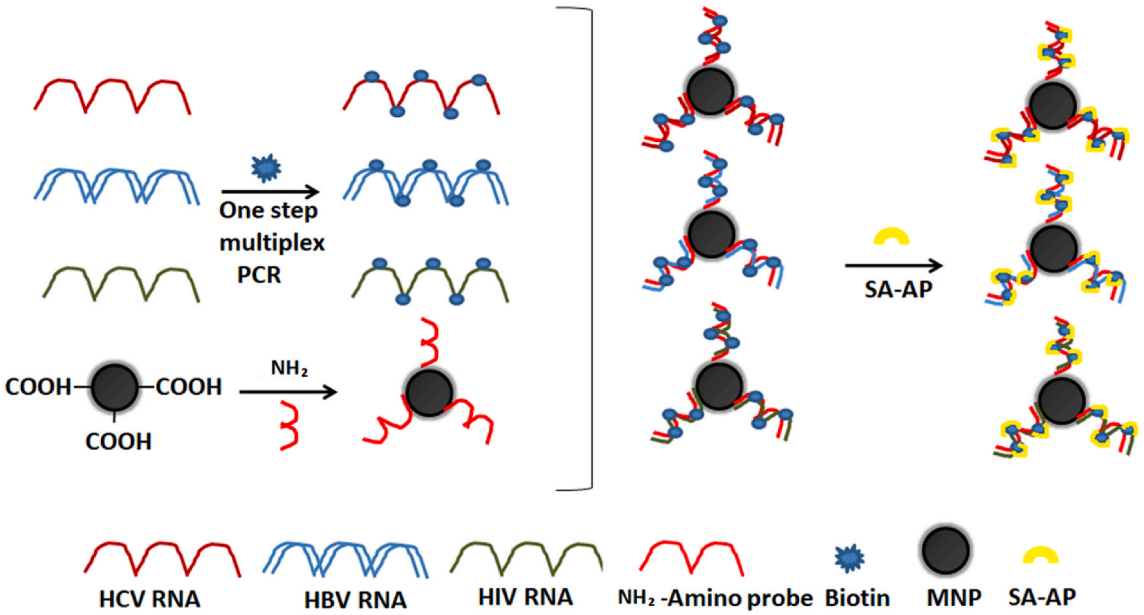


Fig. 6. An illustration representing biomimicry of MNPs that mimic the cell membrane of the host (virus) to enhance the detection (reproduced and modified figure according to Ref. [93]).

Extraction of blue ribbon nucleic acid remains the main feature for genomic research as well as for the biosensors improvement focused towards testing for nucleic acids. RNA of Hepatitis C virus (HCV) and the accelerating number of HCV diseased patients has amplified the interest leading to the enhancement of operative and consistent practices for initial disease detection. This method of recognition of HCV depends on enzyme-free MNPs used for extracting nucleic acids besides measuring CL signal. Particular buffer environments facilitated the adsorption of nucleic acids onto the surface of MNPs. CL reading regarding HCV had been attained by incubation of RT-PCR yields labeled with biotin along MNPs labeled with the probe in addition to SA-ALP (streptavidin-modified basic phosphatase). Consequences permitted positive CL recognition of HCV [83].

Fe_3O_4/SiO_2 (magnetite nanoparticles coated by silica), as well as optimal buffers, have also been used to separate two sorts of genomic DNA including Epstein-Barr virus (EBV) together with hepatitis virus type B (HBV), to further recognize viruses present in serum by PCR. Acquired preliminary statistics specify that Fe_3O_4/SiO_2 nanoparticles delivered improved sensitivity to detect them, in comparison to microparticles of silica-functionalized magnetic particles. Such buffers accompanied by Fe_3O_4/SiO_2 nanoparticles segregate EBV and HBV to detect virus based upon amplification of PCR regarding two-fifty base-pair fragments of "nuclear antigen encoding gene" particular to EBV and four-thirty-four basepair gene fragments particularly to HBV. Efficacy for purification of EBV and HBV employing synthesized nanoparticles came to be more desirable and valuable in comparison to microparticles of Fe_3O_4/SiO_2, commercially available. The time necessary for the isolation of DNA consuming these nanoparticles had been considerably shortened because of the rapid attraction of nanoparticles towards magnets within fifteen to 20 s. While microparticles take 2–3 min. Supplementary experimentations engaging Fe_3O_4/SiO_2 nanoparticles for isolating nucleic acid out from other viral pathogens present inside blood samples are underway [96].

Viral-induced nanoassembly of MNPs was fabricated from monodisperse MNPs bonded to virus-surface-specific antibodies in the existence of particular particles of viruses. They exhibited improved magnetic properties and were distinguished via magnetic resonance methods (NMR/MRI) which exactly permitted highly selective and sensitive viral detection within the composite biological medium for instance suspension of cells, blood, lipid emulsions, cultural media, as well as complete tissue. The established scheme can precisely identify herpes virus-1 in addition to adenovirus-5, at a concentration of 5 particles of virus present in 10 μL, and not requiring PCR amplification and massive preparation of samples. It is also self-regulating, not depending on optical characteristics of the solution, permitting viral detection in compound unclear solutions. The labeled analysis represents a delicate process as compared to contemporary ELISA, also the bonding of virus to surface of solid is not required. Moreover, this technique presents a great potential for detection of HSV and ADV viruses circulation by *in vivo* MRI [97].

Fluorescent MNPs were utilized to identify avian influenza viruses including H1N, H9N2, as well as H7N9 instantaneously. Superparamagnetic nature along with intense magnetic nanoparticle reaction could efficiently trap targets and then separate them requiring no pretreatment of the sample. These MNPs will be used for counting distinct particles aimed at complex detection accurately. The aforementioned process possesses easy steps for amplification of the signal, unusual sensitivity for detection, as well as pronounced perspective to diagnose different diseases at early stages [76].

RT-LAMP (Reverse-transcription-Loop-mediated isothermal amplification) has also been combined with carboxyl modified magnetic nanoparticles for detection of H7N9 RNA of influenza virus. It includes the procedure of CL, where molecules used as probes get bounds to ALP (alkaline phosphate) enzyme modified with streptavidin. Chemiluminescence signal was recorded indicating virus presence inside the sample. The method of extracting viruses gets rationalized by employing this methodology in RT-PCR. It permits better recognition consuming not as much of time. Additionally, it grasps significant potential to detect and analyze viruses, specifically avian influenza virus [98]. An innovative system for POC testing formulated on MNPs was developed for automatic real-time adenovirus detection. The results obtained by this experiment and from commercialized systems were similar, verifying system reliability [99]. An economical immunoconjugate magnetic nanosystem was developed to detect NS1 protein of dengue virus calorimetrically, consuming NS1 antibodies that were attached to MNPs (magnetite) surface covalently. The developed system has ability to identify NS1 in case of infection or reinfection. The given process possibly modified to detect proteins related to evolving infections caused by viruses, in particular existing COVID-19 epidemic [100].

5. Magnetic nanoparticles in diagnosis of coronavirus (COVID-19)

Molecular diagnostics and investigation of pathogenic viruses for instance coronavirus are based on extraction and segregation of nucleic acids. Epidemics at large scale caused worldwide deficiency concerning registered marketable chemicals as well as bio-safe labs for securely achieve analysis. Hence, early detection of nucleic acids is immediately desirable to address the problems.

Currently, detection of COVID-19 based on RT-PCR is comprehensively used. This is a well-timed and accurate diagnostics procedure but is still constrained due to the long duration and extensive manpower necessity. To deal with this difficulty, the modification of MNPs and procedure to extract RNA aimed at probable recognition of coronavirus was reported. Nanoparticles of zinc ferrite had been synthesized using combustion, followed by functionalization with poly (vinyl alcohol) modified with silica and carboxylate. Characterization of prepared MNPs verified properties as well as functionalities at nano-scale. The suggested methodology was able to isolate and extract the viral RNA from some samplings by a computerized system. Taking comfort and skillfulness into consideration, this procedure may pointedly reduce the time of operation regarding existing diagnosis of coronavirus at molecular level [101]. Zinc ferrite (ZNF) magnetic nanoparticles had also been synthesized via economical sol-gel process that was auto-combustive. They were further functionalized by polymers having with carboxylic groups (CPoly) as shown in Fig. 8. Among magnetic nanomaterials, zinc ferrite (ZnF) was selected owing to its extraordinary chemical stability, soft magnetic behavior, easy preparatory methods, and biocompatible nature [102]. In view of influential interactions of carboxylic groups with nucleic acids, modified MNPs enable prompt in addition to prospective RNA adsorption. It is a facile and provident procedure and an efficient alternate for prevalent methodologies [101].

The multifunctional chitosan-coated lithium zinc ferrite MNPs integrated with graphene oxide magnetic nanocomposites (CHLZFO-GO MNC) were well produced by sol-gel auto combustion and ultrasonication. In this method, zinc-doped lithium ferrites were first coated with biopolymer (chitosan) and then incorporated into sheets of GO to introduce carboxyl groups. The prepared nanocomposites were spherical in shape and crystallite sizes were found in the nanometric range (~19 nm–35 nm). The experimental magnetization values are appropriate for the effectual and vigorous extraction procedure of RNA leading to potential detection of SARS-CoV-2 in COVID-19 patients. The protocol for extraction includes a combination of lysis/binding buffer with CHLZFO-GO MNCs in a single step, followed by washing, elution, and to end assembling the extracted RNA for RT-PCR. The CHLZFO-GO/RNA complex can be used directly for RT-PCR reaction without the elution step. Hence, the likelihood of getting false-negative results in RT-PCR protocol can be more reduced. The RT-PCR method combined with these MNC is easy, reasonable, time-saving, and many operatives and thus can be seen as a probable substitute for conventional RT-PCR techniques. MNC-based extraction can be an inventive technology to isolate RNA from swabs for fast COVID 19 tests at a larger scale [103].

The existing epidemic of unusual coronavirus disease pulls wide-reaching fears because of its extensive incubation time and durable contagion. Due to this, there is an undeniable necessity for quick and consistent detection of the pathogens of SARS-CoV-2 to prevent its spread. Magnetic biosensors especially the giant magnetoresistive (GMR) biosensor along with MNPs can be very sensitive and promising biosensing devices for rapid detection of SARS-CoV-2 S-protein and +ssRNA obtained from biological samples (blood, urine, serum, etc.). This is an alternate route to develop for sorting out COVID-19 patients and thus protect the outbreak of COVID-19 to regain a normal pace in the world [104]. The potential activity of MNPs on SARS-CoV-2 and HCV by molecular docking studies was also investigated. The proposed model revealed that iron oxide nanoparticles particularly Fe_2O_3 and Fe_3O_4 interacted efficiently with SARS-CoV-2 S1-RBD (receptor binding domain) and HCV (Hepatitis C virus) glycoproteins, E1 and E2. It was established that Fe_3O_4 made a more stable complex with S1-RBD while for HCV E1 and E2, a more stable complex was made with Fe_2O_3. Thus these revealed interactions to be related to configurational changes in viral structural proteins and succeeding virus inactivation. This showed the potential application of MNPs to control diverse viral infections

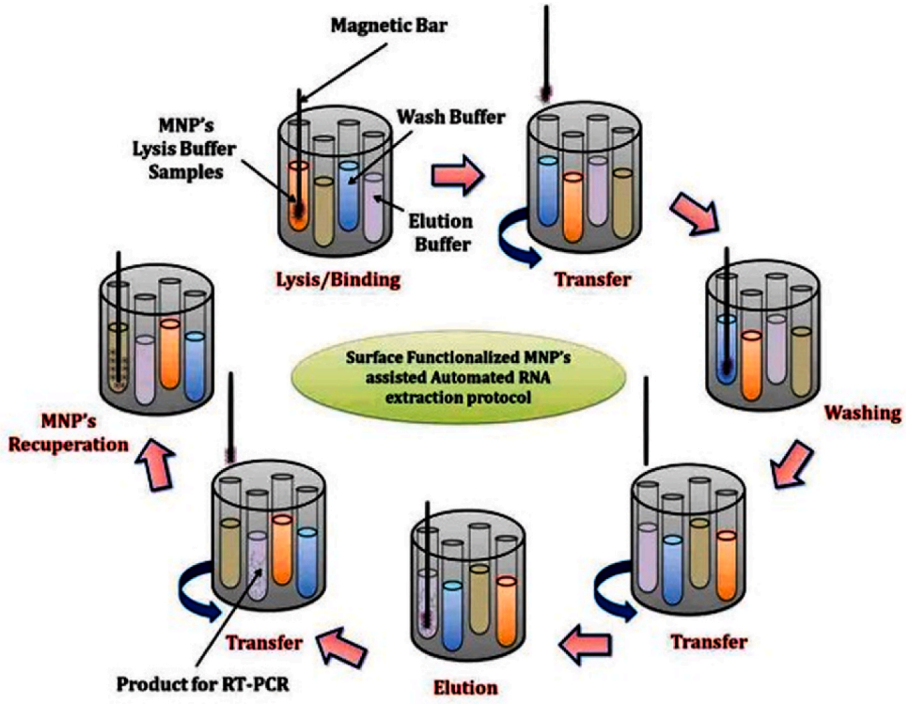


Fig. 7. Probes functionalized with amino groups, to capture target sequences of HCV, HBV, as well as HIV, distinctly bound to MNPs surface-functionalized with carboxylic groups. SA-AP gets attached to biotin. Then, CL was measured after adding AMPPD [77].

[105].

Even though molecular analysis depending on PCR has been extensively practiced in medical analysis presently, still well-timed and precise diagnosis is restricted on grounds of laborious and inefficient operations of these methods. To resolve this problem, pcMNPs were synthesized by functionalizing MNPs with pc (poly (amino ester) bonded to carboxyl groups) for designing method of extraction of RNA based on pcMNPs meant for sensitive identification of SARS-CoV-2, triggering virus for COVID-19 as shown in Fig. 9. This technique involves lysis as well as bonding stages in one step. Prepared complex of pcMNPs-RNA were immediately inserted into successive RT-PCR reactions. The basic route purified viral RNA from compound samples in 20 min exploiting uncomplicated manual way, else automatic upgraded methodology. Through recognizing 2 dissimilar sections (N gene and ORFlab) in RNA of virus, 10-copy sensitivity along with strong relation ranging from 10 to 100,000 copies referring to corona pseudo-viral particles were attained. Advancing from the easiness and exceptional executions, this firsthand method of extraction strongly decreases the restoring time and functioning requirements in existing molecular diagnosis of COVID-19, particularly for the primary clinical diagnostics [94].

Poly-amino magnetic nanoparticles (Poly–NH_2–MNPs) were prepared by functionalizing MNPs by polymer having negative charge to extract and purify RNA of viruses, which possibly be executed for detecting coronavirus substantially. MNPs were synthesized with simple as well as economical co-precipitation technique. This is followed by process of hydrolysis consuming APTES (3-aminopropyl triethoxysilane). The poly (amino ester) was prepared through polymerization of diacrylate-amine employing 1,4-butanediol diacrylate and 6-aminocaproic acid. In last, Michael addition methodology was used to coat amino-MNPs (NH_2-MNPs) by the poly (amino ester) [106]. Entire coating of MNPs with polymer to yield Poly–NH_2–MNPs gives preferred negative charge to extract RNA properly, as displayed in Fig. 10. Synthetic procedure allows implementation around 50,000 RT-PCR tests simultaneously to detect coronavirus. However, no reduction in signal obtained by RT-PCR was observed with increase in nanoparticle concentration present in solution. So it is requisite to perform additional investigations by altering or modifying size, type, in addition to coating of MNPs with the aim of getting an optimized material to enhance the response of application in qRT-PCR. But this systematic protocol can be used as a benchmark for extracting RNA of better quality afore their possible execution in PCR. This provided a solution to the recognition along with regulation of eruptive spread regarding novel coronavirus although budget restrictions of the country in addition to availability/facility of laboratory or chemicals throughout this confirmed: "International Public Health Emergency" [107].

In another method, the SARS-associated coronavirus gene was detected by consuming functionalized MNPs along with a PCR assay. First functionalized silica-coated SPIONs were used to capture and enrich target complementary DNA (cDNA) of SARS linked coronavirus from the mixture of target cDNA and non-target cDNA. Moreover, the enriched target cDNA were amplified via common symmetry PCR. After that, it was particularly isolated from the double strands PCR products by application of silica coated SPIONs again. Lastly, the amplified target cDNA was detected using silica coated fluorescent nanoparticles as signaling probes. The results indicate that the target cDNA can be examined effectively with LOD of 2.0×10 (3) copies. Non-specific amplification was also inhibited through this method. Additionally, this procedure is fast and promising for viral detection [108].

Consistent biosensing based on MNPs is one of the most promising approaches for rapid and highly sensitive detection of biomolecules to control the outbreak of SARS-CoV-2. In another approach, SARS-CoV-2 with was detected using functionalized MNPs through measuring their magnetic response in an AC magnetic field. For this method, mimic SARS-CoV-2 containing spike proteins and polystyrene (PS) beads are utilized for experiments. Functionalized MNPs were employed as sensors to detect a mimic virus consisting of 100 nm PS beads integrated with SARSCoV-2 spike proteins (Fig. 11). Experiments on AC susceptibility (ACS) spectra and magnetic particle spectroscopy (MPS) signal of samples with different mimic virus concentrations were performed. Results showed that the binding performance between mimic SARS-CoV-2 and functionalized MNPs enhances the effective Brownian relaxation time and changing the MPS signal. Suggested approach permits the quick detection of mimic SARS-CoV-2 with LOD of 0.084 nM (5.9 fmole). This method has pronounced potential to design low-cost and POC device for sensitive diagnostics of SARS-CoV-2 [109].

6. Conclusions and perspectives

Currently, nanotechnology focuses to develop strategies and protecting from catching the virus in the first place. The usage of nanoparticles, for extracting nucleic acids, enrichment of target analytes, in addition to detection of nucleic acids, offers the huge possibility to advance process that is presently accessible for diagnosis, or else advancement regarding different nano-based technologies. They both are urgently prerequisites for multiplexed detection and early diagnosis of diseases. The excellent features of nanoparticles, comprising their strong electrochemical and optical properties, biocompatibility, controllable sizes, and cost-effectiveness play a vital role in a broad range. These properties can be easily tuned by surface functionalization using various substrates, offering incredible potential for practical applications. Nanoparticles used for viral diagnosis offer a more sensitive, specific, economic, and easy to use diagnostic kits for detecting the pathogenic virus in comparison to conventional techniques. Conventional diagnosis and detection approaches typically (i) need a long duration between collection of sample and result interpretation, (ii) have low sensitivity (iii) experimental processes are difficult, (iv) lack specificity, and (v) may have high false-negative rates. However, nanoparticles-based tools have the potential to overcome these

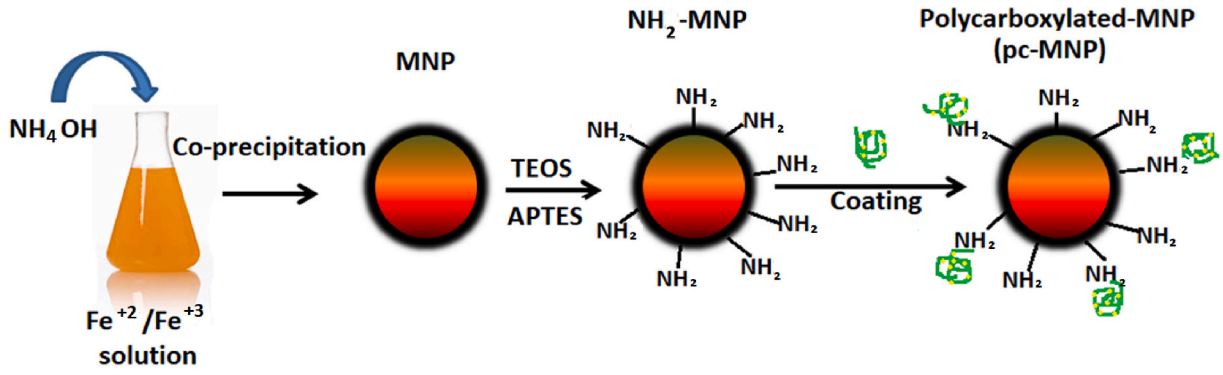


Fig. 9. Schematic of pcMNPs synthesized by functionalization of MNPs with pc (Poly (amino ester) having carboxylic groups). It is designed for extracting RNA of virus to precisely recognize COVID-19 virus [94].

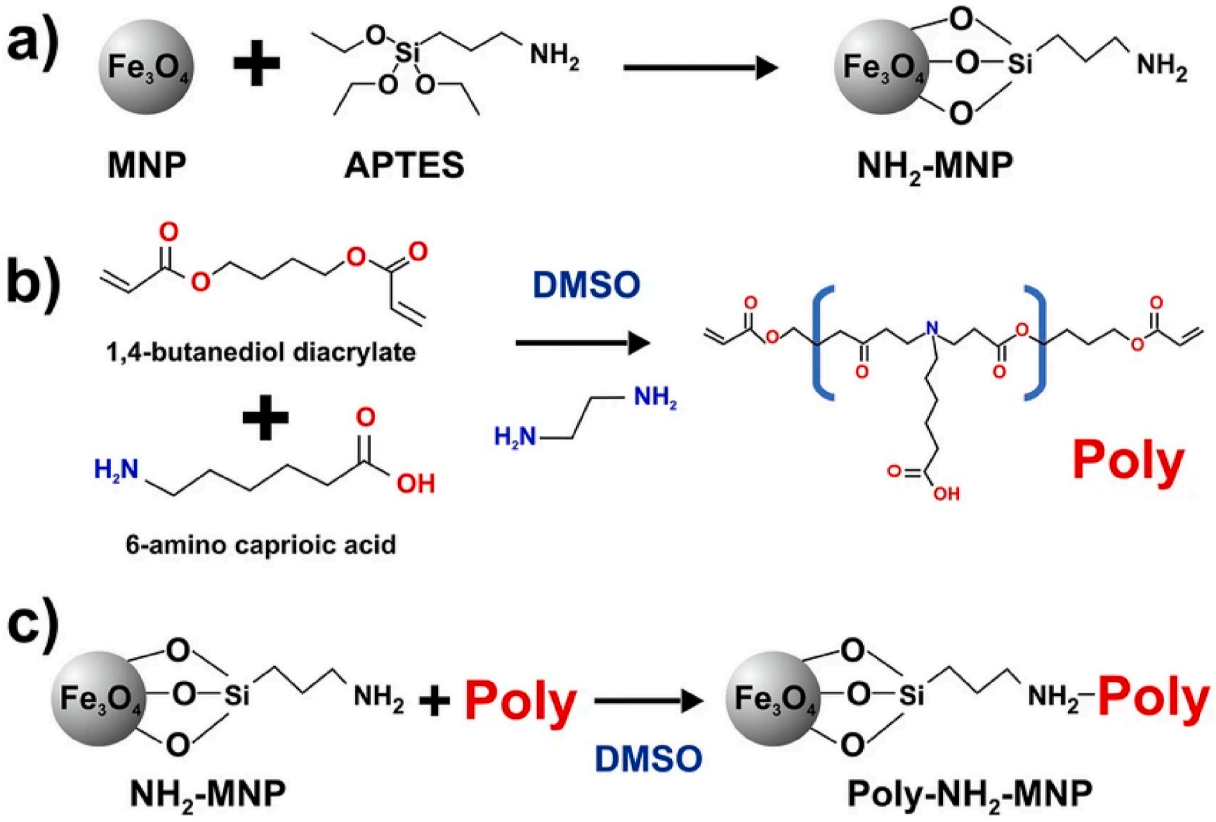


Fig. 10. Schematic representation of the MNP synthesis. **a)** Synthesis of amino-magnetic nanoparticles (NH_2-MNP), **b)** Poly (amino ester) is synthesized by the combination of 1,4-butanediol diacrylate + 6-aminocaproic acid at DMSO solution via diacrylate-amine polymerization, and **c)** The final amino-magnetic nanoparticles coated with the poly (amino ester) material are synthesized by following a Michael addition methodology (reproduced and modified figure according to Ref. [107]).

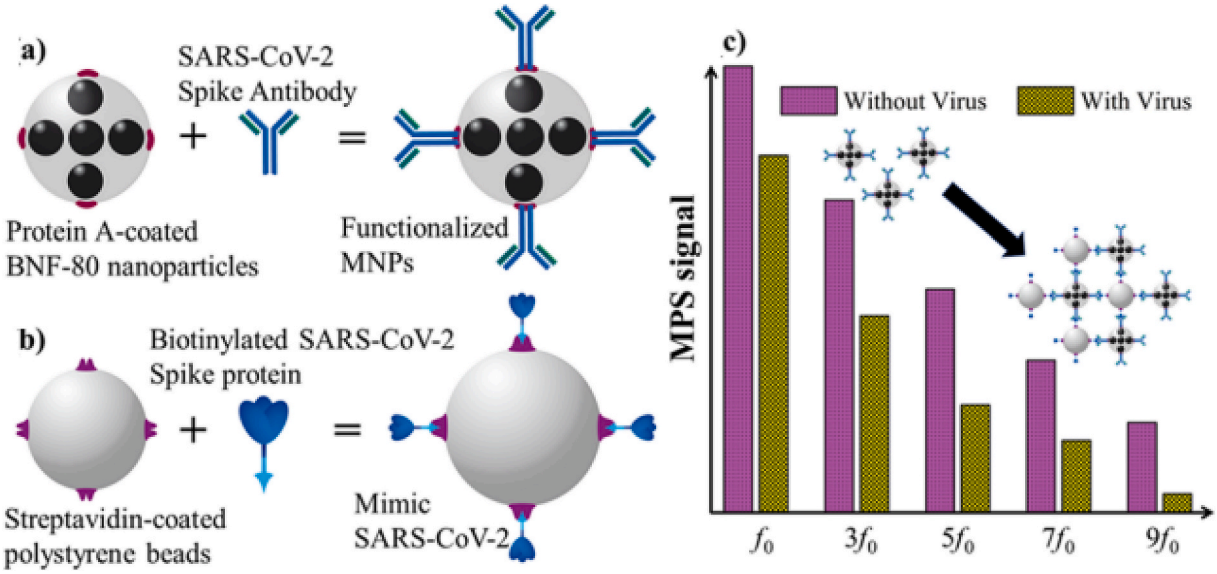


Fig. 11. a) Schematic of functionalized MNPs, **b)** schematic of mimic SARS-CoV-2, and **c)** schematic of the MPS signal with and without mimic virus (reproduced and modified figure according to Ref. [109]).

limitations. They play an important role in rapid and sensitive diagnosis of several viral infections that allow early treatment and monitoring of positively identified patients, therefore saving suffering and lives. The application of MNPs for diagnosis has seen some positive examples including viral extraction and detection. These magnetic nanomaterials are the results of development made in the production and characterization of these materials in addition to appropriate functionalization. The opportunity to have diverse surface chemistry to provide functional groups and surface ligands on these MNPs makes these nanomaterials directly relevant for viraldiagnosis. The combination of extraction, enrichment, and detection permits the lowering of detection limit expressively. Magnetic nanoparticles for viral extraction to

detection characterize a significant alternative involving progressing exploration. MNPs enable development of analytical devices that can recognize biologically selective substances present inside complex matrix sample with no long treatments of samples. These devices produce highly specific responses in the form of signals that are produced due to biological recognition using MNPs [34].

Despite countless benefits possessed by MNPs in comparison with orthodox techniques, research about toxicities as well as potentially harmful nanoparticle impact is further necessary. Thus engineered magnetic nanoparticles unified with conventional antiviral properties through multi-functionalizing are favorable materials designed for research in the biomedical field in addition to clinical practice. Certainly, an excessive effort is a prerequisite for presenting transportable as well as reusable strategies having the ability to categorize viruses along with better precision and accuracy. Ultimately, progress in the field of nanotechnology will turn out to be an evident invention for medication for ceasing the spread of diseases caused by viruses and also offer a healthy and better life to possibly infected patients. The integration of magnetic nanoparticles into a disposable lateral flow test platform is also in focus to screen patients for the COV1D-19 virus. Recently not any lateral flow test particular to coronavirus strain is available. They do not require capable technicians as well as supplementary lab apparatus to be used as screening equipment, assisting grouping of individuals. Researchers are soon to propose more precise, economical, also handy kits for diagnosis to identify viral pathogens including the novel coronavirus relying on exclusive properties of MNPs. Efforts are also in the process to explore the potential of MNPs to obtain better sensitivity, selectivity and simultaneous detection. They considerably participate to detect, diagnose, and understand, in addition to treat diseases because of viruses. It also assists to reduce viral eruptions in future.

MNPs need to be upgraded to meet application necessities rapidly for extraction and detection in magnetic field externally applied. Stability regarding MNPs directly affects its application therefore MNPs should be modified with suitable functionality that increases surface compatibility along with efficiency for bonding ligands. Presently, due to limited available information in regards to basic as well as clinical examination, current options for treating and managing coronavirus includes new nanoparticles and therapeutic drugs. Though, attention is required before forming any premature elucidations because still scientific testings in clinics are under way, plus temporary experimental statistics are not being available yet. Need for an accepted as well as effectual vaccine to treat existing coronavirus, aim is tracking along with diagnosing diseases easily in early phases. This forces medical precaution to move from reactive to proactive form. For early detection of viral infections, an urgent need is to develop new, fast, effective, and applicable technologies in terms of real-time diagnosis. The incorporation of MNPs with molecular diagnostic systems can be used to develop fully-automatic and closed nucleic acid detection assays. With enhanced sensitivity and less required time to detect, there would be prominent impact in biomedicine, detection at clinical level, together with other biomedical areas. Nevertheless, as researchers working with nanoparticles, we consider that only by operative and close by association between various stakeholders of society will we be able to combat current pandemic as well as to react rapidly to any future global health emergencies.

In future prospective, FDA-approved-MNPs should be employed into clinical trials for viral diagnosis. Moreover, due to their biocompatibility, MNPs should be used for manufacturing antimicrobial fabrics for instance coats, gloves, masks, head nets, bed sheets, overshoes, and, pillow covers. This will be an advanced measure to control viral infections in hospitals. There is a need of simple and cost-effective nanomaterial-based products for the prevention, diagnostics and treatment of viruses. Through research and development, nanotechnology could help in refining diagnostics sensitivity using only a small amount of biological sample. The conventional methods could also be improved to activate host immune response against the viruses. One of the main challenges is to guarantee the safe usage of nanomaterials. The employment of biodegradable nanoparticles is important to ensure their usage inside human body. *In vivo* studies should also be more investigated to understand the toxic behavior of nanoparticles for long term use in human body. An operative methodology for large-scale synthesis with accurate control over size, surface modifications and other parameters at minimum cost is critical particularly for early diagnosis. We visualize that nanotechnology is a powerful tool to combat ongoing COVID-19 and more investigations are essential to add new systematic and methodological knowledge to increase the use of magnetic nanomaterials in management the COVID-19 outbreak and future epidemics.

Credit contribution statement

Sumera Khizar: Writing and editing review. Abdelhamid Elaissari: Editing and finalizing review. All authors have read and approved the final manuscript.

Credit author statement

This is a declaration on behalf of my all co-authors that the manuscript is our original work and has not been published or accepted for publication elsewhere. Sumera Khizar drafted the original manuscript. Abdelhamid Elaissari assisted in editing and finalizing the manuscript. All authors have read and agreed to the published version of the final manuscript. We have cited the names of the authors whose published materials are used in the manuscript. We hope that the submission of this proposal would be considered for acceptance in **TALANTA.**

Declaration of competing interest

The authors declare that they have no competing financial, professional, and personal interests that might have influenced the presentation of the work described in the manuscript.

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Appendix A. Supplementary data

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