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EMERGENCE OF NANOTECHNOLOGY AS A NEW DELIVERING SYSTEM IN CLINICAL SETTINGS

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*Abstract***— The possibility of obtaining novel antimicrobial drugs through size reduction, as well as an increase in multidrug resistance among microbes, have prompted us to search for newer therapy options. The evolution of nanotechnology exhibits wealth of ideas for humanity. This results in boundless innovation for the scientific community. Nanotechnology breakthroughs and their applicability in microbiology, healthcare, diagnostics, and therapeutics have shown significant impact on human being during twentieth century. Nano-compositions or nanoparticles have recently received a lot of attention because of their unique and novel properties, such as high surface to volume ratios, drug encapsulation and drug delivery, early detection of diseases and unique optical properties which help to eliminate the limitations of traditional therapeutic and diagnostic offerings. Nanomaterials are rapidly being employed in new products and systems, having significant implications in a wide range of fields such as in medical field, electric industries, automobiles, cosmetics, space and defense. Nanotechnology has enabled the detection, identification, and imaging of chemical and biological substances, as well as the detection of biomarkers of disease aetiology. This article provides a broad overview of existing nanotechnological developments in clinical settings including the medication administration, bacterial identification, tissue healing, cancer diagnostics and treatments, COVID-19 therapy and nano-vaccines, with the objective to set up systematic strategies in productive lines of future research for the applications in clinical settings.**

Keywords—**Clinical settings; COVID-19; Nanotechnology; Nanoparticles; Nanostructures**.

I. INTRODUCTION

Independently, the field of nanotechnology and clinical microbiology have augmented technology and science respectively. Although, the advent of several secondary health issues heightened the need for multidisciplinary research that united nanotechnology and clinical microbiology. Astonishingly, there is a two-way reciprocity between them: first is the employment of Nano technological techniques for clinical microbiology and second is appropriate application of microorganism in the creation of therapeutically significant nanoparticles [1]. The fusion of these two domains have resulted in novel approach in addressing the health-related issues. Nanotechnology is that branch which includes nanoscale science and entails manipulating matter on a size of order 1 to 100 nm. The word “nano” comes from the Greek word “nanos” which means “dwarf” [2]. Nanotechnology advancements began in 1959. Physical, chemical and biological properties of materials differ significantly from those of individual atoms and molecules at nanoscale. The goal is to understand better and to create materials, technologies and systems that uses new features [3]. Novel nanotechnology advancement and their application in medicine and pharmaceuticals have now transformed considerably. The chronological developments that took place is summarized in Table 1 [4].

The applicability of most prevalent pathogen detection techniques in evolving countries is restricted due to high cost and short shelf life of reagents. The Enzyme linked immunosorbent assay (ELISA) and Polymerase chain reaction (PCR) both necessitate considerable sample preparation and have lengthy turnaround times and delaying time responses [5]. Eventually, this led to characteristic usage of nanotechnology in clinical microbiology. The distinctive traits of nanomaterials like magnetic, luminescent, electrical and catalytic capabilities allow for the progression of diagnostic assays that are inexpensive, rapid and accessible without the requirement of the sample preparation [6]. Microbiology is influenced by development of nanoscience in numerous ways. It enables the investigation and imaging of a process down at the molecular level. It aids in detection and evaluation of molecular identification and self-assembly patterns [7]. Microbiologist employ nanotechnological approaches in areas like changing nanoscale structures, visualizing single molecules or fragments and discovering structural organization in microbes that are alive [8].

Table 1 Chronology in nanotechnology

Year	Events of advancement	Ref.
1959	First perception and notion of nanotechnology by Richard Phillips Feynman	[4]
1974	Norio Taniguchi invented the word "nanotechnology".	
1981	Discovered Scanning tunneling microscope (STM): used for imaging biological surfaces with resolution to the sub-molecular scale.	
1986	Discovered Atomic force microscope (AFM): used to photograph cellular structures and monitor the structural dynamics of cell walls in response to stress.	
1991	Invented carbon nanotubes.	
2002	Magnetic nanoparticles were employed to demonstrate tumor hyperthermia regression in mice.	
2007	First human trial was done by Dr. Johanssen and co-scientists for the treatment of cancer by hyperthermia.	
2011	Epoch of molecular nanotechnology started.	

Nanostructures and nanoparticles

A nanostructure is defined as an entity with at least one dimension of 100 nm or less. Nanotechnology have put a lot of emphasis on new frontiers of nanoscience's application to various fields related to medical biology [9]. Various nanoscopic carriers have been developed to produce positive diagnostic outcomes. They include bio-based nanoparticles, dendrimers, nanocantilevers, nanopores, nano emulsions, liposomes, polymeric conjugates are the few examples of nanostructures [10]. Figure 1 illustrates various types of nanoparticles.

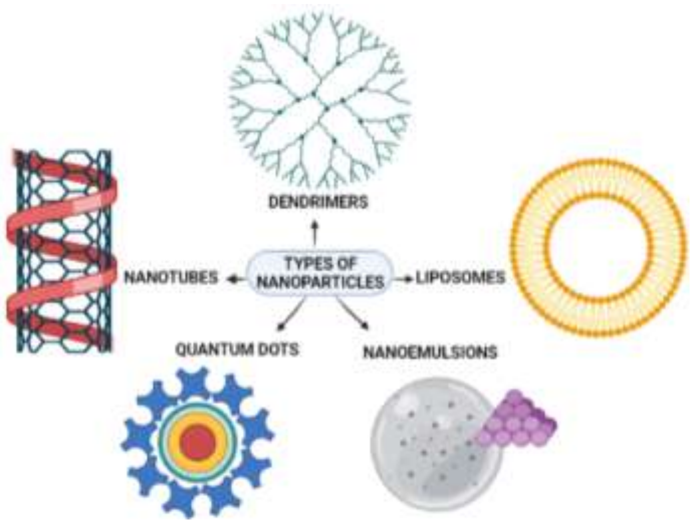

Fig 1. Types of nanoparticles

A list of nanoparticles is presented with their medical applications in Table 2. In drug delivery, nanoparticles are covered with targeting agents (e.g., conjugated antibodies), which circulate through the blood arteries and reaches the target cells, where drugs are delivered directly into the cells. Some nanoparticles have antibacterial efficacy against different types of bacteria [11].

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Table 2 Different types of nanoparticles and their wide applications

Nanoparticles	APPLICATIONS	Ref.
Nanotubes-bucky tubes	Eradicates pathogens, particularly drug-resistant bacteria like methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant Enterococcus, and multidrug-resistant Mycobacterium tuberculosis (MDR-TB)	[10]
Liposomes	Utilized as a vehicle for medications such as foramphotericin B, which is used to treat fungal infections, to deliver medications to specific cells and given IV, or IM but not orally (since it would be destroyed in the GIT).	[10]
Dendrimers	Imaging, antibacterial capabilities (against MRSA and Pseudomonas), immunization, and cancer therapy.	[12]
Quantum dots (QDs)	Imaging agents in business (through production of fluorescence light), used as biosensors capable of detecting infections. For example- Carbon quantum dots have remarkable bactericidal action against E. coli, S. aureus, P. aeruginosa, and Salmonella enterica serovar Enteritidis bacteria.	[10]
Nano-emulsions	Properties are bactericidal and viricidal and used for hydrophobic medication administration.	[20,21]
Microbivores	Used in septicemia, which involves in the removal of blood. For example - Vasculomobile microbivores follow cytokine gradients and collect at sites of infection, thus increasing their microbicidal efficiency.	[10]

Dendrimers

They are branching molecules with a defined size, shape and a high degree of molecular homogeneity. They possess highly functionalized terminal surface and both hydrophobic and hydrophilic molecules can be encapsulated by them. Dendrimers plays a very important role against the microbial infections and diseases. For example, P. aeruginosa is one of the most important biofilm-forming bacteria, with a significant influence on several chronic conditions such as cancer and cystic fibrosis [12]. P. aeruginosa possesses a bacterial specific lectine (LecB) that binds to fucose, a mucin found in the epithelial mucosa, and hence plays an important role in biofilm formation. In this scenario, several peptidic dendrimers coated with fucose-derived groups suppresses P. aeruginosa biofilm development by preventing pathogen agglutination and serving as antimicrobial nanocarriers [13]. Sonawane and co-workers [14] demonstrated that a lipid-dendrimer hybrid nanoparticle (LDHN) technology may efficiently administer vancomycin against MRSA infections.

Nanocantilevers

These detectors have been successfully implemented in detecting hazardous diseases as well as viral particles in the air. These silicon biosensors have the capacity to vibrate at different frequencies when germs cling to them on a regular basis [15]. Nanocantilevers (thicknesses ranging from 10 nm to 90 nm) provide significantly greater detection limits and need less sample. Studies have shown that using nanocantilevers to identify specific DNA sequences may eliminate the need for the DNA-amplification phase requirement by microcantilevers and other approaches [16]. Nanocantilevers have previously shown promising results in detecting antibiotic resistance in Escherichia coli [15]. As the nucleic acids, signal microbiome-related skin conditions (e.g., atopic dermatitis) are present at low quantities in skin-related samples, nanocantilevers has been employed to identify them [17].

Nano-emulsions

These are nanoscale emulsions used to enhance the delivery of active medicinal substances. These are the thermodynamically stable isotropic systems in which an emulsifying agent, such as surfactant and co-surfactant, is used to combine two immiscible liquids into a single phase [18]. Electrostatic attraction between the cationic charge of the emulsion and the anionic charge of the target microbe drives the nano-emulsion particles to fuse with lipid-containing organisms. When a sufficient number of nanoparticles bind to the pathogens, a portion of the energy contained inside the emulsion is released [19]. The active component and the energy released both disrupt the pathogen's lipid membrane, causing cell lysis and death. The Michigan Nanotechnology Institute for Medicine and Biological Sciences has created a nano-emulsion that exhibits broad spectrum action against bacteria such as E. coli, Salmonella spp., S. aureus, certain enveloped viruses (HIV, Herpes simplex), fungi (Candida, Dermatophytes), and B. anthracis spores [20]. According to Rinaldi and co-workers [21] studies showed that chitosan coated nano-emulsions (NEs), extracted from Thymus vulgaris and Syzygium aromaticum essential oils (EOs) were observed to be a viable and effective intranasal formulation against multi-drug resistant gram-negative bacteria like methicillin-susceptible Staphylococcus aureus and carbapenem-resistant Acinetobacter baumannii and Klebsiella pneumoniae.

Liposomes

Liposomes are specialized delivery vehicles that enhance the capacities of active medicinal substances in a variety of ways. Lipid nanoparticles are liposome-like structures that are specifically designed to encapsulate a wide range of nucleic acids (RNA and DNA), making them the most widely used non-viral gene delivery method. With their flexibility and adaptability, they are one of the most well-established nanomedicines in cancer treatment and bioimaging [22]. Liposomes have a lipid bilayer structure that protects and solubilizes both hydrophilic and hydrophobic molecules, similar to the biological cell membrane. It can be utilized to deliver antibiotics to their intended target [23]. For example, Rapid liposome-based methods, have been used to detect cholera and botulinum food-borne toxins. For prophylaxis against group A Streptococci, a cationic liposomes encapsulating lipopeptide-based vaccine (nano-vaccine) has been created that may be given by intranasal passage [10].

Gold nanoparticles

Gold nanoparticles (AuNPs) are distinct from gold particles in that the latter is a yellow inert solid, whereas AuNPs are a wine-red substance with antioxidant characteristics. AuNPs can be synthesized in a variety of sizes ranging from 1 nm to 8 μm. AuNPs can interact with the epidermal barrier, increasing the delivery and penetration of high-molecular-weight active drugs [24]. Gold and silver nanoparticles are the potential nanotools that are frequently utilized for the transport of biomolecules, particularly thiol-containing polymers such as nucleic acids and antibodies. For example, when subjected to laser light, AuNPs had a greater bactericidal impact on S. aureus. Gold nanoparticles have been discovered to be effective against Gram-positive Corynebacterium pseudotuberculosis which causes bacterial infection characterized by external abscesses or ulcerative lymphangitis/cellulitis [25]. Gold nanoparticles have been investigated as a possible medication and gene delivery method in cancer treatment. The ability to create a stable combination of vancomycin and gold, as well as its efficacy against several strains of Enteropathogenic Escherichia coli (EPEC), Enterococcus faecium, and Enterococcus faecalis (including vancomycin-resistant strains), has also been established. Similarly, ciprofloxacin complexed with gold nano-shells demonstrated significant antibacterial action against E. coli. [26]. On the other hand, the actual potential of gold nanoparticles has yet to be discovered in future intensive research effort.

Methods used in nanotechnology and their applications in clinical microbiology

The storming use of methods in Nanotechnology demonstrates how biological information may be obtained simply, rapidly, cheaply and then evaluated, vastly expanding the potential for attaining preventative medicine. Nanotechnology is an emerging field of study that aims to influence matter at the atomic and molecular level, hence nanomedicine has become one of the most important fields of nanotechnological study since it is undeniably beneficial to contemporary medicine [27]. Nanotechnology allows diagnosis at the molecule and single cell levels, and so represents a significant advancement in molecular diagnostics.

Nanoarray

Gold or silica nanoparticles supported on thin silicon layers can be used to create nanochips for the rapid detection of biomolecules. Nanochips can test samples in a very short period of time because of its tiny size. In conjunction with PCR detection techniques, the nanochip device allows quick identification of a wide range of clinically relevant mycobacterial species. In this Nano-gen, Nanochip Molecular Biology Workstation is used, where the probes are aimed against the relevant mycobacterial species like M. tuberculosis, M. avium or M. triplex [28]. The probes selected represents the epidemiology of mycobacterial infections in hospitals, but the panel of probes can clearly be amended based on the patient group to whom diagnostic investigation is assigned [29]. Nanoarray spots have been used for screening of very small number of individual proteins. It has been utilized to identify HIV 1 viruses in plasma [30].

Quantum dots (QDs)

The breakthroughs in quantum dot synthesis, first was discovered in 1980 by Alexic Ekimov and Louis E. Brus, boosted fluorescence imaging for both in vitro and in vivo applications. Quantum dots, which are semiconductor nanocrystals are used as fluorescent dyes in biology and medicine [31]. The surface of quantum dot can be freely adjusted to meet the demands of the application purpose and they have been widely used in biological science research. For example, a selective biosensing of S. aureus was outlined, utilizing quantum dot and further was modified with chitosan, which used avidin-conjugated quantum dot to detect ferritin in human serum by an avidin–biotin method [32]. The findings of the preceding research demonstrated the optical benefits of quantum dots in biological detection [33].

Nano-sequencing

This is a real-time single-molecule sequencing approach in which a DNA sequence of interest is passed through a nanopore. A nanopore is essentially an extremely small hole with a nanoscale diameter. Nanopore sequencing is a subset of a bigger area that use nanopores for molecule and biomolecule measurement and detection [34]. Nanopore sequencing has been applied for observing and management of outbreaks of new infectious diseases, the identification of drug-resistant pathogenic microorganisms, and the identification of disease-related microbial community characteristics [35].

Nanobots

A nanobot is a tiny machine that is programmed to do a specific task with nanoscale accuracy. Alternative names for them include nanorobots and nanoids. There are various applications of nanorobots in the fields of medical procedure, nervous system science, dentistry, haematology, microbiology, malignancy therapy etc. [36]. Nanorobots measures the amount of nitric oxide synthase (NOS) in the cerebrum and if the level of NOS exceeds a certain threshold (such as 100 proteomic signal transduction), it indicates the presence of an intercranial aneurysm. Nano dentistry uses nanobots dentrifices (dentifrobots) as mouthwash or toothpaste, as it covers all subgingival surfaces, metabolizing any trapped organic matter into harmless and odorless fumes. Pathogenic bacteria found in tooth plaque are discovered and eliminated using correctly equipped dentifrobots [37].

Applications: Current status and future scope for nanotechnology in clinical microbiology

Nanotechnology has been the biggest tool in the field of medicine and its development. Nanomaterials have served in various ways as the biomedical applications such as skin ulcer healing, bone tissue engineering, and smart drug delivery systems. It plays a very important role in identification of bacteria, viral detection, vaccine designing, cancer diagnosis and even in COVID-19 treatment. Figure 2 illustrates various therapeutic uses of nanotechnology.

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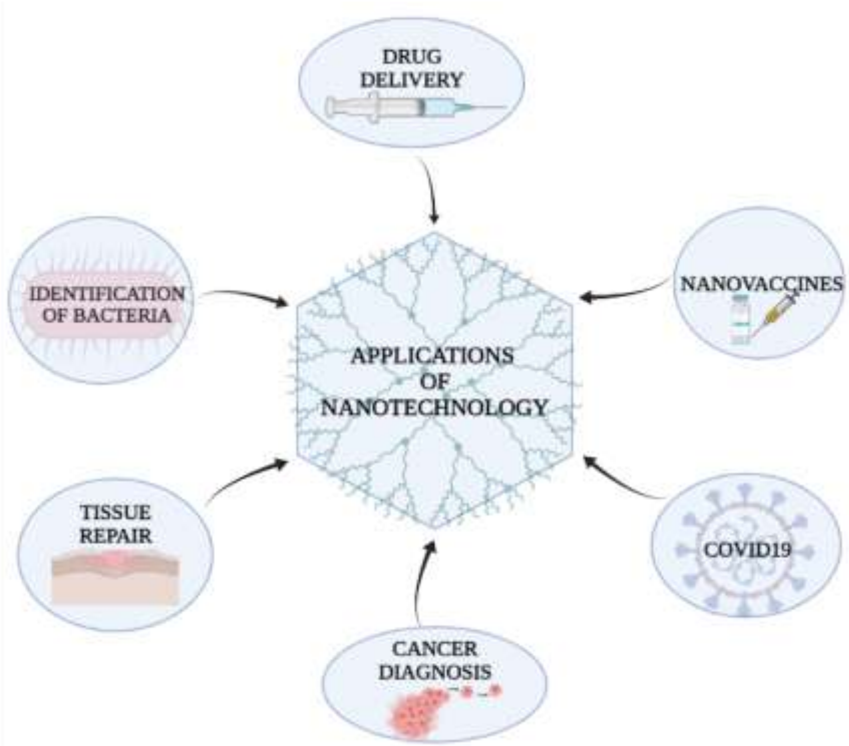

Fig. 2 Clinical applications of nanotechnology.

Drug delivery
Nanotechnologies are delivering a significant contribution in this field by developing innovative mechanisms of drug administration. Some of these strategies have proven to be beneficial in a clinical environment and nowadays these are currently being employed [38]. An ideal medication delivery system consists of two components: drug release control and targeting capability. By selectively targeting and eliminating dangerous or malignant cells, side effects can be drastically avoided, and therapeutic efficacy can be assured [39]. Furthermore, regulated drug release has the potential to decrease the side effects of drug. Because of their tiny size, nanoparticle drug delivery methods have fewer irritating responses and increased penetration into the body, thus allowing intravenous and other administration routes. For example, doxorubicin, a very lethal medication, may be administered directly to tumor cells using liposomes (Doxil®) without damaging the heart or kidneys [40].

Identification of bacteria
In medical identification, rapid and precise detection of harmful microorganisms is critical. Most traditional discernment procedures have disadvantages such as limited sensitivity or a delay in obtaining results. Effective approaches have previously been studied, such as ferrofluid magnetic nanoparticles and ceramic nanospheres. For example, a bio-conjugated nanoparticle-based bioassay for in situ pathogen quantification needs just 20 minutes to detect a single bacterium. Sensing of Phage Triggered Ion Cascade (SEPTIC), is another nanotechnology-based approach for bacteria detection. It employs a nano equipment with two antenna that function as electrodes. SEPTIC provides rapid detection and identification of live pathogenic bacteria on the scale of minutes, with unparalleled specificity [41]**.** Optical biosensing of bacteria has been made feasible with the use of quantum dots and metallic nanoparticles. For example, Bacillus subtilis, has been found at a concentration of 2.5fM (femtomolar) i.e. (2.5×10^{-15} M), whereas Salmonella enteritidis was observed at a concentration of 0.2fM [4].

Tissue repair
Tissues are group of cells which works in such a manner that it gives some functionality to the body. There are four types of tissues – connective tissues, nervous tissues, muscle tissues and epithelial tissues. Joining of tissues is important to repair the cuts, skin, cartilage in joints etc. This can be done by using chromophores or dyes as absorbers of laser power. Gold nanoparticles plays an important role in tissue repair as it is quite stable and can be tuned to desired laser wavelength in infra-red region. Gold particles absorbs the heat and this heat is used to repair the tissues, without any stitches reducing surgery pain and infections [42].
As our society's population ages, the avoidance of skin illnesses, as well as the improvement of overall body, have become a requirement. As a result, while the usage of biodegradable and nature-oriented nonwoven tissues have altered the structure of pharmaceuticals, the natural polysaccharides polymers are increasingly being created and sold in cosmetics such as beauty masks. The use of chitin nanoparticles and nanocomposites in tissue regeneration and skin rejuvenation is becoming more common [43].

Cancer diagnosis
Cancer is a significant cause of mortality and a major public health concern worldwide. Up to 2018, it had been predicted that 18.1 million new cancer cases may be diagnosed and 9.6 million cancer-related deaths may occur [44]. Cancer is a disease characterized by uncontrolled cell growth that spreads from a primary focus to other sections of the body, eventually killing the patient. The early detection is possible due to nanotechnology-based diagnosis. Targeted drug delivery is essential as it does not kill the healthy cells unlike chemotherapy [45]. Fluorescent, nano porous, water soluble and biocompatible silica nanoparticles loaded with camptothecian, taxol, toxic drug (such as β-lapochene) are successfully delivered in animal models to cancer cells and destroyed [46].
Phototherapy is another method in which gold coated with silica nanoparticles are used to target the cancerous cells. To improve cancer imaging, a second near-infrared (NIR) window (NIR-ii, 900-1700 nm) has been created with greater tissue penetration depth, spatial and temporal resolution. In addition, the production of silver-rich Ag_2Te quantum dots (QDs) with a Sulphur source has been claimed to enable for the observation of higher spatial resolution pictures throughout a broad infrared range [47].

COVID-19
COVID-19, usually occurs due to SARS-CoV-2 (severe acute respiratory syndrome) infection, has been influencing the health of human being for about more than last one year. An epidemic of SARS-CoV appeared in early 2000 and similarly spread of MERS-CoV causing infection happened in early 2010 [48]. Researchers in nanomedicine have investigated the molecular processes of vectors in order to build delivery methods that may be employed in a number of applications. Nanoparticles (NPs) and viruses operate on the same size, making nanotechnology a potent tool for vaccine development and immune-engineering. Nanoparticles can mimic the structural and functional features of viruses, and nanomedicine could be the greatest option to new vaccine development methods [49]. SARS-CoV-2 entrance and life cycle can be targeted with NP treatment. The S protein is the most critical element in preventing SARS-CoV-2 from entering through the initial membrane fusion step. Therapeutic NPs can thus be created to hinder the S protein from attaching to host cells, preventing SARS-CoV-2 entrance. Dexamethasone, is the first SARS-CoV-2 treatment medication, created by utilising nanotechnology. Therapy of SARS-CoV-2 infections employing an anti-edema and anti-fibrotic mechanism has

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been documented, and successful administration and treatment may be predicted using different nano-formulating Dexamethasones [50].

SARS-CoV-2 causes infection on the mucosal surface of the eye or nasal cavity, making mucosal therapy the most effective treatment option. Because of the cavity's rich capillary plexus and huge surface area, delivery through the nasal cavity is not only straightforward and affordable, but also non-invasive, and the nanoparticle is swiftly absorbed. The surface charge, size, and shape of the NPs are significant parameters to consider when optimizing the mode of administration to the nasal cavity, and they play a vital role in ensuring successful and safe therapy [51].

Nano-vaccines

Vaccination have proven to be the most successful method of eradicating infections. Evolving medication resistance against infectious illnesses and chemotherapy-related toxicities in cancer necessitate the creation of an emergency vaccination to rescue humanity. Nano-vaccines have the potential to increase targeted delivery, antigen presentation, activation of the body's innate immunity, a high T cell response, and safety in the fight against infectious illnesses and cancer [52].

For example, Yersinia pestis, the causative agent of pneumonic plague, causes a fatal illness when not treated. Presently, there is no FDA-approved vaccine against this infection; however, USAMRIID (United States Army Medical Research Institute of Infectious Diseases) has produced F1-V, a recombinant fusion protein that has been demonstrated to elicit protection against pneumonic plague. Many F1-V-based vaccine formulations need prime-boost vaccination to produce protective immunity, and reports of fast induction of protective immunity are scarce. Another is the polyanhydride nanoparticle-based vaccinations (i.e., nano vaccines), which due to their dual role as adjuvants and delivery vehicles have also proven to improve the immune responses [53]. Figure 3 shows the general benefits of nanotechnology by improving the identification of bacteria and virus, visualization of drug interactions, reducing time for identification of new drug and increasing throughput.

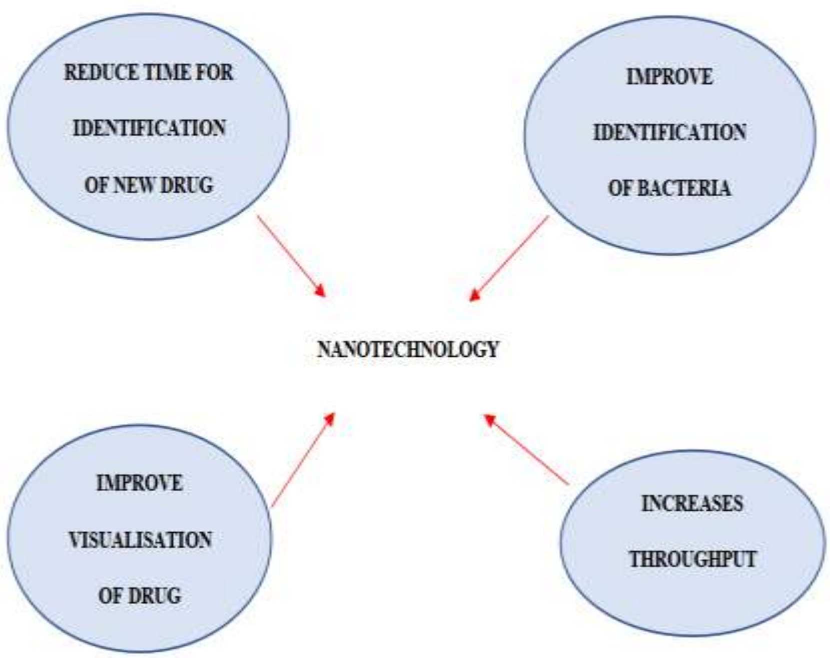

Fig. 3 Benefits of Nanotechnology

II. CONCLUSION

There is no question that nanotechnologies have aided the improvement in patient's quality of life by offering a platform for advancements in the microbiological, biotechnological, medicinal, and pharmaceutical industries. They have also made healthcare operations easier, from diagnosis to therapeutic treatments and follow-up monitoring. There is a continuing effort to discover and develop innovative nanomaterials to enhance illness diagnostics and treatments in a focused, accurate, powerful and long-lasting manner, with the ultimate goal of making medical procedures more personalized, less expensive and safer. It is proposed that nanotechnology can play a critical role in the improvement of medical microbiology by curing infections, boosting immunity, and saving countless lives. In conclusion, there is a need to emphasize on the fundamental benefits of nanotechnology as well as the limitations in clinical application. Due to the complicated scenario created by COVID-19, it is thought that the current platform will need to be adjusted in order to improve the efficiency of research in numerous disciplines throughout the world. As a result, nanotechnology and nanomedicine can act as viable solutions in the research and innovation prototype.

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