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Review Article



Nanorobots in Medicine: Advancing Healthcare through Molecular Engineering: A Comprehensive Review

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Abstract

Nanotechnology, particularly nanorobotics, has emerged as a transformative force in modern medicine. Nanorobots, designed at the molecular scale, hold promise for a range of medical applications, including targeted drug delivery, early disease diagnostics, minimally invasive surgeries, and precise infection control. Their unique ability to interact with biological systems at the cellular level opens avenues for significant advancements in treatment protocols, potentially overcoming current limitations in traditional therapies. This review delves into the development, mechanisms, and diverse medical applications of nanorobots, highlighting their structural components, energy sources, and propulsion methods. Additionally, we explore specific case studies in cancer treatment, infection control, and surgical innovations, assessing both the advancements and challenges associated with nanorobotic technologies. The goal is to present a comprehensive overview that underscores the potential of nanorobots to revolutionize patient care and set the stage for future research in this burgeoning field.

Introduction

Nanotechnology

The ability to produce vast structures with essentially novel molecular organization by working at the molecular scale, atom by atom, is the very core of nanotechnology [1]. It describes the creation, manufacturing, and use of materials that fall within the nanoscale (< 1 nm - 100 nm) range. Nanoparticles' distinct physical and chemical characteristics, especially their small dimensions and large surface-to-volume ratio, enable this technology to get past obstacles and reach biological systems and molecules [2]. Scientists anticipate gaining the benefits of nanotechnology's use in nearly every aspect since they believe it to be the science of the future [3,4]. By increasing the precision, sensitiveness, and speed of medical examinations, nanotechnology has the capability to completely transform the diagnostics industry [5]. Many medical difficulties, including illness diagnosis, drug discovery, tailored medical procedures, cancer therapy, pharmaceutical discoveries, and the newest medical equipment and procedures, are currently improving the usage of nano-biotechnology, from diagnosis to treatment [6]. In the field of delivery of drugs, new research approaches

are growing because of the emergence of nanotechnology. Chronic intracellular infections could gain benefit from the use of drug delivery systems created with nanotechnology [7].

Nanorobotics

The field of nanorobotics, which is a subfield of nanotechnology, studies the design, programming, manufacture, and control of nanoscale robots [8]. A multidisciplinary topic that is expanding quickly is nanorobotics, which deals with the creation and application of devices the size of molecules [9]. Fundamentally, nanorobots are nanodevices that are used to treat or protect humans from infections. The world's first nanorobot computing system for single-cell study and manipulation was developed by Professor Toshio Fukuda, who was the founding father of micro/nanorobots around the early 2000s [10]. Carbon is the primary element utilized in nanorobots due to its strength and inertness in the form of fullerene and diamond. The additional elements, which can be used on a nanoscale, are silicon, fluorine, sulphur, nitrogen, oxygen, and hydrogen. To prevent the human immune system from attacking them, they often have an external passive diamond covering [11].

They are created to precisely carry out specific functions or tasks on nanoscale dimensions of 1 nm - 100 nm [12]. Target identification, medication administration, and minimally invasive surgery are some of the main medical uses for nanorobots [13,14]. It is believed that the toxicity issue caused by excessive medication usage would be resolved by determining the exact delivery ability of micro/nanorobots within the intended region [15]. The creation and application of small robots, or nanorobots, capable of carrying out surgical operations with extreme efficiency and precision is known as surgical nanorobotics [16].

Scope and purpose

The goal of the review on nanorobots in medical applications is usually to explore the new opportunities of these tiny devices in the field of medicine. Designing and building nanorobots, understanding their processes of action, and using them for targeted medicine administration, illness diagnostics, and therapy are all part of its goal. Through tailored biosensing, the paper highlights how nanorobots might improve imaging methods and facilitate early illness identification in diagnostics. It looks at their capacity for accurate medication administration, reducing adverse effects, and optimizing therapeutic efficacy. The paper addresses the prospect of nanorobots to carry out minimally invasive surgical operations, enabling increased accuracy and quicker recovery periods. Highlighting the developments in nanotechnology, evaluating the present level of research, talking about the difficulties and constraints in using nanorobots in practice, and speculating about potential future routes for their development are the goals of the review. The review's ultimate goal is to inform and promote additional research in the area by highlighting the revolutionary possibilities of nanorobots in enhancing patient outcomes and transforming medical procedures.

Development and mechanism of nanorobots

Design and fabrication of Nanorobots

Material used in designing a nanorobot: The biocompatibility of components was the main factor taken into account while designing nanorobots, which operate at nanoscale sizes inside tumor tissues and cells. The majority of materials used to make nanorobots are biocompatible or biodegradable. When their functions are completed, these biodegradable compounds can disintegrate or vanish. Nanoparticles should be able to do a variety of precise functions in the interim, such as detecting the existence of tumor cells or tissues, delivering and releasing nanocargoes in response to physical signals, identifying specific disease biomarkers, detecting changes in local pH and temperature, and more [17-20]. The nanorobot's body will be made of carbon nanotubes because of their inherent ability to absorb near-infrared light

waves, which are harmless when they pass through human cells. To prevent collisions, the nanorobot's body is equipped with ultrasonic sensors. Flagella motors, a type of rotary motor with remarkable torque generation capabilities, power a nanorobot by propelling an extended, slender, and helical filament that extends multiple cellular structures into the surrounding medium. These aid in the cell's decision-making process based on changes in the proportion of vital nutrients in the environment [21].

Components of nanorobots: A nanorobot's many parts include its power source, fuel buffer tank, detectors, motors, manipulative devices, computers onboard, pumps, pressure tanks, and structural support. A nanorobot's substructures include:

- A. Payload:** A little dosage of medication or substance is contained in this empty space. The medication might be delivered to the location of disease or injury by the nanorobots moving through the blood.
- B. Small camera:** The nanorobot could have a small camera. When moving the nanorobot through the body by hand, the user may control its direction [22,23].
- C. Electrodes:** The electrode on the nanorobot might use the blood's electrolytes to create a battery. By creating an electric current and heating the cancer cells to death, these projecting electrodes may also be able to destroy the cells.
- D. Lasers:** These lasers have the potential to burn cancer cells, blood clots, and arterial plaque [23].
- E. Ultrasonic signal generators and microwave emitters:** These are used to kill cells, such as malignant cells, without breaking them. A nanorobot might destroy the malignant cell without rupturing the cell wall by utilizing ultrasonic signals or precisely calibrated microwaves to dissolve the chemical connections within the cell. As an alternative, the robot may heat the malignant cell sufficiently to kill it by emitting microwaves or ultrasonic signals.
- F. Swimming Tail:** Nanorobots enter the body by propulsion. Movement is accomplished by the motor, and mobility is achieved via manipulating arms or mechanical legs. The software used to simulate nanorobots in a fluid environment where Brownian motion predominates is called control design. To find the target molecules, the nanorobots are equipped with chemical sensors [24].

Types of nanorobots:

- A. Pharmacyte:** This nanorobot has dimensions ranging

from one and two micrometers in size. Using the transmembrane injector mechanism, the payload held in onboard tanks of the nanorobotics system can be injected straight into the cytosol or released into the proximal extracellular fluid, depending on the needs of the mission [25].

- B. Microbivores:** Often referred to as nanorobotic phagocytes, microbivores are nanorobots that mimic artificial white blood cells. The diamond and sapphire microbivore is a spherical device with a main axis diameter of 3.4 μm and a minor axis diameter of 2.0 μm . It is composed of 610 billion structural atoms that are properly aligned. It breaks down into smaller molecules after trapping the bloodstream infections. Microbivores' primary job is to use phagocytosis to absorb and break down bloodstream infections. It takes 30 seconds for a microbivore to complete a full cycle of phagocytosis [26].
- C. Respirocyte:** This artificial red blood cell-related nanorobot is an oxygen carrier. Endogenous serum glucose is used to generate the power. This artificial cell can administer acidity and provide tissues with 236 times greater amounts of oxygen every unit volume than red blood cells (RBCs) [27].
- D. Clottocyte:** According to theoretical design, a mechanical platelet or clottocyte that is artificially created should achieve hemostasis in around one second [28]. It is a 2.5 μm -diameter, spherical, serum-oxyglucose-powered nanorobot with a compactly folded fiber mesh within. To effectively stop the bleeding, every mesh would be positioned on the one next to it and draw in the red blood cells. In comparison to the normal hemostatic mechanism, clottocytes respond 100–1000 times quicker [26].

Preparation method of micro/nanorobots: The two primary manufacturing approaches for micro/nanorobots are top-down and bottom-up. These include the roll-up process, laser direct writing 3D printing technology, and physical vapor deposition techniques (direct deposition and grazing angle deposition). Wet chemical synthesis and template electrochemical deposition technologies are part of the bottom-up approach, and they will be discussed individually below:

- A. Physical vapor deposition technology:** It is necessary to do physical vapor deposition in a very clean vacuum environment. The primary procedure involves converting the large target into gaseous molecules and atoms, which are then deposited to create nanofilms on the sample surface. It encompasses electron beam evaporation, vacuum thermal evaporation, and magnetron sputtering. Direct deposition and grazing angle deposition are the two primary categories of physical vapor deposition. The Janus microsphere robot is typically processed using direct deposition, which involves tiling the microsphere on the substrate surface and directly depositing a functional film material on the top layer of the microsphere. The functional film is unable to be deposited on the bottom half of the microsphere due to blockage, allowing the formation of the Janus microsphere robot [29]. A physical deposition method with a dynamic tilt angle is the grazing angle deposition technique. Gaseous atoms block their own surface diffusion because of the self-shadowing effect, and real-time modification of the deposition angles may be used to construct complex nanostructures.
- B. Self-winding technology:** This technique involves progressively depositing multiple layers of distinct materials. During this process, various stresses are preset using the material's strain difference, and the asymmetric stress is then released following the wet etching of the sacrificial layer. Ultimately, the self-coiling structure spontaneously coils into a spiral or tubular shape when under stress. Mei, et al. [30] created a range of tubular micro/nanorobots with distinct material components by using self-coiling technology to achieve the coiling of diverse inorganic compounds (Pd/Fe/Pd, TiO_2 , ZnO, Al_2O_3 , SiN/Ag, and C) films. Furthermore, Zhang, et al. [31] used Reactive Ion Etching (RIE), wet etching, and multi-step photolithography to remove prestress from InGaAs/GaAs/Cr composite microscrew robots.
- C. Direct writing with laser technology for 3D printing:** Direct Writing with Laser The optical polymerization effect is the foundation of 3D printing technology, which is capable of processing any 3D microstructure with high precision. Functional elements (Ni, Fe and Fe_3O_4) may then be physically vapor-deposited or adsorbed to successfully drive micro/nanorobots. By using femtosecond laser polymerization, Li, et al. [32] were able to create fishtail-like micro/nanorobots and use physical vapor deposition of Pt to create bubbles that drive themselves in hydrogen peroxide. In particular, bubbles may jet in parallel thanks to the fishtail's multichannel, significantly increasing the microrobot's speed and thrust.
- D. Electrochemical template deposition technology:** Using a redox reaction, metal or alloy is deposited from the matching salt solution using electrochemical template deposition technology. Because of its low cost and ease of use, electrochemical deposition is

a great method for producing huge quantities of micro/nanorobots. Different auxiliary templates may be chosen to deposit different micro/nanorobots in diverse forms, such as spiral, rod, and tubular. For electrochemical deposition, the most used auxiliary template is porous alumina membrane (AAO). For the purpose of target metal accumulation, a metal electrode layer was specifically sputtered onto the surface of AAO prior to electrochemical deposition, and it was thereafter placed into the electrolyte. Following a redox reaction, the micro/nano structures that were deposited were produced. After that, the deposited AAO was placed in solutions of sodium hydroxide and nitric acid, respectively, to eliminate the metal electrodes as well as templates. The micro/nanorobots that had been prepared were finally gathered. Gao, et al. [33] created hollow cone-shaped micro/nanorobots using porous aluminum film. The robots were self-driven and created by breaking oxygen peroxide jet bubbles that passed via metal Pt in the cone-shaped cavity.

E. Wet chemical synthesis: The primary goal of wet chemical synthesis is to use chemical reactions to reduce the target material's compound solution to simple structures like spherical, rod-like, and peanut-like. The management of the structure thus produced is comparatively low. To create a magnetic peanut-like micro/nanorobot, Lin, et al. Combined FeCl_3 , NaOH , and Na_2SO_4 using the hydrothermal synthesis technique in an electric oven set at 100°C for seven days. The rolling and rolling motion modes were achieved by the micro/nanorobots when they were powered by a magnetic field that was external. Additionally, Janus (Si , TiO_2) rod-like self-electrophoresis micro/nanorobots were made using the wet method by Dai, et al. [34].

Mechanism of action of nanorobots

Micro/nanorobots may move collectively as well as alone. The driving mode will have an impact on the biocompatibility, controllability, and speed of movement of micro/nanorobots, which will impact their use in biological beings. The proactive motion of micro/nanorobots primarily depends on converting a local chemical (such as H_2O_2 , urea, etc.) Or physical energy (such as light, ultrasound, magnetic fields, etc.) Or by microorganisms or cells (such as sperm, etc.) Toward mechanical propulsion in order to overcome the difficulties in low Reynolds fluid [35].

A. Chemical propulsion: Myosin and other protein biomotors in nature catalyze the breakdown of adenosine triphosphate, also known as ATP to provide intracellular propulsion. Motivated by them, during the last ten years, a range of micro/nanorobots made of catalysts have shown a high level of propulsion via

chemical processes. Among them, the catalyst's job is to react with the fuel on the robot's surface, and the inert substance is employed to build the asymmetric structure. The simplest and most extensively researched fuel is H_2O_2 . In addition to using materials like their own platinum (Pt) to drive or employ self-electrophoresis mechanisms, micro/nanorobots may also catalyze the breakdown of H_2O_2 to produce bubbles, which will help them move [36,37]. High H_2O_2 concentrations are potent and inhospitable to living things. Thus, alternative in-situ fuels other than H_2O_2 must be developed in order to achieve practical applications, particularly when chemical driving is utilized for driving micro/nanorobots in biological systems; that is, the raw materials should be natural components in biological fluids. For example, self-propulsion can be achieved by combining biodegradable zinc or magnesium with the stomach's acidic environment to produce hydrogen, leaving behind a non-toxic byproduct [38]. And a catalytic process by substituting an enzyme for Pt, allowing a range of biomolecules, like glucose or urea, to be used in lieu of the fuel [39].

B. Physical propulsion: Since the majority of external field-driven micro/nanorobots run on light, ultrasonic, or magnetic fields rather than fuel, they are more versatile in terms of control movement and are biocompatible and sustainable. Setting up acoustic settings is not that difficult. Without causing harm to the human body, sonic waves may travel across solid, liquid, and air media, or deep into biological tissue, activating micro/nanorobots from the outside. The photoreactive materials used to build the light-driven micro/nanorobot primarily consist of photocatalytic, photorated, and photothermal materials. These photoactive materials are capable of absorbing light energy to start photocatalytic, photopolymerization, and photothermal conversion events when exposed to light [40].

C. Biological propulsion: Bio-driven micro/nanorobots are mostly bio-mixed microbots composed of human components and living microorganisms (cells). Sperm and bacteria are examples of microbes that may be employed as engines for propelling bio-mixed microbots because they can merge with somatic cells, which greatly increases the safety and biocompatibility of micro/nanorobots [41]. This capacity allows sperm to propel itself via whiplash. An example of a bio-mixed microrobot system is a four-arm, printed in 3D magnetic tubular microstructure that uses motion sperm cells as an energy source and medication carrier. By encapsulating large quantities of medications in the sperm membrane, this sperm hybrid micro/nanorobot

can shield the pharmaceuticals from the effects of enzyme breakdown and bodily fluid dilution, which is not possible with purely synthetic micro/nanorobots or other vectors [42]. *E. coli*, often known as *Escherichia coli*, is another frequently utilized biological driving source. To finish the loading and targeted release of medications, Alapan, et al. Utilized *E. coli* as a power source in conjunction with magnetically coded red blood cells, which were controlled by the magnetic field utilizing their regulated motion [43].

Energy sources for nanorobots

The two driving modes for nanorobots are passive drive and active drive [44]. The driving components are what allow a nanorobot to move and operate. The former is employed for bodily entrance and nanorobot control, whereas active drive powers the nanorobot using a membrane, pumps, electric nanomotor, or onboard molecular motor [45]. The work requires a sufficient energy source because energy is lost during movement, running, and information transmission; this runs counter to the nanorobot's size restriction. Energy may be obtained internally from microchemical cells and transformed forms like ATP motors, fuel cells, and so on. Two types of external energies are further distinguished: one uses contact to disperse energy as current or light, while the other uses an onboard converter to transform external energy [44].

Applications of nanorobots in medicine

Numerous functions related to diagnosing, tracking, and treating critical illnesses can be carried out by medical nanorobots. The human body has precise places and targets to which these nanorobots may deliver medications. The following are some possible uses for nanorobots: Gene therapy, drug administration, body monitoring, dentistry, surgery, cancer diagnosis and treatment, delicate procedures, diagnostics, and controlling infections [46].

Diagnostics

Micro/nanorobots have demonstrated strong capabilities in the areas of sensing detection, detoxification, and purification in recent research. Controllable driving features allow microrobots to actively hunt for things to be cleaned, resulting in a significant increase in the efficiency of detection and removal [47-49].

A. Early disease detection: It is anticipated that nanorobots would facilitate minimally invasive surgery, medicinal treatments, and novel diagnoses [50,51]. A novel computational and analytical method was presented to support nanorobot research and development [52,53]. Biomolecular computing, genetic advancements, and nanoscience methods can all be used to improve medicine through biological nanorobots.

Nanodevices for manufacturing and positioning mechanosynthesis of rigid materials were introduced [54,55]. The viability of biocomputers, a viable precursor to future nanoprocessors and nanorobots, has been proven by recent advancements in biomolecular computing [56]. Given the ability of nanorobots to move through blood vessels, they can aid in early illness identification and medication administration [57]. When used as medication transporters for timely dose regimens, nanorobots enable the chemical components to remain in the bloodstream circulation for extended periods of time as needed [58,59]. Target identification and medication delivery can be aided by programming nanorobots equipped with chemical nanobiosensors to detect varying amounts of beta-catenin and E-cadherin as medicinal targets in both primary and metastatic stages [60-62]. For the identification and actuation of medicinal targets by nanorobots in another type of brain therapy, chemical signals can also be helpful. With more effective neurotransmitter delivery, the nanorobot may help guide potential immunotherapy therapies and aid in the early detection of Alzheimer's disease [63,64]. Early cancer detection and target-specific drug/gene delivery are two of the top research areas where nanomedicine will be essential. Effective target treatments are among the most recent developments in drug delivery that are utilized in pre-symptomimetic and diagnostic procedures [65].

B. In vivo imaging: At a penetration depth of 2 mm, the micro/nanorobot is easily identified in the *in vivo* environment. Its position in a mouse vein is tracked in real-time using the technique of optical coherence tomography imaging, which gives feedback on the micro/nanorobot's movement *in vivo* [66]. Numerous methods, including radiography, fluoroscopy, and CT scans, are based on X-ray imaging. Fluoroscopy appears to be the most effective method among these for localizing nanorobots. Navab, et al. have utilized it for visual servoing techniques and needle orientation control in animal investigations [67]. The way acoustic waves interact with human tissue is the basis for ultrasound imaging. Ultrasound imaging finds extensive usage in medical settings due to its non-invasive nature. It has little negative health consequences and offers affordable real-time imaging. Nanorobots may be manipulated via ultrasound imaging. Among the difficulties and drawbacks of ultrasonic imaging are its inability to pass through the atmosphere and its propensity to scatter off bones. Ultrasound imaging technologies can only penetrate a few millimeters into the human body, which limits their scanning area [68]. The micro/nanorobots were found in the mouse's belly during a single-photon emission

Tomography scanning that followed the epithelial imaging. For micro/nanorobots, magnetic resonance imaging is an alternative to photoacoustic imaging. The spiral microcones robot, which is made using spirulina microalgae in magnetite suspension, has extremely smooth magnetism from a straightforward immersion technique. Due to the benefits of *in vivo* fluorescent imaging, the spiral robot demonstrated magnetic resonance signals, intrinsic fluorescence, natural deterioration, and optimal cytotoxicity without modifying its surface. It can track noninvasively in deep organs or superficial tissues using magnetic resonance imaging and autologous fluorescence, and it can move steadily in a variety of biological fluids. Mice were given subcutaneous and abdominal injections, and magnetic resonance imaging revealed a micro/nanorobot group in their stomachs [69]. They possess microchips with human molecules superimposed on them. When the molecules identify an illness, an electrical signal is transmitted from the chip. Additionally, they can be utilized to track blood sugar levels [70]. Ultra-small, ultra-paramagnetic iron oxide nanodevices coated with biomolecules are employed in therapeutic settings. Clinical Diagnosis Importance of Nanodiagnostics Particles are utilized to identify cancer cells. Certain antigens or target molecular indicators on the particles attach to the positive cells and cause a particular signal that can be picked up by Magnetic Resonance Imaging (MRI). The microscopic particles are safe to inject into the patient's bloodstream. A rising number of people are interested in using nanomaterials for biological imaging because of their diverse inherent physical features [71,72]. In order to offer anatomical details and to monitor the therapy response in real-time, nanoparticles of magnetic iron oxide have been employed extensively as MRI contrast agents for tumor imaging [73,74]. The fluorescence for *in vitro* research, imaging is the method of choice since it is quick and offers real-time imaging. Although it offers extremely high sensitivity and resolution in 2D, nanorobot localization in 3D might be difficult. Nanorobots must typically have their surfaces modified further for this technique to work, and it can only penetrate to a certain extent into human tissue. This technique has been widely applied to nanorobot tracking *in vivo*. Applications in ophthalmology include oxidative stress management, intraocular pressure measurement, choroidal new vessel treatment using nanoparticles, preventing scarring following glaucoma surgery, treating retinal degenerative disease using gene therapy, prosthetics, as well as regenerative nanomedicine [75]. Due to their biodegradability, biocompatibility, and ability to be precisely regulated

by the base pairing of the nucleotides, multilayer films and DNA-based capsules hold considerable promise [76]. It is hoped that these DNA capsules will be used to diagnose a number of illnesses with distinct recognized biomarkers, including cancer.

Drug delivery

DNA is used to create the hexagonal barrel-shaped nanorobot, which can carry a range of payloads. Two "locks" made of short strands of DNA called aptamers, which may attach to antigen targets, hold it together. The robot performs its function when the locks are unlocked in response to antigens on the outer layers of particular cells [77].

A. Targeted drug delivery: Effective utilization in a variety of biological applications depends on the micro/nano vehicles' ability to carry out their assigned tasks. In order to effectively project the nanorobot as an efficient sensor or means of delivery for theranostics (a mix of the words therapies and diagnostics) applications, it is necessary to carefully evaluate its structure, shape, and propulsion source [78]. Active distribution to the place of interest is made possible by autonomous micro/nanomotors because of their directed movement, tissue retention, and penetration capabilities. For this reason, the method usually entails encapsulating the medication, gene, or protein inside micro/nanorobots, launching them to the designated location, and utilizing physiological or external criteria to trigger their release [79]. Early-stage tumor cell identification within the patient's body is possible with nanobots equipped with biosensors [80]. According to Kumar, et al. scientists have genetically altered salmonella bacteria that carry tiny robots called bacteriobots (3 μm), which are attracted to tumors by compounds released by the malignant cells. These shield the patient from the negative effects of chemotherapy by delivering the medication straight to the tumor while sparing the healthy cells [81]. Systemic circulation, as well as the force plus navigation needed for targeted distribution and tissue penetration, are essential for drug delivery nanobots. Drug delivery vehicles should possess special capabilities that include tissue penetration, controlled navigation, and pushing power in order to precisely deliver therapeutic payloads to specific disease areas. The ability of motor-like nanobots to swiftly move and deliver therapeutic payloads straight to disease sites should increase therapeutic efficiency and lessen systemic adverse effects of extremely hazardous medications [82]. A multilayered tubular polymeric nanomotor encased with the anticancer drug doxorubicin was created by Wu et al. Using a porous membrane template to aid in layer-by-layer

assembly [83]. The loaded medication was successfully delivered to the tumor cells by the nanomotor [84]. The precise transfer of the plasmid DNA (pDNA) to human embryonic kidney tissue has also been accomplished using magnetic helical microswimmers. When they came into touch with the cells, the pDNA-loaded motors discharged their genetic payload [85].

B. Controlled release mechanisms: Combining magnetically driven microswimmer mobility with light-triggered drug delivery in light-triggered release nanorobots was accomplished by creating a double-helical, magnetically powered microswimmer that releases DOX on-demand in response to an external light stimulation [86]. The change in phase of the gelatin hydrogel for a rapid release of DOX was made possible by the NIR irradiation-controlled photothermal action of the gold nps, which produced an effective biomedical therapeutic drug distribution platform.

By using effective chemical propulsion into the stomach fluid, magnesium (Mg)-based acidic-driven micromotors in pH-responsive nanorobots have been shown to be able to neutralize gastric acid both independently and over time [87]. When the stomach acid neutralizes the magnesium-coated pH-responsive polymer layer of these micromotors, the encapsulated payload—in this case, dye as a model payload—is released on its own. These micromotors were tested in mice and showed no discernible toxicity or disruption of stomach function. All things considered, these micromotors have the unusual twin functions of pH-responsive release of drugs and acid neutralization, making them a very attractive framework for pharmaceutical delivery to treat a range of stomach disorders. Another experiment used a mouse model to treat stomach infections caused by bacteria (*Helicobacter pylori*) using identical synthetic catalytic magnesium-based micromotors filled with the antibiotic clarithromycin [88]. When the medicine was released, the magnesium within the micromotor neutralized the stomach acid locally, boosting the drug's efficacy without appearing to be harmful. Drugs might be effectively put into these magnesium-based micromotors that run on acid to demonstrate a noticeable bactericidal effect. A pH-responsive polymer-coated gold nanowire nanomotor driven by ultrasonic (US) was assessed [89]. Before it reached the intracellular area, the encapsulated caspase-3 (a model enzyme) was shielded from release and inactivation by the nanomotors. The eudragit polymer covering was broken down by exposure to elevated intracellular pH, which released the enzyme and resulted in cell death [90].

C. Surgery: Minimally invasive surgery: The robot system, known as the Da Vinci surgical robot, has been used extensively to help surgeons do surgeries in order to increase performance and success rates. The

forementioned techniques will still cause severe harm and need long-term recuperation for individuals. The use of noninvasive and minimally invasive techniques is crucial to reducing surgical pain and recovery. Micro/nanorobots excel in noninvasive therapy because of their tiny size. Furthermore, a micro/nanorobot can operate by penetrating biological tissues with sufficient force produced by a magnetic motor, allowing for local surgical therapy [91]. In order to eliminate infections, Chen, et al. controlled magnetic bacteria-microrobots by directing magnetic fields toward their target [92]. In order to target and adhere to *Staphylococcus aureus*, the researchers first maneuvered the magnetotactic bacteria-microrobot within the microfluidic chip. The oscillating magnetic field might drastically lower *Staphylococcus aureus*'s vitality when it is paired with the microrobot. Simple mixes or solutions containing solely *Staphylococcus aureus* cannot be eradicated, despite the fact that magnetic targeting devices may kill the bacteria. According to these findings, a potential technique for targeted treatment of micro/nanorobots is the employment of magnetic targeting devices [93].

Blood clot removal and artery cleaning: One nanobot that is intended to function as artificial platelets is called Clottocyte. Within a second, hemostasis would be fully achieved. The normal hemostatic system takes 2–5 minutes to finish the entire process, whereas the reaction time is 100–1000 times quicker [94]. Blood loss and clotting time have decreased with the use of nanobots as clottocytes. Again, it is discovered that certain individuals get unusual blood clots. The use of corticosteroids to treat this anomaly is linked to adverse consequences such as allergic reactions, lung damage, and hormone secretion. Clottocytes are an alternate therapy that doesn't have these negative effects [95]. It is possible to identify and eliminate the plaque or blood vessel obstructing elements that cause myocardial infarction using nanobot molecules. While the traditional method of treating myocardial infarction, such as angioplasty, is dependent on surgical expertise and occasionally has adverse consequences, the procedure that nanobots follow is impervious to these [96]. Heart bypass surgery is used to treat coronary artery disease in patients. To improve blood flow to the cardiac muscles, this is done. The procedure may bypass many arteries, however, there are certain risks associated with this approach. An alternative method of operation is to utilize a nanorobot. An electric motor is coupled to the inner region of the nanorobot, which is connected to the outside region for circulation. The electric motor is integrated with a rotating needle, a camera, a microcontroller, and an arterial thermometer. Everything will be managed by the microprocessor [97,98]. To track the motions of the nanorobot, radioactive material is injected into the outside area. With a magnetic switch, this may be changed at any moment. The induced nanorobot is capable of removing

the plaque and pulverizing it into tiny bits. Upon completion of the action, it is extracted by instructing the nanorobot to attach itself to a blood artery that is readily accessible from the exterior [99].

Cancer treatment

In the early stages of cancer growth, tumor cells are detected using nanorobots equipped with chemical biosensors, or nanosensors. Malignant cells throughout the body will be detected by this nanosensor. Nanorobots can assist with such crucial parts of cancer treatment because of their ability to travel as bloodborne gadgets. Early identification of tumor cells within the patient's body can be accomplished using nanorobots equipped with chemical biosensors [100-102].

A. Targeted cancer therapy: A nano bioelectronics-based hardware architecture is presented for the use of nanorobots in cancer treatment. Salmonella bacteria that have undergone genetic modification are attracted to tumors by substances released by cancerous cells. Upon reaching the tumor, the bacteria's tiny robots, which are roughly three micrometers in size, autonomously release drug-filled capsules. By delivering medications straight to the tumor, the nanorobot—dubbed bacteriobot by the team—attacks the tumor while protecting healthy cells, minimizing the negative effects of chemotherapy on the patient [101,102]. The transferrin protein, which can identify tumor cells and a polymer combination are used to create the nanorobots. A chemical biosensor that can be utilized to identify tumors would be included in the nanorobots. To help with target identification and medication distribution, medical nanorobots equipped with chemical biosensors may be configured to detect varying concentrations of beta-catenin and E-cadherin. Additionally, the nanorobot could transport the treatment ingredients to the cancer location [103].

B. Photothermal therapy: Due to its benefits in deep tissue penetration and tumor selectivity, photothermal treatment has drawn a lot of interest [104-106]. Recent years have seen the combination of photothermal treatment and micro/nanorobots produce more effective tumor therapy than passive photothermal agent delivery. The on/off movement of stomatocyte nanomotors during active photothermal treatment has been shown for *in vitro* use. In order to kill cancer cells, stomatocyte nanomotors were shown to travel in a certain way toward cancer cells and have an impact on them by photothermal ablation [107].

Infection control

Effective instruments for identifying biological dangers and removing their powerful effects are the latest microrobotic techniques.

Fighting bacterial infections

Spores produced by certain bacteria can withstand treatment and can persist for decades in the environment. For instance, the electrodeposition approach was utilized to develop (COOH-PPy): poly polystyrene sulfonate (PEDOT)/Ni/Pt multilayer microrobots for the treatment of *Bacillus anthracis* (*B. anthracis*), a hazardous spore that causes anthrax in people and animals. Through covalent bonding, the anti-B antibody has been altered to guarantee the spore's capture by the carboxyl chains on the molecular robot's exterior. The Pt layer of the molecular robot, which uses H₂O₂ fuel to create O₂ bubbles, supplies the propulsion mechanism, while the Ni layer serves as a magnetic guide. 90% of the nanorobots were able to drift in aqueous solutions at a speed of about 250 μm s⁻¹ when 3% H₂O₂ was present, according to the research. One example of a dynamic multifunctional system that can quickly identify, isolate, detect, and destroy biological threats is this approach [108].

Clearing pathogens

The most frequent cause of pediatric UTIs is *E. coli*, which also has an irreversible impact on water quality [109]. Delezuk, et al. for instance, investigated the use of self-propelled microrobots based on alginate and chitosan to remove *E. coli* from tainted liquid. Magnesium (Mg) and water first interacted to initiate propulsion. The constructed molecular robots can move up to 36.5 μm/s in drinking water and 72.6 μm/s in seawater, according to their findings. In ten minutes, the molecular robot's bacterial killing effectiveness was 96%. Another experiment in San Diego County found that the eco-friendly micro-/nanorobots, which are likewise based on chitosan, were able to kill over 90% of *E. coli* [110]. The magnetic helix-based physiologically interfaced platelets membrane-coated nanorobots (PL-nanorobots) have the ability to attach to bacteria and other pathogens via the human platelets' plasma membrane. One crucial characteristic of platelet-mimicking nanorobots is their resistance to biofouling, which enables them to be effectively and permanently driven in biological fluids [111].

Challenges, limitations and future perspectives

Biocompatibility issues

Nanorobots must exhibit exceptional biocompatibility to minimize immune rejection and toxicity in human systems. Despite advancements in biomaterials, ensuring long-term safety remains a critical challenge. The interaction of nanorobots with complex biological environments often leads to unpredictable immune responses, necessitating further innovation in material engineering and coating technologies to achieve greater physiological compatibility.

Manufacturing complexity

The production of nanorobots involves intricate fabrication processes requiring high precision and scalability. Techniques such as self-assembly, microfabrication, and molecular design are resource-intensive and present challenges in reproducibility and cost-efficiency. Overcoming these barriers requires integrating advanced manufacturing methods, including 3D printing at the nanoscale and automated systems, to streamline large-scale production.

Regulatory and ethical hurdles

The regulatory landscape for nanomedicine is still evolving. Establishing standardized guidelines for testing, clinical trials, and commercialization is crucial. Additionally, ethical concerns surrounding the use of autonomous nanomachines in living systems demand rigorous oversight to prevent misuse and ensure patient safety.

Authors' perspectives on advancements

Nanorobots signify a revolutionary leap in precision medicine, with the potential to overcome the limitations of conventional therapies. Emerging advancements in propulsion systems, energy efficiency, and sensor technologies may enable nanorobots to navigate intricate biological environments with precision. Future applications could extend to personalized medicine, where nanorobots are programmed to target patient-specific genetic and molecular profiles.

Furthermore, interdisciplinary collaborations between materials scientists, biomedical engineers, and clinical researchers are essential for addressing current limitations. Integration of artificial intelligence and machine learning in nanorobotics may also unlock innovative diagnostic and therapeutic capabilities.

Conclusion

The integration of nanorobotics into medical practice represents a frontier that blends engineering precision with clinical efficacy. The application of nanorobots in targeted drug delivery, diagnostics, and minimally invasive surgeries has already demonstrated encouraging results, showcasing their potential to enhance treatment specificity and minimize systemic side effects. However, several challenges, such as biocompatibility, manufacturing complexity, and regulatory hurdles, must be addressed to translate laboratory achievements into clinical reality. Continued interdisciplinary research and collaboration are essential to overcoming these obstacles. As technological innovations evolve, the horizon for nanorobots expands, promising a future where precision medicine becomes the norm, leading to better patient outcomes and more personalized healthcare solutions.

Declarations & author's contributions

M.A. carried out all the literature searches. V.G. and M.A. carried out the writing of the manuscript. All the authors have read and approved the final version of the manuscript.

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