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Nanotechnology in Medical Applications; Recent Developments in Devices and Materials

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Abstract

Nanotechnology has had an important place in the scientific world since the 1980s. With the development of technology and science over time, great change and progress have been made in the field of nano technology. With its different usage areas, the word nanotechnology is still maintaining its place in the first ranks today. This technology, which contributes to many branches of science such as physics, chemistry, biology, medicine, and engineering, deals with nano-sized substances. Nano-sized materials with unique physicochemical properties, which have been designed and used in medicine, have been developed for the prevention, diagnosis, and treatment of disease. It aims to minimize the side effects of nanotechnological therapeutic drugs designed for very important diseases such as cancer, dermatology, and infectious diseases. In recent years, there has been great interest in the development of new drug delivery systems. Cancer disease, which has an important place in nanotechnology applications, is caused by uncontrolled cell division and proliferation. The treatment methods used for this disease, which is caused by genetic and environmental reasons, vary depending on the genetics of the person and the type of cancer. Nanotechnology in the treatment of cancer disease; studies on healing damaged tissue, preventing division, and preventing damage to healthy tissues during the treatment process have been examined. Coronaviruses are a family of viruses that cause upper respiratory tract infections. The use of potential nanoparticle-based vaccines and drugs to treat infectious diseases caused by coronaviruses has been studied. Nanoparticle-based therapeutic drug applications are used in dermatology as well as in the diagnosis, prevention, and treatment of cancer and coronaviruses. MRI, CT, and PET are the commonly used diagnostic imaging methods in the diagnosis of these diseases. Contrast media are usually used in diagnostic imaging methods. These contrast agents have been developed thanks to nanotechnology. The advantages provided by nanotechnology are a source of hope for the diagnosis and treatment of these diseases. In this study, the transfer of the drug to the target structure where it will act, the use of nanomaterials in the prevention or treatment of various diseases, and the production of contrast media of diagnostic imaging devices were mentioned.

Keywords: Nanotechnology; Cancer; Covid-19; Drug Delivery; Dermatology; Medicine

1. Introduction

Nano is derived from the Greek word “nanos” meaning dwarf. Nano is literally one billionth of the physical size. Nanostructures, approximately 100 to 1 nanometer in size systems correspond to any size length, width, or thickness between 1/10 million meters and 1/1 billion meters. Systems operating in these dimensions show different characteristics from normal systems in their physical behavior [1]. Many studies conducted in this context are associated with nanotechnology. Nanotechnology is based on the principle of producing a much cheaper, higher quality, more durable, more functional, and useful product with a high layer value and taking up very little space, using less matter and energy by controlling atoms. Nanotechnology is a multidisciplinary field that encompasses a wide variety of devices in engineering, biology, physics, and chemistry [2], [3], [12]–[21], [4], [22]–[28], [5]–[11]. These differences, which are described as nanoscience and nanotechnology, have continued to progress in various fields such as civil, military, medicine, communication, genomics, and robotics in the world for about 10 years [29]. As the properties of materials move from the macroscopic to the nanoscale, many new properties emerge [30]. For example, the conduction property (momentum, energy, and mass) is no longer described continuously but intermittently. Similarly, optical, electronic, magnetic, and chemical behaviors are described as quantum rather than classical [5]. All these developments started a scientific and technological revolution equivalent to the industrial revolution that reshaped the world in the 19th century. At the nanoscale, the properties of materials are completely different from the macroscopic scale, and as we approach the nanoscale, various special and useful new properties emerge. In addition, it is unfortunately not possible to observe the nano dimension when viewed with microscope lenses used with traditional methods. In the century we have lived in, the concept of nanotechnology has an important position as a branch of physics, chemistry, and engineering that is studied on a very molecular scale for functional systems. It includes all the techniques used to create advanced technological and high-performance products. Today, nanotechnology, which has a place in various fields, has an important effect such as making life easier. Economically lighter aircraft, ships, and automobiles are designed with this technology. Again, this technology also provides fuel economy for vehicles. Nanomaterials, sensors, machines, and chip systems are produced thanks to research in the field of nanotechnology. Carbon nanotube, which attracts the most attention and is developed among nanomaterials; is a high-density, rather rigid, and rod-shaped structure. Since the rod shape is hollow, it is quite light and can be easily placed anywhere. Following the work of carbon nanotubes around the world with great interest, NASA recently announced that it will also use carbon nanotube designs for space exploration. Nano chips enable technological devices such as computers and mobile phones that we use in daily life to work much more effectively. Nanotechnology; machinery such as machine design, motor, key, outer cover and impeller are made much more effective and efficient thanks to this technology [31]. The science of nanotechnology, besides its wide range of uses, shows itself in every field that is beneficial for humanity, its development, and transformation at the molecular level. Nanotechnological developments are used with increasing interest in the fields of mathematics, chemistry, physics, computers, pharmacy, and medicine [6], [32]. One of the most preferred areas of nanotechnology is materials science. Material making, manufacturing, and development take the first place [33]. Advances in nanotechnology are used to obtain smaller and more functional products. The use of this technology in the medical field is that it leads to many studies that changed human life with the repair and treatment of damaged nerve cells at nanoscales [34], [35]. In addition, textile is one of these areas. It is possible to make differences in the structure of the fabric with nanotechnology; waterproof, fireproof, wrinkle-proof, etc. materials with specific properties can be obtained. Computers, phones, and their accompanying technological devices offer a wide range of nanotechnology applications. Nanotechnology is used in the production of quantum computers, which have information processing power far beyond the capacity of computers and accompanying technological devices that we have already used. Quantum computers are often used to solve extremely complex problems, the working principle of which is quite different from the devices we use in daily life. Nano electricity, on the other hand, allows

the development of areas such as signal, sensor, and display systems developed for vehicles [32]. Developments in astronomy, space, and aeronautics generate very high economic bills and the materials used are quite heavy [40]. With the use of nanotechnology, all materials can be produced in a much lighter, equipped, multi-purpose way [30]. The biggest role in accelerating the breakthroughs of institutions and organizations working in the field of astronomy, such as NASA and Space X, is thanks to this technology [41]. With nanotechnological developments, it is possible to make engines that offer higher efficiency with less fuel. This means the production of environmentally friendly systems [42]. Especially in the field of production and transportation, both environmentally friendly and highly efficient applications are one of the areas brought by nanotechnology. With the correct use of this technology, it is possible to achieve a cleaner environment [2]. The benefit of nanotechnology in the agriculture and food sector is quite remarkable. This technology has an important place in the repair, processing and modification of animal and plant genes for the continuation of the generation [43]. With the increase in the human population day by day, it is expected that the foods developed with this technology will have a much larger place in our lives in the future [44]. The defense industry is one of the areas where countries allocate the most budgets around the world. Nanotechnology, which has high potential in military applications, enables the production of new generation products such as weapon systems and improved bulletproof, waterproof, camouflage clothing. Most of the studies in this field are in the research and development process. In the future, weapons, explosives, sensors, robotics, engines, etc. created with nanotechnology. systems will begin to be preferred more and more in the defense industry of countries [7], [8]. In addition, the dimensions of the materials used are reduced, so the cost is reduced and the researches carried out in this field are open to development more easily. Nanotechnology has the most striking impact on the development and transformation in the field of medicine and health [36]. This technology, which enables intervention in living systems at nanoscales, plays an important role in the development of devices that communicate with living microorganisms [29]. Nanotechnological devices can repair damaged tissue or parts of the body that cannot be reached under normal conditions [37]. With these devices, diagnosis and treatment processes are carried out in an easier and healthier way [38]. Nanotechnology also attracts great interest in the pharmaceutical industry. With this technology, the effectiveness of existing drugs can be increased, and with the development of nanotechnological drugs, treatment of a previously incurable disease becomes possible [39]. In the introduction, various sectors where nanotechnology has developed and the definition of nanotechnology were briefly presented. Within the scope of this study, nanoscale material structures are defined and nanotechnological devices and application areas are detailed.

1.1. Drug Delivery Systems in Nanotechnology

The use of targeted nano-drug delivery systems is one of the most important areas of nanotechnology use. Transporting the drug to its target structure is one of the biggest challenges facing the pharmaceutical and biotechnology industries. For this reason, researchers have turned their attention to drug delivery systems. Research in the fields of science and developments in biotechnology help the discovery and rational creation of new drugs [45]. Frequent use of drugs brings with it some problems, but these can be reduced with the help of recently developed technologies [46]. Studies in various fields are used to design specific drug delivery methods. These developments led to the creation of specialized drug delivery systems. These systems evolve by releasing bioactive substances at a specific rate and in a chemical reaction for a specific structure. On the other hand, when compared with today's drugs, targeted drug delivery systems make it possible to deliver drugs to the target more effectively and realistically. Another issue is that the active substance cannot pass through the body barriers to reach the target area. Numerous solutions are provided by nanotechnology to the problems that arise with the use of active chemicals [47]. Thanks to the creation of nanocarriers, drugs now reach the target area by crossing the blood-brain barrier, bronchioles in the respiratory system, tight junctions in the epidermis, and anatomical and biological barriers [48]. Due to their improved distribution in limited areas of the body, nanocarriers help dissolve drugs with low solubility. New features in nanocarrier systems reduce drug toxicity and offer more effective drug delivery. As seen in Table 1,

the benefits of nanocarrier drug use are given [49], [50].

Table 1. Benefits Of Using Nanocarrier Drugs [49].

Increasing Drug Accumulation in The Targeted Area
Avoid Dangerous Side Effects
To Ensure the Controlled Administration of Drugs
Avoiding Unwanted Side Effects
Increasing Drug Utilization
Minimizing Drug Breakdown

The surface of the nanotube system should be immobilized with drugs obtained using natural or synthetic polymers. Due to the immune system's recognition of the surface properties of the nanotubes, it is not detected as a foreign body in the targeted area. Due to all these adaptation processes, the drug acts only on the diseased area, Tues in the blood for a long time after application, and is released in the appropriate amount and at the correct rate. Nanoparticles, which have a large number of clinical applications, have greatly influenced the pharmaceutical sector as a result of the advances made in nanotechnological research. Nanoparticles are gaining a desirable position in the pharmaceutical industry due to their useful uses in applications such as direct binding to the active ingredient, trapping, and targeting [51].

1.2. Design of Drug Delivery Systems Based on Nanotechnology

To increase site-specific targeting, medication bioavailability, and uptake of poorly soluble pharmaceuticals, nanoparticles can be employed for targeted drug delivery at the location of the disease [52]. Figure 1 depicts a schematic comparison of non-targeted and targeted medication delivery methods. Many nanomaterials have been used successfully to make anti-cancer drugs, including doxorubicin, 5-fluorouracil, dexamethasone, and paclitaxel [53].

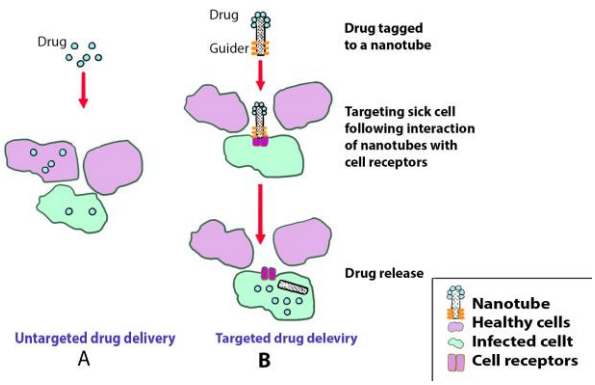

Fig 1. Demonstration of non-targeted and targeted drug delivery methods [53].

Micelles and liposomes serve as precursors of nano-drug delivery systems. Additionally, Figure 2 shows dendrimers, nanoparticles, and quantum dots. These systems minimize the amount of active substance removed from the body and ensure that the concentration of active substance in the blood remains at the ideal therapeutic level for a long time, and this is how real substance use occurs. As a result, the benefit potential of the drug increases [54].

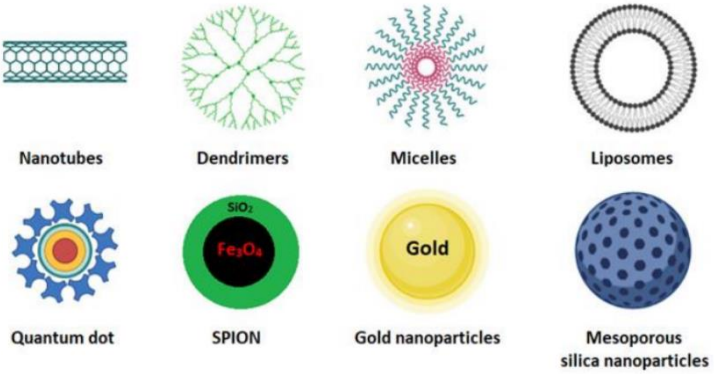

Fig 2. Some nanocarriers are used as smart drug delivery systems [55]. Reprinted by permission from Elsevier.

1.2.1. Micelles

Micelles are similar to liposomes formed when amphiphilic copolymers self-assemble, as shown in Figure 3, and are systems with a lipid or polymer structure of about 10 nm. The ability to easily and repeatedly produce mycelium is one of its key benefits. Another benefit is that they increase their absorption by making active molecules with low solubility due to their hydrophilic and hydrophobic groups such as vitamins, enzymes, and steroids. They are chemical compounds similar to polymers in many ways. Like polymers, they are made in the process of organic synthesis and consist of repeating structures (monomers). Its structure is completely controllable. Dendrimers and dendrimer polymers have particularly useful nanostructures for well-defined drug delivery systems. Co-surface groups are chosen in drug delivery system applications due to their good encapsulation talent and highly controlled chemistry [49], [56].

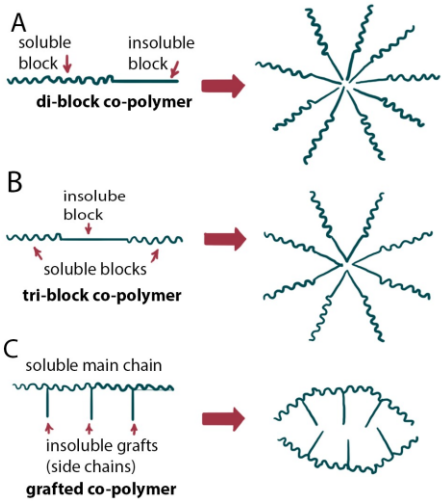

Fig 3. Micelle Formation Mechanism from Copolymers [57].

1.2.2. Liposomes

Liposomes are vesicular systems with a phospholipid bilayer structure ranging in size from nanometers to several micrometers. Liposomes, which are very important in drug formulations, have become a subject of considerable attention due to their adaptability and ability to intensify the therapeutic effect. Numerous problems, including minimum solubility, low bioavailability, short half-life, and strong side effects of drugs, have been substantially solved thanks to liposomes. Pharmaceutical researchers have now decreased the medicine toxicity and negative effects. Liposomes are used in cancer diseases because they can improve vascular permeability in tumor tissues [58].

2. Nanotechnology in Dermatology

Dermatology is a branch of medicine that aims to diagnose and treat diseases related to the skin, nails, hair, sweat glands, and skin, and prevent possible diseases. The detection and treatment of skin diseases, uses methods such as skin examinations, blood tests, surgical tests, chemical peels, laser treatments, skin surgery, and microscopic examinations for skin disorders, while at the same time, it is managed by a dermatologist in the diagnosis and treatment of skin diseases. Dermatologists treat skin cancer, eczema, psoriasis, acne, rosacea (rose disease), melanoma (skin cancer), dermatitis (inflammation of the skin), hair extensions, nail irritations, preservatives, and many other skin conditions by diagnosing them [59]. Dermatology is a wide field and is divided into many subheadings within itself. These are clinical dermatology, dermatological surgery, cosmetic dermatology, pediatric dermatology, dermatopathology, derma immunology, dermatological oncology, dermatological control, and dermatological pharmacology. The treatment methods in dermatology may vary depending on the type of disease. Topical medications are medications that are applied directly to the skin, hair, or nails and are used to treat diseases such as acne, psoriasis, and eczema [60]. Systemic drugs, on the other hand, are drugs taken by mouth or by injection and are used in the treatment of dermatological diseases affecting the entire body [61]. Light therapy involves exposure to natural sunlight or artificial light sources and is very effective in the treatment of diseases such as psoriasis, vitiligo, and eczema [62]. Cryotherapy is used to treat warts, skin lesions, and some types of skin cancer using extreme cold [63].

Surgical methods, surgical techniques are used for the removal of skin lesions or tumors. Laser therapy, on the

other hand, is effective in the treatment of problems such as spots, hair loss, and capillary treatment. Some dermatological problems are treated with dietary and lifestyle changes.

The field involving the use of nanotechnological methods for the detection and treatment of skin diseases is called nano dermatology. Nano dermatology is a term that refers to the diagnostic and therapeutic use of nanotechnology in the field of dermatology and cosmetology [64], [65] The use of this innovative technology in dermatology and cosmetology is revolutionary in the treatment and diagnostic methods of many skin diseases [66].

In addition, studies in this field are investigating the potential advantages of using nanotechnology, especially in the treatment of skin diseases and drug carrier systems. These studies offer a clear future for dermatology. Nanotechnology is a technology that allows materials to be produced and manipulated in very small sizes. The equivalent of this aspect of nanotechnology in dermatology is to ensure that drugs are transported to the skin tissue in a more targeted manner and that the treatment of skin diseases is more effective [67]. Nanoparticles, which are an important material used in nanotechnology, can have many shapes and can be soluble or insoluble, soft or hard. Particles produced at high temperatures, viruses, and allergens are among the natural sources of nanoparticles. They are small-sized particles and thanks to this, they can penetrate deep into the skin, and easily move to the targeted area on the skin. It is applied in topical medicines, and systemic treatments and is mainly interested in inflammatory skin diseases, aesthetic dermatology, and malignancies (malignant tumors) [67].

2.1. Applıcatıons of Nanotechnology in Dermatology

Nano dermatology is an exponentially growing field and offers an overview of the potential applications of nanotechnology in dermatology. There are many nanotechnology researches and applications in the field of dermatology. According in the ninth month of 2011, Friedman et al. conducted a study aiming to evaluate the primary perception and understanding of nanotechnology in dermatology teaching programs in the USA. The participants in this study answered the questions asked by giving answers such as I disagree, I strongly agree, I am undecided, I disagree, I strongly disagree and at the same time using a scale with a certain score. As a result, some of the participants in this study did not participate in any educational activities related to nanotechnology, while others agreed that this topic needs more education and should be included in the dermatological specialty curriculum. Likewise, while some of the participants agreed that it would contribute to advancements in the detection and treatment of skin diseases, others recognized the value of intensifying scientific research and funding nanotechnology. However, a large part of the participants responded positively to the need for further research to assess the safety of nanomaterials. If we look at the answers given in this research, the value and importance of nanotechnology in dermatology are understandable [68].

The applications of nanotechnology and nanoparticles in dermatology include new areas in medical diagnosis, follow-up, and improvement. Nanotherapeutic, a term referring to the medical applications of nanotechnology, is a treatment method aimed at increasing the delivery and effectiveness of therapeutic agents through the use of nano-sized materials. Drug therapy, immunotherapy, and gene therapy are among the main areas of nanotherapeutics. In short, nanotherapeutics have developed applications in both systemic and topical treatments, and the benefits of these applications are related to aesthetic dermatology, the treatment of malignancies (tumors), and inflammatory skin diseases [67]. The skin consists of two main layers: the epidermis and the dermis. The functions specific to the cutaneous mainly depend on the characteristics and structure of the epidermis. This structure creates a seamless investment on the entire surface of the body and is locally specialized for the production of skin extensions, hair, nails, and glands [67].

The epidermis consists of a large number of keratinocyte layers, and the differentiation of the basal layer of these keratinocytes on the surface occurs within a specific timeframe. In this process, the morphological transformations of keratinocytes give rise to four different histological layers. The stratum spinosum, stratum granulose, and stratum corneum are these four different histological layers [69]. The change in skin color tone depends on these three parts:

Melanin, carotene, and hemoglobin. Only melanin is produced in the skin. Melanocytes are specialized cells that are located in the basal layer of the epidermis and prolong the process of numerous branching cells between the surrounding keratinocytes. Decongestant melanocytes are located in the basal layer of the epidermis. Melanocytes have the tyrosinase enzyme necessary for the synthesis of pigments [70]. While the malignant progression of melanocytes leads to melanoma, their non-cancerous progression results in moles and freckles [67].

The dermis consists of two layers, the superficial papillary layer, and the mesh layer. Fibroblasts, macrophages, mast cells, lymphocytes, and dendritic cells are 5 different cell types of the dermis. The dermis, due to its structure, has a skin-protective property. Part of this feature is provided by the rich presence of lipids in the stratum corneum. Many skin diseases can cause changing barrier functions caused by qualitative and quantitative changes in the composition of lipids [67], [71] Disruption of the skin barrier and dysfunction occur in other cutaneous disorders such as dry skin ichthyosis (fish scale disease), atopic dermatitis (eczema), and Netherton syndrome [72]. Changes in filaggrin synthesis and decrease in keratohyalin granules, and metabolic changes of ceramides lead to deterioration of epidermal barriers, transepithelial water loss, and environmental factor-sensitive inflammation and xerosis (dry skin) in atopic dermatitis. Atopic dermatitis determines xerosis with a strong sensitivity to these disorders and an increase in trans epidermal water loss [71].

In atopic dermatitis, the integrity of the epidermis' stratum corneum barrier can be compromised due to various factors such as the keratinocyte differentiation process, genetic defects, and extracellular lipid matrix. For the impaired stratum corneum barrier to regain its function, certain improvements are needed. In addition, the active barrier functions present in the skin indicate that there is a limited range of molecules that can be transmitted to the layer of the epidermis that needs to be reached. For this reason, only small-sized molecule characteristics determined by capacity or advanced encapsulation can penetrate the stratum corneum [73]. In this case, intercellular lipids that lead to barrier Decay, all current developments in nanotechnology, diagnostic and preventive purposes, foresee the development of a new generation of drug carriers in dermatology [73].

Nano-sized carrier systems consist of four main classes; self-formed lipid systems (, solid lipid nanoparticles (SLN), liposomes, nano-emulsions, micelles, nanostructured lipid carriers (NLC), microemulsions, polymer systems (polymeric micelles, dendrimers, polymeric nanoparticles) and nano suppressions and pro-colloidal systems. These systems are used in different fields due to their characteristics such as high stability, load-bearing capacity and storage possibility, high surface area, and load-bearing capacity [67].

2.1.1. Nanoparticle Based Therapeutics

For nanoparticles to achieve effective therapeutic applications, they need to overcome the stratum corneum barrier and enter the cells. This entry can perhaps be performed using receptor-based processes. To enable nanoparticle transmission, many techniques such as gene guns, microneedles, ultrasound, electroporation, and tape stripping have been developed to disrupt the barrier of the stratum corneum. These methods increase the permeability of the stratum corneum, allowing nanoparticles to reach cells more effectively. Research on the therapeutic applications of nanoparticles usually focuses on three main areas. These areas are skin cancer diagnosis and targeted therapies, immunomodulation and vaccine applications, antimicrobial therapies, and wound healing [64]. The main focus of skin cancer diagnosis and targeted therapies is the diagnosis and treatment of metastatic melanoma, the most dangerous of skin cancers. Many of the potential drugs used in this disease fail clinically due to insolubility. Nanoparticles are an important choice for treatment in this direction, as more different types and higher concentrations of drugs can be delivered into the nanoparticles and overcome them. In recent research, multimodal silica nanoparticles have been identified to target M21 melanomas. Tumor retention was increased by adding integrin labeled with peptide 124I, RGDY, a long-lived positron-emitting radionuclide because polyethylene glycol limits the uptake of non-cancerous cells. Laminin receptor-binding peptide is also often used to increase nanoparticle retention. In this case, it has been shown that positron-emitting silica nanoparticles can be successfully used in the fields of tumor targeting and nodal mapping [64].

Immunomodulation and vaccination applications through the skin, like other areas, are of great importance for the skin. The main route to allergen sensitivity is the skin. Langerhans cells (LCS) and dermal dendritic cells, which present antigens through a protein called CD1a, are two important antigen-presenting cell types found in the skin. Nanoparticles have gained importance in this field for transcutaneous immunomodulation due to their antigen transport, adjuvant function, and accumulation in hair follicles. Although lipophilic and polymer particles are widely used here, these particles are prone to degradation. The hard insoluble nanoparticles can stay on the skin for longer and contain lower adjuvant. However, more research needs to be done on this issue. It is promising that nanoparticle-based vaccine administration has a positive impact however, it increases undesired immunological effects in individuals with sensitive skin. It has been stated in some studies that carbon nanotubes stimulate the immune system, provide macrophage activation, proliferation of T lymphocytes, synthesis of cytokines, and induction of antibody response. TiO_2 nanoparticles, on the other hand, have also been shown to exacerbate the development of atopic dermatitis-like skin lesions after co-exposure to mite allergen. UVR, on the other hand, is known to trigger skin barrier defects and may increase allergen sensitivity. However, research on how exposure to TiO_2 and UVR exacerbates atopic dermatitis-like symptoms and how the immunosuppressive effects of UVR may affect nanoparticle immunomodulation remains insufficient [64].

Studies conducted for antimicrobials and wound healing, show that topical applications of nanoparticles can be used for their applications in this field. These studies conducted on the use of silver nanoparticles show that these nanoparticles have the potential for use in wound healing applications due to their antimicrobial properties. At the same time, the design of nanoparticles that release nitric oxide stands out as a promising approach to accelerate the wound healing process and reduce the risk of infection. These studies evaluate the effects of nanoparticles on different types of wounds and types of microorganisms and provide new recommendations on how these materials can be used in wound healing applications. Topical application of these nitric oxide-releasing nanoparticles made of tetramethyl orthosilicate, polyethylene glycol, and chitosan components, which release nitric oxide, have significant effects against cutaneous methicillin-resistant Staphylococcus aureus infection when topically applied. Nano Ag (nano silver) is used in many products such as soaps, food storage containers, socks, washing machines, and surgical masks due to its antimicrobial, antibacterial, and odor-reducing properties. However, in addition to human skin exposure, it is known that it can lead to health problems such as bluish greying of the skin as a result of excessive use. Therefore, it is thought that nano-Ag may be of concern from the point of view of human health and safety [64].

2.1.2. Innovative Product Formulations for Consumers

Photoprotection: The utilization of nanoparticulate TiO_2 and zinc oxide (ZnO) in sunscreens has witnessed a significant increase in recent times. These nanoparticles have less skin whitening effect compared to sunscreens with organic ingredients and help to produce more effective products. In addition, they are aesthetically more preferred because they can scatter, capture, and reflect UV rays. However, understanding the particle size of TiO_2 and ZnO nanomaterials is necessary, particularly regarding their properties such as skin penetration protection and phototoxicity effects. It is known that TiO_2 and ZnO nanoparticles are risk-free when in contact with healthy skin. However, it should be taken into account that further tests may be required when skin health is compromised. It is still not known for sure whether the injured skin in this case allows higher penetration. In certain conditions such as hyperkeratotic psoriasis thickening of the horny layer can reduce this condition. When nanoparticles interact with UV radiation, free radicals and reactive oxygen forms are formed. These reactive oxygen forms can damage the DNA of cells and cause mutations. In addition, these forms can also harm proteins and lipids, causing permanent cell damage. That is, together with UV radiation, the reactive oxygen forms formed and generated from nanoparticles cause significant damage to skin cells [68].

Cosmetic: Nanomaterials and nanobiotechnology are providing new benefits for cosmetics and pharmaceuticals. Especially in skin care, nanoparticles are used to deliver useful substances to the skin. Delivery systems such as nanovesicles, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC) have been developed for both

pharmaceutical and cosmetic applications. SLN and NLC form a lipid layer on the skin, preventing the evaporation of water and increasing skin hydration levels. These carrier systems are advantageous over vesicles because they can contain a higher amount of effective ingredients due to their high stability. As a result, the effective ingredients reaching the action site increase, and skin penetration is optimized [68].

Nanotechnology makes it possible to produce nanoparticles that are used in the cosmetics industry and help protect substances that are sensitive to oxidation or affected by moisture. Chitin nanofibrils, on the other hand, are a natural polysaccharide obtained from shellfish. These nanofibrils are easily metabolizable and have environmentally compatible properties. It also helps to rejuvenate the skin by activating the growth of keratinocytes and fibroblasts, regulating collagen synthesis, and controlling cytokine and macrophage secretion. In addition, it is known to have an effect on photoaged skin and promote wound healing [68].

Skin problems, especially in cases such as atopic dermatitis, become sensitive to skin irritants. Therefore, emulsions with effective ingredients are currently used to retain or transform allergens. Nanoparticles, on the other hand, can be used to distribute these substances more evenly and are also used as antioxidant carriers to protect the skin. Corticosteroids, which have numerous applications in the field of dermatology, are also associated with nanoparticles. In addition, nanoparticles are also used in cosmetic products. Chitin nanofibrils activate fibroblast and keratinocyte proliferation. Macrophage regulates collagen synthesis and cytokine release. Additionally, it is known that photoaged skin has positive effects on its appearance and promotes wound healing by reducing hypertrophic scar formation. Liposomal formulations are also used for skin problems, and they minimize undesirable effects such as cutaneous atrophy that can occur with chronic applications. Podophyllotoxin encapsulated in SLN has equivalent effects to steroids in the treatment of genital warts. Hopeful results have also been obtained with the liposomal T cell inhibitor Cyclosporine A. Moreover, nanoparticles provide higher tolerance, improved protection, and superior effects. Clotrimazole, Psoralens, Dibranol, Methotrexate, and other various antifungal drugs are also included among these substances [68].

3. Nanotechnology Applications in Covid-19 Disease

Viruses have developed various molecular mechanisms for entry into cells during evolution. These mechanisms include long-term survival within cells and abilities such as affecting or modifying host defense mechanisms [74]. The high efficiency of viruses in gene transfer has inspired the development of non-infectious recombinant viral vectors for use in gene therapy applications. To increase the safety of viral vectors, studies have been carried out to develop non-viral drug delivery systems inspired by the natural abilities of viruses [35], [37] Researchers working in the field of nanotechnology have designed various nanosystems that can mimic the gene transfer capacity and high contagiousness of viral vectors. By understanding the molecular mechanisms behind these vectors, it has been possible to develop delivery systems used in different fields such as cancer treatment and regenerative medicine. Nanotechnology not only develops new means of delivery inspired by virology but also plays an important role in the fight against viruses [78], [79].

Coronaviruses are a family of viruses that cause serious ailments in humans and animals. When the literature is examined, it is seen that it also affects non-mammalian animal species. Covid-19 which affects the whole world has been recognized as a pandemic by the World Health Organization as of January 2022. When the virus structure is examined, it is observed that the glycoprotein structure found on its surface is responsible for pairing into the cell and its transfusion [80].

3.1. Nanotechnology Applications in Covid-19 Treatment

3.1.1. Exosomes

Exosomes are of great interest in terms of therapeutic safety and effectiveness when delivered to cells. Exosomes

as potential biological nanocarriers for the treatment of coronavirus have been identified in several clinical applications [41], [42]. These studies include factors such as immunization, and long-term transmission due to their ability to escape at a small size based on characteristics such as the slightly negative zeta potential, and the ability to penetrate tissue effectively [81], [83]. Exosomes can be developed optionally with indirect engineering and direct engineering approaches [84]. In the indirect engineering approach, cells cultured with therapeutic agents or genetically modified artificial exosomes are used. In a direct engineering approach, therapeutic agents are loaded directly into exosomes separated from the source cell, and these loaded exosomes are then transferred to the target tissue [85]. There are three stages in the formation of exosomes through endocytic cellular; endocytic vesicle formation through plasma membrane invagination, induction of multivesicular bodies (MVBs) by inward budding of the limiting late endosomal membrane, and exosome formation by merging MVBs with the plasma membrane [86]. Exosomes have been evaluated as immunogenic factors in the treatment of coronavirus infection. Exosomes composed of coronavirus S protein produce neutral antibody, which is increased by initial vaccine preparation followed by useful adenovirus vector vaccine. Scientists have said that these synthetic exosomes can be used for therapy. To confirm the incorporation of the coronavirus S protein into exosomes, exosomes with chimeric protein functions are made for use as a coronavirus vaccine [87]. In addition, in the treatment of coronavirus pneumonia in October, researchers propose to use exosomes as drug delivery systems [82]. Exosomes can migrate to the target organ for immunotherapy because they have hypoimmunogenic properties [41], [48]. Currently, this method has been used to treat coronavirus [81].

3.1.2. Metal Nanoparticles

Metal nanoparticles, especially gold nanoparticles, and silver nanoparticles, are nanotechnology methods that have been studied in detail in the treatment of viral infections. These nanoparticles are being used to develop a new method to reduce and eliminate the severity of infection. For example, it has been determined that colloidal silver nanoparticles with a size of 3-7 nm can be highly effective in the treatment and prevention of viral infection in the early stages of respiratory infections [89]. Silver nanoparticles (30 nm) found in magnetic hybrid colloidal systems stand out as a promising nanosystems with the potential to inactivate the virus. These systems can interact with virus proteins by Decoupling between thiol and silver ions [90]. The anti-coronavirus activity of silver nanoparticles has been observed in silver nanoparticles with diameters between 2 and 15 nm. Dec. Immunofluorescence studies conducted have shown that silver nanoparticles with a size of 10 nm coated with polyvinylpyrrolidone completely block the coronavirus, but silver nanoparticles with a size of 100 nm cannot do this [91], [92]. Metal nanoparticles can be used on various surfaces to prevent the spread of coronavirus [52]. In addition, gold nanoparticles show the ability to trigger an immune response when internalized by antigen-presenting cells, which suggests that they have the potential to develop vaccines [93], [94].

3.1.3. Metal Oxide Nanoparticles (Mops)

Recently, many studies have been conducted on the antimicrobial properties of metal oxide nanoparticles [95], [96]. Various mechanisms of action make metal oxide nanoparticles an effective antimicrobial agent [97]. It has been observed that viral strains have developed resistance to therapeutic methods used by metal oxide nanoparticles. For example, the antimicrobial properties of iron oxide nanoparticles (IONPs) have been studied against the influenza virus (H1N1), dengue virus, and rotavirus [90], [98], [99] Iron oxide nanoparticles have been approved by the FDA and are used as biocompatible for the treatment of anemia [100]. Iron oxide nanoparticles are thought to interact with proteins on the surface of the virus, preventing the virus from binding and entering the host cell. The results have shown that iron oxide nanoparticles can be used as a promising antiviral agent in the prevention or treatment of infections. Therefore, it can be said that iron oxide nanoparticles may be a promising candidate in the treatment of coronavirus patients. Other iron oxide nanoparticles are characterized by properties such as cytotoxicity,

biocompatibility, and usability. There are also studies on the antiviral effects of ZnO nanoparticles [101], [102]. One study examined the antiviral properties against H1N1 and showed that polyethylene glycol-coated ZnO nanoparticles have higher antiviral activity and lower cytotoxicity than pure ZnO nanoparticles. It has been determined that ZnO nanoparticles can be used as an effective antiviral nanomaterial for the treatment of coronavirus [102], [103]. In addition, super magnetic iron oxide nanoparticles can be used as a contrast agent for magnetic targeting and magnetic resonance imaging (MRI) [102], [104]. Lipid-coated super magnetic iron oxide nanoparticles can enable the transport of antiviral agents to targeted sites [102], [105]. The potential of the antiviral properties of these nanoparticles can be attributed to the fact that they adsorb to viral surfaces and subsequently cause local changes, such as glycoprotein agglutination. In this way, the virus is prevented from entering the cells and multiplying. Therefore, it is these nanoparticles that offer great potential for the treatment of coronavirus [62], [66], [67].

3.1.4. Quantum Dots

Quantum dots (QDs) are semiconductor particles that exhibit strong fluorescence at certain wavelengths. They have shown potential in Point-of-Care (POC) applications for viral assays and demonstrated sensitivity in the detection of viruses [108]. Carbon quantum dots (CQDs), a type of functional quantum dot, can be used as therapeutic tools against human coronaviruses. These nanoparticles, depending on their concentration, can interfere with the function of the virus, in particular by interacting with the S-protein [109]. In recent years, cationic carbon quantum dots based on curcumin have been developed using hydrothermal techniques to combat coronaviruses [110]. QDS plays an important role in the treatment of human coronaviruses. For example, one study observed the antiviral properties of seven different CQDs against HCoV-229E infection. The CQDs, which are approximately 10 nm in size, were synthesized by hydrothermal carbonization method using synthetically modified carbon precursors. These cards exhibited high solubility in water when combined with ethylenediamine/citric acid and boric acid. The concentration of CQDs affected virus inactivation [109]. The inhibition of HCoV-229E entry into host cells is probably attributed to the interaction between the functional groups of CQDs and the entry receptors of the virus (Figure 4) [111].

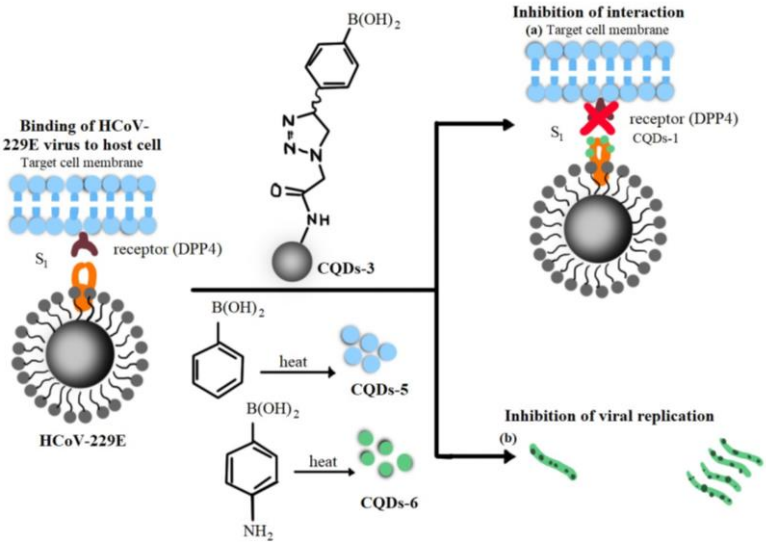

Fig 4. Carbon quantum dots prevent the S protein receptor of the coronavirus from binding to host cells [111]. Reprinted by permission from Elsevier.

Another study suggested that triazole-based CQDs could serve as antiviral agents for the treatment of coronavirus (Figure 5). CQDs are composed of hydrophilic functional groups that make them suitable for a variety of biomedical applications. They can act as multi-targeted inhibitors by blocking viral entry, RNA synthesis, and replication [110]. Therefore, the regulation of the concentration of CQD is very important in the control of the viral load in the body. CQDs have been found to reduce the accumulation of reactive oxygen species and reduce the expression of pro-inflammatory cytokines when exposed to the virus. CQDs derived from glycyrrhizin acid have exhibited potent antiviral properties against RNA viruses [112]. It is expected that CQDs will not only prevent coronaviruses and human RNA viruses from entering host cells but also have virucidal properties. However, it is important to note that the response of different viruses may vary and CQDS may require further evaluation in terms of their antiviral strategy [112]. QDS, including semiconductor nanoparticles, can also produce antiviral radiation by interacting with light. These interactions can disable viral components such as the viral membrane, DNA, RNA, and viral proteins, thereby affecting their function (Figure 6) [113].

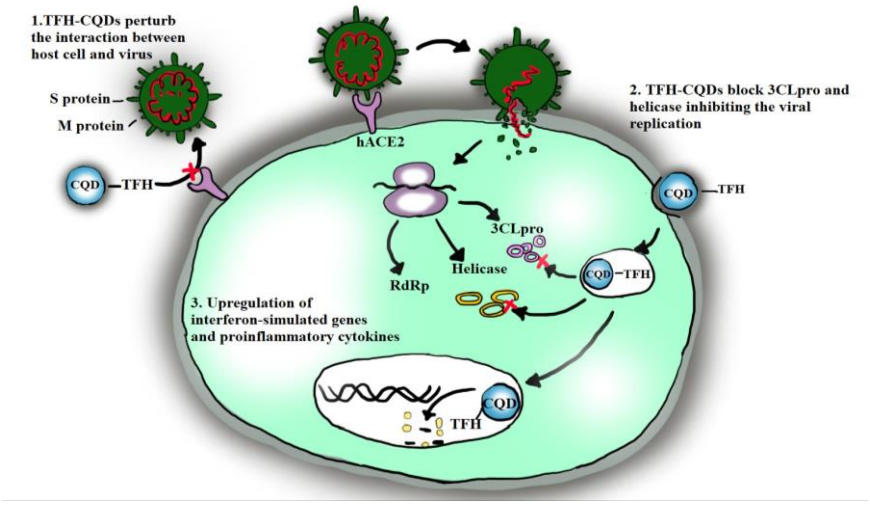

Fig 5. Triazole-based CQDs were used for use as an antiviral agent to treat coronavirus [112]. Reprinted by permission from Elsevier.

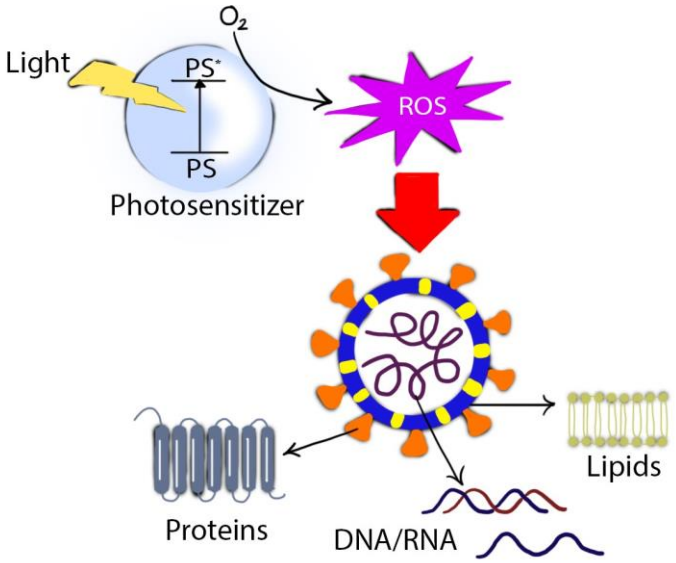

Fig 6. Semiconductor nanoparticles can produce antiviral radicals by interacting with light [113]. Reprinted by permission from Elsevier.

4. Nanotechnology in Cancer Disease

Cancer is a very influential and serious disease worldwide, but it is also a difficult disease to prevent. It is a possible condition that this disease, which occurs when cells grow uncontrollably and multiply rapidly in any tissue or organ in the body, ends with death. More than 200 types of cancer have been identified according to their location, proliferation, and tissue [114]. Although many factors trigger the occurrence of the disease, genetic factors come first. Although many factors such as environmental conditions, types of food consumed, and psychological factors open the door to cancer, the biggest cause is genetic deformation. No matter what the factors that cause cancer are eventually, there is a deterioration in the genetic material of the cell [115]. Although there is often an increase in the diagnosis of cancer as a result of research and scientific studies, the mortality rate remains at the same level and the absence of an increase according to the diagnosis can be a source of hope that cancer can be prevented [116]. Cancer is a personal disease, and the fact that everyone has a different structure causes them to give different responses to treatments. The progress of nanotechnology is developing in the medical world in various methods in October in addition to types of treatment [117].

4.1. Diagnosis and Treatment of Cancer

Early diagnosis of cancer is the most important condition in the proliferation of cells by spreading and when the mutation is detected at the initial stage, measures can be taken against the disease and stopped. In the presence of individuals who have or have had cancer in the family, a person should attach importance to regular check-ups and can chart a path for early detection. X-rays, blood tests, tomography scans, magnetic resonance imaging, endoscopy, and genetic imaging tests are methods that can be used in the early diagnosis of cancer [118]. The main treatment methods for cancer disease are radiation therapy, chemotherapy, and surgical intervention (removal of cancerous tissue) [118], [119]. Each type of treatment has disadvantages as well as advantages, and there are differences in the results depending on the structure of the person during this treatment process. Therefore, there is no single source of

solution that gives a definite result [120].

Radiotherapy: Ionizing radiation is used to stop the proliferation and spread of cancer cells. A certain amount of energy is supplied to the treated area by x-rays, gamma rays, or accelerated subatomic particles. With this energy efficiency, it is prevented from dividing and multiplying by disrupting the genetic material in the cell [121]. Healthy cells that are exposed to damage during the procedure, on the other hand, recover themselves over time and continue to function. Radiotherapy is a local treatment that affects the area where it is applied. It is used in cancer types such as the brain, breast, prostate, blood, lymph, and uterus [122].

Chemotherapy: It is a type of treatment used before the surgical procedure, such as radiotherapy [123]. This treatment, which can be called drug therapy, allows the cancer cell to spread, and slow down its growth, and the cancer cell can be controlled [124]. This process, which is performed with drugs such as alkylating agents, anti-metabolites, anti-tumors, antibiotics, and mitotic inhibitors in chemotherapy, is a treatment method used for many cancers such as leukemia, lymphoma, and sarcoma [125].

Surgical method: It is a method used for diagnosis and diagnosis of cancer by biopsy from the organ or tissue where it is located so that the cell does not spread and multiply. When it comes to the risk of removal without damaging a healthy organ or tissue, it is preferable to reduce and remove the mass with radiation therapy or chemotherapy before the surgical method is applied [126].

Gene therapy: A gene is an inherited part of DNA that is responsible for cell activity. The purpose of treatment is to transfer the therapeutic gene to the diseased (mutated) gene [127]. It is the transfer of the P53 gene that is a frequent subject of research in this treatment. It participates in the DNA structure and stops cancer by activating transcription. There is no certainty about how it binds to the cancer cell and provides stopping or destruction [128]. While the P53 gene is expected to be treated when it enters the cell, there is also a risk that it may mutate and turn into a tumor [129].

4.2. Cancer and Nanotechnology

Radiation therapy used in cancer disease is a procedure that has advantages as well as disadvantages in chemotherapy and surgical procedures. The risk of recurrence, organ loss, and failure to get the same results depends on a person's genetics in many types of cancer, the result cannot be considered positive, which can lead to a worse course of events. Loss of function in a healthy cell exposed to radiation is the same as when chemotherapy drugs are given to a healthy cell, and they can lead to serious damage [130]. The development of nanotechnology and the beginning of its use in medicine provides a significant advantage for human health in the treatment of cancer. It is now more useful to use treatment methods with nanotechnology, since the methods used in cancer treatment may pose a risk of harm as well as benefit [131]. The main goal of nanotechnology is to develop effective therapeutic agents that act on diseased tissue while destroying healthy tissue without damaging it. The advantages of nanoscale treatment can be easily adjusted, therapeutic diagnosis and diagnostic methods are that the cancerous cell is targeted and no damage is caused to another cell [132].

4.3. Nanotechnological Tools for Cancer Diagnosis and Treatment

Important tools developed for treatments in nanotechnology can be examined in four articles.

4.3.1. Nano-Cantilever

In the developed nano devices, Nano-Cantilever is an important device developed for early diagnosis of cancer. It is a biosensor mechanism using semiconductor materials in this device formed with proteins and antibodies. This device is designed to see a cancer cell, it can be detected by bending and bending, visible with laser beams (Figure 7) [132].

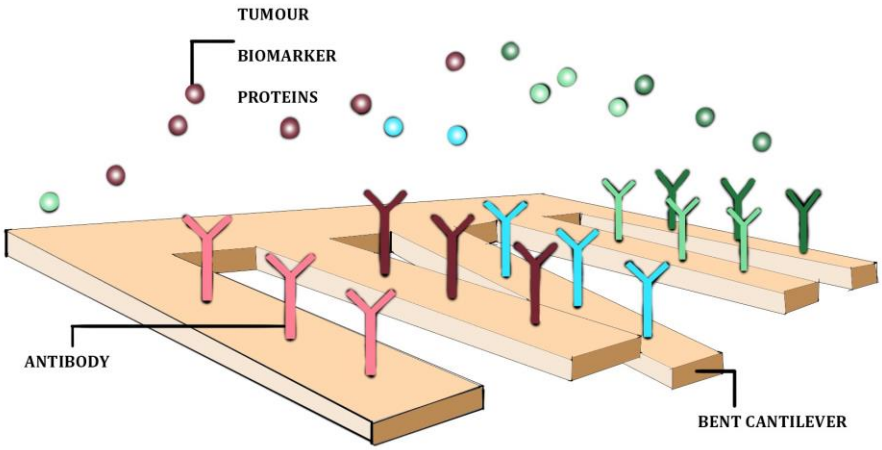

Fig 7. Nano-Cantilever working mechanism [133]. Reprinted by permission from Elsevier.

4.3.2. Quantum Dot

QDs are nanocrystalline structures composed of semiconductors. They are crystals produced to identify and observe diseased tissue or cells. These crystals with optical and electrical properties can absorb and emit, in which case it is a great advantage to be able to provide many images from a single light source. Thanks to Quantum Dot, it provides the opportunity to provide nanoparticles with therapeutic potential in imaging processes. Thanks to biocompatible coatings, its sensitivity can be designed depending on the type of cancer [134].

4.3.3. Nanoshell

A Nanoshell is a nanoscale covered with silicon at its center, with a gold layer on it, produced for diagnosis and treatment. Anticancer drugs that need to be given according to the type of cancer are placed on the outer surface of the Nanoshell sphere and directed directly to the cancerous cell. Before the NS is sent, the infrared ray is absorbed by this method, and the interior of the sphere accumulates with heat of destructive intensity. Heat is prevented from damaging the healthy cell by ensuring that it is destroyed only by acting on the harmful cell [135].

4.3.4. Dendrimers

Dendrimers are versatile polymers designed for drugs or imaging. This mechanism, which is produced as a drug carrier, is a nano sphere produced to transport drugs in its internal cavity or on its surface. These nanoparticles with high binders work with magnetic resonance imaging [34]. Ligand binders are placed on its surface and an anticancer drug is placed in its internal cavity to bind to a cancerous cell or tissue and prevent damage to a healthy cell [136].

5. Nanotechnology in Diagnostic Imaging

5.1. What Is Diagnostic Imaging?

There are various non-invasive methods used by patients for medical diagnosis and determining the causes of the disease. Diagnostic imaging is the process of imaging structures inside the body to make an accurate diagnosis for patients. It helps doctors to detect and diagnose problems that are present in the body [137]. These imaging techniques can be used to detect fractures, cancers, infections, tumors, and other diseases. Diagnostic imaging can help diagnose diseases early and provide a better response to treatment. There are many types of imaging available in diagnostic imaging.

5.2. The Diagnostic Imaging Techniques

Positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT) are some of them.

5.2.1. Magnetic Resonance Imaging

Imaging-based diagnostic techniques, magnetic fields, and radio waves are used to image the internal structure of the body. Radio waves are sent to the tissue and the cells are stimulated. A magnetic field is created by water molecules in the body. Magnetic resonance imaging (MRI) measures the behavior of hydrogen atoms reacting to the magnetic field generated by water molecules in the body and can present them in detailed images [138] Through special interfaces, the behavior of hydrogen atoms is converted into an image in a computer environment (shown in Figure 8) [139]. Magnetic resonance imaging (MRI) is considered a safer imaging method. Because ionizing radiation is not used like X-rays. Another advantage is that it does not contain ionizing radiation. Magnetic resonance imaging (MRI) is used to diagnose many diseases. Magnetic resonance imaging (MRI) is used in the detection of many diseases such as brain tumors, brain damage, stroke and other neurological diseases, spinal problems, lumbar and cervical herniation, spinal cord injury, heart diseases, complications after a heart attack and heart valves, liver and kidney tumors, gallbladder problems, musculoskeletal system diseases, joint inflammation, bone tumors, and fractures, women's health, sinus problems, sinus tumors, sinusitis, blood vessel and circulatory system diseases, thrombosis, vascular occlusion and aneurysms. Magnetic resonance imaging (MRI) is used in the detection of many diseases such as brain tumors, brain injury, stroke, and other neurological diseases, spinal problems, herniated disc and neck, spinal cord injury, heart disease, complications after a heart attack, and heart valves, liver and kidney tumors, gallbladder problems, musculoskeletal diseases, joint inflammation, bone tumors and fractures, sinus problems, sinus tumors, sinusitis, blood vessels and circulatory system diseases, thrombosis, vascular occlusion, and aneurysms. Magnetic resonance imaging (MRI) is not primarily used as a diagnostic tool for all diseases because it is more expensive and takes longer than other methods. The images that come in a closed MRI are more detailed. Closed MRI allows more diseases to be diagnosed than open MRI. Thanks to the magnetic field strength, it is possible to scan faster. Another advantage is that it allows you to capture high-quality images. However, there are disadvantages as well as advantages of closed MRI. To better diagnose the disease, the images need to be clear. For this reason, the patient must remain immobile. Patients with obesity disorders may not be able to fit into the machine. Another disadvantage is that the closed MRI system is noisy. Your doctor may be able to provide you with headphones or earplugs to prevent you from hearing this sound. Jul. However, open MRI is quieter than closed MRI. Open MRI and closed MRI also have different image quality. In addition, closed MRI diagnoses more diseases than open MRI. The MRI procedure can take about 30 to 60 minutes, and the patient must be comfortable.

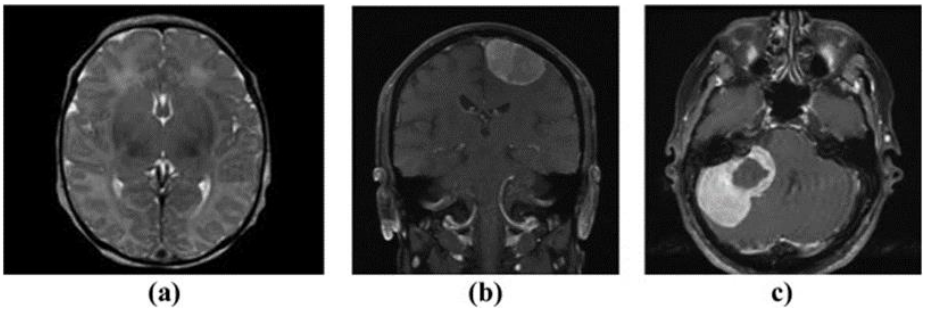

Fig 8. A computer-generated MRI image has been provided [139]. Reprinted by permission from Elsevier.

5.2.2 Computed Tomography

Computed tomography (CT) creates cross-sectional images of structures inside the body thanks to X-rays. It helps medical personnel in the detection and treatment process in 1971, computed tomography (CT) was used for the first time in the UK [140]. Computed tomography (CT) is a non-invasive diagnostic imaging technique [140]. It is also known as a frequently used imaging technique. For computed tomography (CT), first of all, the patient lies on a bed similar to a stretcher (shown in Figure 9) [141]. An X-ray tube is used when computed tomography (CT) is performed. This X-ray tube rotates around the patient and X-rays are sent [140]. Cross-sectional images are formed thanks to X-rays passing through different parts of the body. Computed tomography (CT) transfers the resulting cross-sectional images to the computer. Thanks to these images, your doctor diagnoses your disease. When using the computed tomography (CT) method, it may be necessary to use contrast media in some cases. The contrast agent is either given to drink or injected intravenously according to the recommendation of your doctor. Computed tomography (CT) is used to diagnose many diseases. Computed tomography (CT) is used to diagnose many diseases such as head and neck diseases, chest diseases, abdominal and pelvic diseases, musculoskeletal system diseases, and blood vessel diseases. computed tomography (CT) is used when diagnosing many diseases, such as blood vessel diseases.

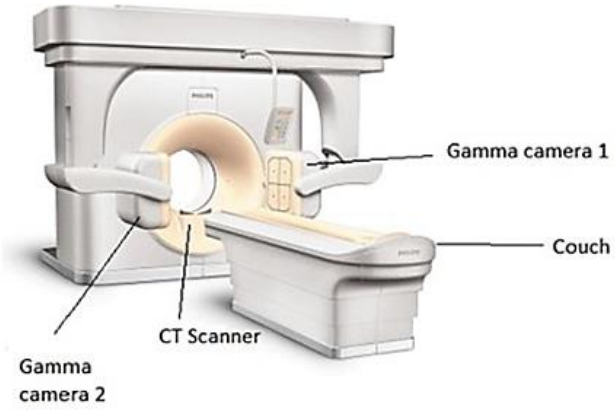

Fig 9. A computed tomography scanner is depicted in the image [141]. Reprinted by permission from Elsevier.

5.2.3. Positron Emission Tomography

Positron emission tomography (PET) is a noninvasive diagnostic imaging technique used in the early and definitive detection and treatment of diseases [142], [10]. It is a frequently used method in diagnostic imaging techniques [142]. It creates three-dimensional, colorful images. For this, radioactive material is used [143]. This substance collects in cells that use a lot of energy. A radioactive substance is injected into the body. The cells in the body absorb this substance. Cells emit a particle called a positron. Positron emission tomography (PET) detects positrons emitted by radioactive material. Tissues that absorb radioactive material emit radiation. As a result of scanning, these tissues appear brightly (shown in Figure 10) [144]. Positron emission tomography (PET) is used when diagnosing cancer, neurological disorders, heart diseases, and infections. In addition, PET is also used for the separation of Alzheimer's and dementia disease. The disadvantage of positron emission tomography (PET) is that it is costly.

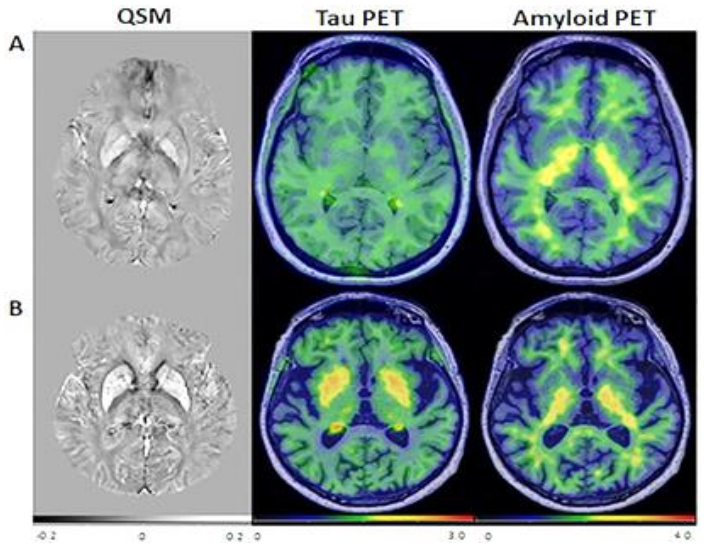

Fig 10. The bright tissues resulting from the scan are shown in the image [144]. Reprinted by permission from Elsevier.

5.3 Nanotechnology in Diagnostic Methods

Nanotechnology is a field that deals with designing, manufacturing, studying, and applying the properties of materials and devices at very small scales such as atoms, molecules, and large molecules. Studies conducted in this field show that the properties of materials and devices can be controlled at the atomic and molecular levels. Nanotechnology appears in many diagnostic imaging methods such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission technology (PET). In diagnostic imaging methods, contrast agents are often the materials of choice to provide visual differences in the resulting images by interacting with incident radiation [145].

5.3.1. Gadolinium Ions

It is known today that many contrast agents based on gadolinium (III) ions are often used in clinical applications. Gadolinium ions are a contrast agent used in magnetic resonance imaging (MRI). Gadolinium ions, whose

paramagnetic properties are quite strong, have an important place because of these properties. Ions are toxic, but if ligands are selected Decently, gadolinium chelates, which have no toxic effects on the body and show a high level of stability, can be among the compounds that can be produced. Gd-DTPA is one of the most Frequently used chelates. Gadolinium, which is used in the production of MRI contrast agents, allows more advanced products to be obtained by using it in various nanoparticle formulations. These formulations concentrate more gadolinium ions in the target tissue, allowing for more sensitive results in high magnetic fields. Gadolinium ions can also be added to organic and inorganic nanoscale scaffolds. Among the promising candidates for the formulation of future paramagnetic contrast, Decouples are gadolinium oxide nanoparticles [146]. The current status of gadolinium nanostructures, polymer, liposome, and inorganic nanoparticle types is preclinical. Gadolinium chelates are in clinical use [147].

5.3.2. Superparamagnetic Iron Oxide Nanoparticle

SPION is another commonly used contrast agent in magnetic resonance imaging (MRI). By causing the T2 relaxation time of the surrounding water protons to decrease, it improves the imaging quality by leading to the formation of signal gaps in T2-weighted images [148]. It has a superparamagnetic property. Thanks to this feature, it can be used in in vivo imaging applications. SPIONs exhibit a higher magnetic response compared to other paramagnetic materials, especially when a strong magnetic field is applied. Iron oxide is known as a non-toxic substance, but its use in high doses may increase the risk of iron toxicity. The current status of the polymer-coated iron oxide nanoparticle types of SPIONS is at the stage of clinical use and some clinical trials [147].

5.3.3. Bi_2S_3 Nanoparticles

It is a new contrast agent developed for use in computed tomography (CT). Bismuth citrate and sodium sulfide are formed by precipitation. Then it is coated with a polymer such as polyvinylpyrrolidone (PVP). It provided more absorption in X-rays compared to iodine-based contrast agents. The current status of Bi_2S_3 nanoparticles is preclinical [147].

5.3.4. Gold Nanoparticles

Gold nanoparticles are a beautiful contrast agent for computed tomography (CT). It is less toxic than other contrast agents [149]. Gold nanoparticles have been compared with iodine and an increase in x-ray absorption has been observed [150], [151]. Good imaging with low x-ray energy is an advantage for gold nanoparticles. In this way, the patient will have been exposed to a low dose of radiation. Gold nanoparticles have been applied in vivo in live mouse models. It shows little accumulation and high quality display is provided. Gold nanoparticles have provided an efficient result for tumor detection in computed tomography (CT). A very effective result has been achieved compared to the iodized-based contrast agent. The current status of gold nanoparticles is in the clinical trial phase [147].

5.3.5. Iodized Nanoparticles

It is another contrast agent that is frequently used in computed tomography (CT). The ability to reduce the intensity of X-rays provides an advantage. However, the fact that it triggers the changes that will occur in the target tissue in other tissues and the low circulation time provides a disadvantage. The current status of iodized nanoparticles, polymeric carriers, liposomal carriers, and inorganic nanostructure types is pre-clinical [147].

5.3.6. Radiopharmaceuticals

Positron emission tomography (PET) is usually used in conjunction with computed tomography (CT). Positron emission tomography (PET) can integrate short-half-life radioisotopes into biomolecules such as C, N, O, Fr, and Cu to measure the settlements and metabolism of biomolecules in the organism. It is used when examining fluorodeoxyglucose-type radio ethyl tags, which are used to measure glucose metabolism. Due to their high number of surface functionalities, nanoparticles can be used as suitable platforms for "multimodal imaging" contrast agents by binding with various imaging or therapeutic ligands. Commonly used radio-labeling agents for macromolecules are chelated metals such as $_{64}$Cu, chelates have high dimensions and charged nature. Therefore, since they can affect their pharmacokinetic properties, they face some disadvantages. In radiopharmaceuticals, the current use case of labeled forms of biomolecules is clinical use and preclinical [147].

6. Nanotechnology in Gene Therapy

6.1. Definition of Gene Therapy

Gene therapy is a method developed to be used in the treatment of genetic diseases. It is planned to rearrange the functions of defective genes with gene therapy, which is still a very new field of research, or to replace these genes with healthy ones by gene transfer [152].

6.2. Basic Principles of Gene Therapy

The goal of gene therapy in humans is to treat or change the wrong gene expression within the human body. Gene therapy is a technique used to treat people with genetic diseases. This process takes place through certain steps, which are as follows: The disease-causing gene is identified and extracted, then a healthy gene is added instead of the diseased gene [152].

6.3. History of Gene Therapy

Although gene therapy is one of the most recent therapeutic methods, it has a long history. The beginning of gene therapy in the seventies. When the two scientists Friedman and Roblin put forward a scientific paper entitled "Gene therapy for human genetic diseases" in 1972, and with time, specifically in the eighties in 1984, a system of viral vectors known as retroviruses was created, up to the nineties, which is the period that happened There is a breakthrough in the history of gene therapy, where gene therapy progressed significantly in that period, when the first clinical research approved for gene therapy was conducted, and that was in the United States of America in 1990 and after that gene therapy began to interfere in the treatment of cancer patients in 1992, 1993 and 1999. Clinical trials of gene therapy were put on hold due to the death of Jesse Gelsinger and in 2002 the first successful gene therapy was published. Clinical trials and scientific research have continued to this day. One of the latest successes of gene therapy is the treatment of a girl with acute lymphoblastic leukemia in December 2022 [153], [154].

6.4. Main Categories of Gene Therapy

Gene therapy includes two main types, somatic gene therapy, and germline gene therapy. Somatic gene therapy deals with the treatment of somatic cells and therefore cannot be passed on to new generations, while germinal gene therapy deals with reproductive cells.

6.5. Departments of Gene Therapy

Gene therapy is divided according to the places where healthy cells are injected into 3 types, as follows:

1. Inside the organism's body. "ex vivo"
2. Outside the organism's body. "in vivo"
3. On site**.** "in situ"

Outside the body of the organism, diseased cells are removed from the patient's body, and then healthy cells are injected into the patient's body again. This method is the method used in laboratories. In the body of a living organism, the correct genes are inserted into the patient's body by injecting them into the patient's blood or cerebrospinal fluid. This method is done using viral vectors. On-site, direct injection is made into the infected cell or tissue of the patient's body [155].

6.6. Recent Progresses in Gene Therapy

The drug fasudil used by the Japanese team at Nagoya University as one of the therapeutic methods for patients with schizophrenia is the latest gene therapy to the time of the word of this article. Genetic weakness is one of the reasons for the development of schizophrenia. Copy number variation is one of the main genetic factors associated with the symptoms of schizophrenia. These differences are related to the copy number of the ARHGAP10 gene, which encodes a protein involved in the regulation of the GTPASE Rho family of enzymes. Some research indicated that RhoA was associated with schizophrenia. The research team hypothesized that downstream factors of RhoA could be a target for treatment and identified Rho-related (Rock) kinase as a potential therapeutic target as RhoA/ROCK signaling activates several risk factors for schizophrenia [156].

6.7. The Relationship Between Gene Therapy and Nanotechnology

We can say that the relationship between the field of nanotechnology and gene therapy is evident in how the treatment is delivered to the target cells. It is important to introduce the treatment into the patient's body in a safe way and also in a way that ensures that the treatment reaches the damaged cells or tissues. To make sure of this process, we must monitor the treatment on its way to the cells, whether it is how the treatment is delivered or even monitored, both of which are small nanomaterials that cannot be seen with the naked eye. The greater the accuracy and allocation of these nanomaterials, the more successful the treatment [157], [158].

6.8. Gene Delivery Systems

Gene delivery is the process of introducing an exogenous gene, such as DNA or RNA, into a host cell. Gene delivery must reach the host cell to induce gene expression. Successful gene delivery requires that exogenous genes remain lodged within the host cell with the ability to integrate into or replicate independently of the genome. This requires DNA to be made as part of a vector, which is designed to be able to enter the target host cell to deliver the mutated gene into that cell's genome. In complex multicellular eukaryotes, if the mutated gene is introduced into the

cells of the host's sex line, the resulting host cell can pass the mutated gene on to the offspring of that organism. If the mutated gene is introduced into somatic cells, that gene will remain in the cells of the somatic line, and therefore only in the host organism. Gene delivery is a necessary step in the field of gene therapy by inserting or stopping a gene to obtain certain therapeutic results in patients [159]–[161] One of the methods used to deliver or transfer gene therapy or healthy genes to target cells is physical systems and chemical systems.

6.8.1. Gene Delivery Methods Using Viruses "Recombinant Viruses"

The use of viral vectors is one of the ways to deliver genes to target cells, where the role of this method is concentrated in that viruses can transfer their DNA to the host cell. Also, viruses are characterized by their rapid reproduction in a short time. Many types of viruses have been used in gene therapy, we mention them;

1. Retroviruses.
2. Adenoviruses.
3. Pox viruses.
4. Herpes simplex virus.
5. Lentivirus.

Although there are many advantages to the method of delivering genes to viruses, it also has many disadvantages. Including the transfer of a small part of the DNA to the target cells, in addition to the risks that cannot be signed when the virus is introduced into the body of the organism due to the occurrence of mutations and cellular defects [162].

6.8.2. Methods of Gene Delivery Without the Use of Viruses "Synthetic Vectors"

Gene delivery methods without using viruses are divided into two main parts, which are chemical methods and physical methods. We will briefly mention some examples of these methods [163].

Physical methods used to deliver gene therapy: The physical methods used to deliver gene therapy to target cells are the inorganic method and the non-viral vector method. Examples of physical methods: Electroporation, which is a method used to promote cellular rehabilitation. Magnetic perforation In this method, inorganic magnetic nanoparticles are used [163].

Chemical methods used to deliver gene therapy: The chemical methods used to deliver gene therapy to target cells are the organic method and the non-viral vector method. Examples of chemical methods: are liposomes and polymers [163].

Conclusion

As a result, in this article, drug delivery systems, dermatology, COVID-19, cancer, diagnostic imaging devices and gene therapy, which are nanotechnological applications in the field of medicine, have been mentioned in detail. It is emphasised how important the production of nanotechnological materials is with the increasing human population. It is emphasised that the use of drugs obtained from these nanotechnological materials brings some problems. The effectiveness of nanotechnological applications developed recently with nanotechnological approaches has been seen to bring advanced technological steps. Researchers are designing nanosystems that can mimic the gene transfer capacity and high infectivity of viral vectors by taking advantage of these properties of nanoparticles. It has been emphasised that understanding these molecular approaches through nanomaterial synthesis makes it possible to use delivery systems in different fields such as cancer treatment and regenerative medicine. In addition, it was stated that nanostructures can be used in the detection of diseases such as cancer, tumours and infections with diagnostic and therapeutic imaging devices.

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