Review Article

NANOTECHNOLOGY THERAPY FOR TYPE TWO DIABETIC MELLITUS: CHALLENGES AND FUTURE PERSPECTIVES

Abstract

Nanotechnology, the study and the use of materials and systems in the nanoscale (1–100 nm) has transformed a number of industries, including healthcare. Nanoscience examines structures on this scale, and nanotechnology transforms them into practical applications. The historical development of nanotechnology traces back to ancient times, with early civilizations unknowingly applying nanoscience principles in metallurgy, textile production, and art. However, modern nanotechnology emerged in the 20th century, gaining momentum through key discoveries, government programs, and global research initiatives. Nanotechnology has made major strides in the diagnosis and treatment of Type 2 Diabetes Mellitus (T2DM), providing innovative solutions such as drug delivery nanoparticles and accurate glucose monitoring nanosensors. Notwithstanding these developments, a number of issues with nanotechnology still need to be resolved before it can be widely used to treat type 2 diabetes. These issues include safety concerns, biological consequences, immunological reactions, and regulatory barriers. Future developments in artificial pancreas systems and tailored nanomedicine have enormous potential to enhance patient outcomes. Future developments could completely transform the management of type 2 diabetes by customizing medications to meet the needs of each patient and utilizing nanotechnology to improve drug targeting and glucose regulation.

Keywords: Nanotechnology, Nanoscience, Nanoparticles, Type 2 Diabetic Mellit's, Nanowires Targeted drug delivery

1. INTRODUCTION

Diabetes Mellitus (DM) is a long-term condition marked by a decreased ability to metabolize glucose[1]. Type 2 diabetes, which is characterized by poor sensitivity to insulin and β-cell dysfunction, and type 1 diabetes, which is characterized by decreased insulin production, are the two most prevalent types of diabetes. Hyperglycemia, excessive urine production, compensatory thirst, tiredness, blurred vision, unexplained weight loss, and abnormalities in energy metabolism are all consequences of both[2].

A complex and diverse set of metabolic disorders, type 2 diabetes is typified by elevated blood glucose levels brought on by deficiencies in insulin secretion and/or action[2]. About 462 million people worldwide had type 2 diabetes in 2017, accounting for 1.4 million deaths and 2.5% of all deaths. Of those, 4.4% were in the 15–49 age group, 15% were in the 50–69 age group, and 22% were over 70[3]. 6.28% of the world's population is represented by this, with a prevalence rate of 6059 instances per 100,000[4].

Diabetes alone is responsible for almost a million deaths annually, it is among the top 10 causes of death in adults[5]. The prevalence is slightly higher in men than in women (6219 versus 5898 cases per 100,000), and it peaks around age 55[3]. Type 2 diabetes is predicted to affect 7079 out of every 100,000 persons worldwide by 2030, indicating a steady rise in cases[6]. Type 2 diabetes prevalence varies widely across Ethiopia, ranging from 0.34% in rural Amhara to 15.8% in vibrant Addis Ababa, with a national average of 6.5%[7].

1.1 Pharmacological Intervention of DM

Metformin and insulin have historically been primary treatments for T2DM, assisting in controlling blood sugar levels and managing weightA GLP-1 Receptor Agonist (Glucagon-Like Peptide-1 Receptor Agonist) that was recently licensed for juvenile type 2 diabetes promotes insulin release and mild weight loss. While it necessitates daily injection, forthcoming formulations might simplify administration. Remaining anti-hyperglycemic medications lack approval for youth, underscoring the importance of exercising caution in their use until further research confirms safety and efficacy outside clinical trials[8].

1.2 Non-pharmacological Interventions of DM

Non-pharmacologic interventions play a crucial role in managing youth with T2DM. Weight loss, achievable through dietary changes and increased physical activity, improves insulin sensitivity and glucose control [9]. Very low-calorie diets have shown promising results in adolescents, albeit with challenges in long-term sustainability and nutrient deficiencies. Goals include a 7%-10% reduction in BMI or maintaining a BMI below the 85th percentile for age and sex, emphasizing gradual changes in diet and daily activity[10]. Individualized dietary plans, focusing on nutrient-rich foods and portion control, alongside regular consultations with a dietitian, are essential. Similarly, increasing physical activity to at least an hour daily, including aerobic and strength exercises, while minimizing sedentary behaviors, is recommended for improved outcomes in youth with T2DM.

1.3 Constraints and drawbacks of the existing therapy

The illness and its numerous complications highlight the urgent need for a clear plan of action. The main platform's goal is to provide patients with comprehensive glycemic regulations, which can be achieved by estimating their current glycemic state and studying related disorders in order to provide them with healthcare services.

i. Newer medications such as insulin or sulphonylureas cause hypoglycemia and weight gain.
ii. Gastrointestinal side effects, including nausea, diarrhea, and occasionally lactic acidosis, can occur with biguanides like metformin.
iii. Using thiazolidinedione also causes weight gain, which is concerning because people with type 2 diabetes are already obese iv.Mimetic drug incretions may cause diarrhea, vomiting, and nausea.
v. Drugs with the potential to treat diabetes have been used both alone and in conjunction with insulin and several oral medications, but achieving complete glycemic control is difficult[11].

2. INTRODUCTION TO NANOTECHNOLOGY

The study, design, synthesis, production, modification, and use of materials, systems, and devices at the nanoscale scale (one meter is equal to one billion nanometers) is known as nanotechnology[12]. The study of structures and chemicals at nanoscales between 1 and 100 nm is known as nanoscience, and nanotechnology is the technology that applies this knowledge to real-world gadgets and other uses[13].

It is important to note that the DNA double helix has a radius of 1 nm, while a single human hair is 60,000 nm thick[14]. Nanotechnology offers tiny devices that can autonomously deliver medicine as necessary, as well as sensing technologies that provide more precise and timely medical information for disease diagnosis[15]. Nanomedicine integrates nanotechnology into healthcare, exploring atomic and molecular levels within the 1-100 nanometer range. Its goal is to harness nanoscale phenomena and materials to create unique structures and systems. Nanotechnology components mimic biological structures, with quantum dots resembling proteins and drug-carrying nanostructures resembling viruses. Innovations such as artificial nanostructures that mimic the natural mechanisms of white blood cells and wound-healing molecules to identify and fix biological harm are made possible by this alignment. [16].

2. 1 Historical Background of nanotechnology.

Nanotechnology is a science field that involves both synthesis and the production of different nanomaterials. Nanoparticles are classified as objects of 1-100 nm size that may vary from the bulk material because of their volume Many metallic nanostructures are made from copper, zinc, titanium, magnesium, gold, alginate, and silver[17]. The origins of nanoscience can be found in the fifth century B.C., when the Greeks and Democritus were examining whether matter is continuous and therefore infinitely divisible into smaller pieces or if it is made up of tiny, indivisible, and indestructible particles[18].

At the 1974 international conference on industrial production in Tokyo, Norio Taniguchi coined the term "nanotechnology" for the first time in the scientific community to refer to the development of Nano-sized mechanisms and the extremely thin processing of materials with

nanometer accuracy[19]. In 1986, E. Drexler released "Vehicles of creation: the beginning of the nanotechnology era," which refined Feynman's ideas of nanotechnological strategy[19].

Many significant discoveries and inventions were produced between the second half of the 1980s and the beginning of the 1990s, which had a significant influence on the advancement of nanotechnology. Since then, nanotechnological research and design has significantly increased, publications on nanotechnological topics have sharply increased, practical applications of nanotechnology have expanded, project financing for nanotechnology has increased significantly, and the number of organizations and nations involved in nanotechnology has increased[20].

Through the National Scientific Fund, the US began its first nanotechnology initiative in 1991. The National Nanotechnological Initiative (NNI), which prioritized cooperation between federal departments, was ratified by 2001. Prioritizing nanotechnology for 21st-century economic and national security goals was the initiative's goal. A committee examined worldwide nanotechnology trends prior to NNI's certification, sharing its results with US experts between 1996 and 1998 [20]. The forecast for nanotechnology research over the next ten years was the outcome of the 1999 session of the Interbranch group on nanoscience, nanoengineering, and nanotechnology (IWGN). NNI was formally recognized in 2000 after the Presidential Council on Science and Technology (PCAST) endorsed the IWGN's findings and recommendations that same year[21].

"I dedicate 500 million dollars in the current fiscal year for the state nanotechnology project, which will enable us to manufacture new materials in the future, to identify cancer in a few affected cells, and to achieve other wonderful outcomes," US President Clinton said in a preamble to the National Nanotechnology project [21]. The program is expected to provide significant real-world outcomes and is available for at least 20 years. Similar to the USA, Japan places a high priority on the advancement of nanotechnology[21]. Under the direction of the Industrial and Technical Committee, the Japanese Economic Association established a dedicated nanotechnology department in 2000, and the Framework Plan for nanotechnology research was created in 2001[21].

In Western Europe, countries conduct nanotechnology research through national programs. Nanotech research in Germany is mostly funded by the Ministry of Education, Science, Research, and Technology. The National Physical Laboratory and the Council of Physics and Technology Research are in charge of managing the development of nanotechnology in England. The National Center of Scientific Research directs France's approach. Furthermore, nanotechnology is becoming more and more of a concern for China, South Korea, and other developing countries. Recently, CIS nations have also begun conducting nanotechnology research, usually as part of national scientific initiatives[22].

The 1960s saw the emergence of the nanotechnology paradigm, and the 1980s and 1990s saw the start of its own development. Prior to this, the 1950s can be considered the prehistory of nanotechnology. The scientific and technological revolution of the late 19th and early 20th centuries led to the emergence of managed nanotech development circumstances toward the conclusion of this time[21].

From the 9th to the 17th centuries, Islamic and later European ceramic glazes, known as "luster," incorporated nanoparticles like silver (Ag) and copper (Cu). Renaissance pottery in Italy during the 16th century also utilized nanoparticles, influenced by Turkish methods. In the 13th to 18th centuries, nanowires of cementite and carbon nanotubes were employed in creating "Damascus" saber blades for enhanced strength and sharpness. Despite intentionally producing these colors and properties for centuries, medieval artists and forgers remained unaware of the underlying causes behind these effects[23].

3. THE USE OF NANOTECHNOLOGY

3.1 Uses of Nanotechnology in Medical Diagnostics

3.1.1 The Nanowire

Carbon nanotubes, metal oxides, or silicon can be used to create nanowires (NW), which are nanoscale channels that permit the transmission of electrical current at very low amplitudes. Due to their extremely small size and tiny diameter (about 10 nm), they are sensitive to even the smallest change in electrical characteristics, such as when another molecule is attached to them. Nanowire-based devices offer versatile platforms for very sensitive electrical biological and chemical material detection. By placing nanowires across microfluidic channels, they can detect molecular signatures of particles passing through, aiding in disease diagnosis by identifying altered genes. These systems enable researchers to locate genetic changes associated with diseases with high precision[24].

3.1.2 Nanotubes

These tiny electrically insulated tubes or holes have the ability to identify a single molecule as it travels through them. When the ionic current of the electrolyte solution containing the molecules of interest changes, the electrical current (translocation event signal) changes as well, which is how the molecule is detected)[25]. Nano fluidic devices integrating biochips and nanopores aim to revolutionize DNA sequencing by detecting unique molecular structures of DNA bases. This approach enables enhanced sizing of DNA molecules through multiple measurements on single molecules, improving accuracy. Techniques integrating nanopore-containing Adding membranes to microfluidic devices lowers noise and makes creating nanopore networks easier. for clinical applications[26]

3.1.3 Quantum Dots

The easily produced semiconductor nanocrystals known as quantum dots (QD) have unique characteristics that fall in between those of discrete molecules and bulk semiconductors. QDs have sizes between 2 and 10 nm. They exhibit size-dependent fluorescence characteristics and quantized energy levels[27].

QDs' fluorescent qualities make them appropriate for imaging and cancer targeted applications. They can enter tissues well because of their small size and EPR effect, but in order to avoid the immune system and extend their half-life, they must be coated with PEG. Imaging of several tumors was done using quantum dots connected to tumor-specific antibodies[28]. Particularly advantageous is their capacity to emit narrow spectrum and absorb broad spectrum wavelengths, which allows for the use of a single light source, greatly reducing costs and simplifying data interpretation. Furthermore, no signal amplification is required. Furthermore, while it is feasible to quantify a signal, it is not viable to compare different signals[28].

In order to examine cells in living animals, quantum dots can also be covalently connected with fluorescence microscopy. Immunofluorescence labeling of the breast cancer marker Her2 has been accomplished with the particular cancer. 18Antibodies covalently attached to polyacrylate-capped quantum dots and carbohydrate-encapsulated quantum dots with measurable luminescence are helpful in cancer imaging[27].

3.1.4 The nanobots

Also referred to as nanorobotics, these nanometer (10−9 m) robots have been used in healthcare, pharmacokinetic monitoring of diabetes, early diagnosis, and targeted medication delivery for cancer therapy. For example, when used as toothpaste or mouthwash, nanobot dentifrices can cover all subgingival surfaces, breaking down any trapped organic debris into odorless, innocuous fumes[29]. Using appropriately configured dental robots, pathogenic microorganisms found in dental plaque are located and eliminated. Indeed, it has been suggested that patients will receive injections of nanobots to carry out tasks at the cellular level. Two excellent examples of nanobots are biochips and nanobots[29].

.

3.1.5 Silica Nano spheres

Similar to QDs, inorganic dye-loaded silica particles exhibit long-lasting fluorescence lifetimes, sharp emission peaks, and good photo stability. Their hydrophilic surface makes them suitable for dispersion aqueous solutions. To boost the detection signal, they are typically employed to conjugate optical labels, such as organic or inorganic dye molecules (ruthenium-based and lanthanide-based)[30].

3.1.6 Nano biosensors

Biosensors are chemical sensors, in which recognition processes rely on biochemical mechanisms utilization. They consist of a biological element (responsible for sampling), and a physical element (often called transducer, transmitting sampling results for further processing. Nanomaterials serve as sensitive sensors for medical diagnostics, identifying specific cells or regions in the body. They utilize various forces and parameters to distinguish cancer cells at the molecular level, facilitating targeted treatment delivery. Additionally, Nano sensors detect external changes and relay information to enhance diagnostic accuracy within the body[31].

3.2 Applications of Nanotechnology in Treatment.

3.2.1. Role of nanotechnology in gene therapy

The process of replacing a damaged gene in the DNA that causes a disease with a healthy gene is known as gene therapy. A vector is typically used to introduce the gene into the stem cells[32]. The best targets for gene therapy are stem cells because of their extended lifespan and capacity for self-renewal [33]. When releasing the gene or genes of different sizes, the vector should be extremely efficient and specific. The host immune system should not identify it as an antigen. The inserted gene must be expressed by the vector for the duration of the organism's existence. When the gene is properly integrated into the cells, it prevents and fixes the altered gene's functions and restores the cells' normal ability to operate[34].

Viral vectors, fundamental in gene therapy for years, leverage host machinery for protein synthesis via DNA encoding. Their stable integration into host genomes enables long-term transgene expression. Common vectors like lentiviruses, retroviruses, and adenoviruses are efficient. Risks include immune responses, inflammation, and off-target changes, impairing efficacy[35]. Immune responses may render therapy ineffective and trigger rapid viral clearance upon subsequent exposure. Inflammation, as seen in a case study where a leukemic patient died from adenovirus overdose, highlights potential dangers. Insertional mutagenesis, especially with retroviruses, poses tumor risks by activating oncogenes. Selecting suitable viruses for diverse cell types remains a challenge in gene therapy[36]

When it comes to gene therapy, non-viral nanostructures are safer than viral vectors. Additionally, they rarely elicit immunological reactions and are far less carcinogenic. They are far simpler to prepare than viral vectors. The size of the gene that can be loaded is unlimited, and there is no chance of virus recombination. Among the several nanostructures utilized for non-viral gene transfer are NPs. They are perfect vectors for gene delivery because of their small size, high surface-to-volume ratio, and positive charge, which allow them to deeply permeate membranes[37].

3.2.2 The role of nanotechnology in targeted drug delivery

Nano vectors facilitate precise drug delivery, crucial for avoiding toxic solvents' release elsewhere in the body and minimizing contamination. Their diminutive size enables deep penetration into tumor cells, enhancing cancer treatment efficacy through targeted and localized drug release. This approach allows for continuous controlled drug release at desired levels, reducing overall drug doses and improving therapeutic outcomes. Nanostructures hold promise for overcoming barriers in target-specific drug delivery, offering a viable solution for treating various diseases with minimal side effects[37].

A particle core, an outer biocompatible protective layer, and a linking molecule for enhanced bioactivity are essential components of NPs used for drug delivery. The linking molecule binds the NPs' core to bioactive molecules due to the reactive compounds at both ends. Prior to

medication administration, Nano vectors undergo modification, which involves covering them with ligands such peptides, folic acid, and antibodies. To further improve the selectivity, ligands are affixed to NPs so that they can bind to specific places, in other words, they possess multiple kinds of surface receptors. Given that Nano vectors have special qualities and can undergo a variety of alterations during drug loading[39].

3.2.3Treating cardiovascular diseases through Nano systems

Cardiovascular disorders are responsible for millions of fatalities globally. Complete cardiac regeneration is still challenging, particularly after a myocardial infarction, even though medical advances have increased survival rates for individuals with heart disease. One possible method for therapeutic angiogenesis is stem cell treatment[40]. The longevity and paracrine secretion of genetically modified stem cells can be increased by introducing anti-apoptotic and pro-angiogenic genes. Due to limitations in gene capacity and immunogenicity, viral vectors are unsuitable for gene delivery to stem cells. Bio-compatible nanoparticles demonstrate efficacy in transferring genes to stem cells[41].

A diverse range of nanostructures facilitate gene delivery to stem cells. Liposomes excel due to their ability to prevent nonspecific gene binding and degradation. Polymers offer enhanced target specificity and efficiency. Chitosan alginate nanoparticles, in a study, delivered growth factors to placental cells, enhancing cardiac tissue function at myocardial infarction sites through continuous growth factor release[42]. NPs possess the capability to track and monitor stem cells, with superparamagnetic iron oxide Nano systems (SPIONs) designed to bind to cell surfaces for cellular entry through endocytosis. Additionally, quantum dots offer a means to monitor living cells over extended periods[43]

Hypertension presents numerous complications, such as myocardial infarction, heart failure, stroke, elevated blood pressure, and organ damage like to the eyes, kidneys, and brain. Despite the availability of antihypertensive medications, challenges persist, including short half-lives, limited bioavailability, low water solubility, and adverse effects. Targeted drug delivery via nanotechnology has emerged as a promising solution to address these issues[44].

Nanotechnology offers diverse carriers for hypertension treatment, including lipid carrier NPs, solid lipid NPs, polymeric NPs, liposomes, and Nano emulsions. These exemplify its potential in cardiovascular therapy, particularly non-viral stem cell-based treatments. However, extensive studies on Nano vectors' effects in living cardiovascular models are necessary for safe human application[44].

3.2.4 Nanotechnology in the treatment of ocular diseases

Nanoparticles (NPs) overcome ocular delivery challenges due to their tiny size and variable surface character, efficiently navigating barriers like tear film and ocular surface epithelium. Their biodegradability eliminates the need for surgical removal post-delivery, offering a promising solution for targeted drug transport in the eye with minimal toxicity in the case of anterior eye diseases like cataracts, conjunctivitis, keratitis, dry eye, and corneal injury, treatments typically involve eye drops. However, the corneal barrier significantly reduces drug bioavailability. Nanotechnology-based delivery systems can enhance bioavailability by increasing the retention time of drugs on the eye's surface and improving their penetration[45]. For posterior eye diseases affecting the choroid and retina—such as retinoblastoma, glaucoma, choroidal neovascularization, macular degeneration, and posterior uveitis—eye drops are generally ineffective. To treat these conditions, intraocular injections are often used, but they carry a risk of various unwanted side effects[46]. However, Nano systems have improved the delivery of drugs to the posterior portion of eye and the various Nano systems used for this purpose include Nano vesicles, Nano implants, NPs, and hydrogels[46].

3.2.5 Nanotechnology in the Treatment of Brain Diseases

Brain diseases can be treated more effectively if the challenge of the blood–brain barrier (BBB) can be overcome. The BBB acts as a protective boundary between the circulating blood and neural tissues of the brain, but it is a significant obstacle in treating brain disorders because it restricts drug entry into the central nervous system (CNS) while maintaining brain homeostasis.[47]. Disturbances to the BBB lead to neuro-inflammatory and neurodegenerative diseases like Parkinson’s and Alzheimer’s. Despite this, damaged BBBs impede drug delivery to

the brain. Nanoparticles (NPs) offer a solution, crossing the BBB efficiently to deliver drugs. NPs utilize both organic (e.g., PLA, PLGA) and inorganic (e.g., silica, gold) materials for penetration. Its tiny size, high drug-loading capacity, and imaging prowess make NPs effective in treating such diseases.

4. ADVANCEMENT OF NANOTECHNOLOGIES IN TYPE 2 DM.

Diabetes is a metabolic disorder characterized by chronically high blood glucose levels (BGLs) and an impaired ability to regulate these levels. Type two diabetes, in particular, is marked by insulin resistance, where the body's cells fail to respond effectively to insulin present in the bloodstream [48]. The disease has grown into a significant global public health issue, impacting 25.8 million people in the United States and 382 million worldwide, with projections that the number will rise to 592 million by 2035[49]. Daily insulin injections, aside from being painful, often result in patient noncompliance and carry the risk of dangerous insulin overdoses [50]. Additionally, intermittent blood glucose monitoring may miss significant BGL fluctuations that occur between tests. Therefore, improving blood glucose monitoring systems or achieving a “closed-loop” system between glucose measurement and insulin delivery is highly desirable.

4.1. Use of nanotechnology in the detection of insulin and blood sugar (Diagnosis)**:**

Nanotechnology offers innovative methods for rapidly detecting small quantities of insulin and blood glucose, which represents a critical advancement toward assessing the health of the body's insulin-producing cells. These methods can be pursued through various approaches, such as:

4.1.1 Micro-physio meter

The micro-physio meter, constructed from multi-walled carbon nanotubes, functions as a sensor for continuous insulin monitoring. Its electrically conductive nature allows direct measurement of insulin concentration by assessing the current at the electrode. Unlike traditional methods that sample insulin intermittently, this sensor detects insulin levels continuously, responding to changes in glucose-induced insulin oxidation. This real-time monitoring enables precise insulin concentration tracking, offering significant advancements in diabetes management.[51].

4.1.2 Implantable sensor

Accurate and frequent glucose monitoring is fundamental to effective diabetes management. However, current clinical glucose measurement systems are widely regarded as inconvenient for patients, due to the need for frequent and painful needle sticks. Moreover, the standard practice of intermittent testing often fails to detect dangerous fluctuations in blood glucose levels. Thus, a key challenge in diabetes research is the development of glucose sensors that provide accurate, painless, and frequent measurements, ultimately aiming for continuous glucose monitoring. Advances in glucose sensor technology could have a profound impact on diabetic health, as more precise glucose sensing would enable better insulin dosing and overall diabetes management. One effective method involves the use of polyethylene glycol beads coated with fluorescent molecules to monitor blood glucose levels. In this technique, the beads are injected under the skin, where they remain in the interstitial fluid. When glucose levels in the fluid drop to dangerous levels, glucose molecules displace the fluorescent molecules, causing the beads to emit a glow that becomes visible through a tattoo on the arm[52]. Additionally, sensor microchips are being developed to continuously monitor key body parameters such as pulse, temperature, and blood glucose. These chips are designed to be implanted under the skin and transmit real-time data that can be continuously monitored[53].

4.2. Use of Nanotechnology in the Treatment of Diabetes

Diabetic management traditionally involves injecting insulin due to oral insulin's ineffectiveness. A new approach involves inhaling insulin and achieving controlled release into the bloodstream, eliminating manual dosage adjustments. Nanotechnology offers solutions for insulin delivery, including oral insulin development and microsphere systems for enhanced absorption and targeted release, promising advancements in diabetes treatment.[54].

4.2.1 Development of oral insulin

The large-scale production of pharmaceutically active proteins, like insulin, has become achievable. The oral route is regarded as the most convenient and less invasive method for administering insulin, contributing to painless diabetes management and improved patient compliance[55]. However, one of the main challenges for oral insulin delivery is the intestinal epithelium, which acts as a significant barrier to hydrophilic drugs, preventing them from diffusing through the lipid-bilayer membranes of epithelial cells into the bloodstream[56]. To overcome this, research has focused on enhancing paracellular transport. Various intestinal permeation enhancers, such as chitosan (CS), have been explored to facilitate the absorption of hydrophilic macromolecules. Therefore, a carrier system that shields protein drugs from the stomach and small intestine's harsh environment is necessary for oral administration[57]. Chitosan nanoparticles, in particular, have shown a marked improvement in protein absorption within the intestines compared to chitosan solutions. Insulin-loaded, CS-coated nanoparticles increase their retention time in the small intestine and enhance absorption by penetrating the mucus layer. These nanoparticles temporarily open tight junctions between epithelial cells due to their pH sensitivity or degradability, allowing insulin to be released into the bloodstream through the paracellular route, thereby improving its effectiveness[58].

4.2.2 Microsphere for oral insulin production:

One of the most promising approaches for oral insulin delivery involves the use of a microsphere system, which combines multiple strategies. Microspheres serve as protease inhibitors, shielding the encapsulated insulin from enzymatic degradation within their matrix. Additionally, they act as permeation enhancers, enabling the effective crossing of the epithelial barrier following oral administration[59].

4.2.3 The nano pump

The nano pump, developed by DE Biotech, is a versatile medical device with significant potential applications. Its first notable use is for insulin delivery, where it administers insulin at a consistent rate, helping to regulate blood sugar levels. Additionally, the pump can deliver small, controlled doses of drugs over extended durations, offering precise and sustained treatment[60]. Generally, NPs have Advantages to

- Targeting diseased tissues or cells, minimizing the impact on healthy tissues.
- Improve drug uptake and retention in target areas, increasing therapeutic efficacy.
- Enhancing stability
- Enhancing solubility
- Prevent premature breakdown and ensure the drug reaches its intended destination.
- Extend the circulation time of drugs in the bloodstream, maintaining therapeutic levels over longer periods
- Minimizing off target cytotoxicity
- Stimuli responsive drug release, prevents premature drug releases

5. CHALLENGES AND FUTURE PERSPECTIVES.

Considering the challenges, failures, and successes of nanoparticles in clinical applications is essential for advancing the future of nanomedicine. While nanoparticles offer many beneficial properties, these same characteristics raise concerns about potentially heightened toxicity compared to their bulk material counterparts[61].

5.1 Challenges.

5.1.1 Safety challenges in nanomedicines development

Today, there has been growing concern about the specific toxicities associated with nanoparticle-based medicines. Typically, the standard preclinical toxicology testing protocols employed for any new drug are considered adequate to identify potential tissue-specific adverse effects for nanomedicines[62]. While this serves as a general guideline, it's important to note that certain products may necessitate additional, specialized testing to address their unique behaviors. For instance, materials that persist in the body—those that are not easily excreted, eliminated, or metabolized and tend to accumulate in particular tissues for prolonged periods—are likely to require a comprehensive evaluation of the long-term consequences of their persistence, as mandated by regulatory agencies[63].

On the other hand, nanomaterials that are proven to be rapidly cleared from the body might not require such extended testing. A key aspect unique to nanomedicines is ensuring the safety of the nanoparticulate system as a whole. Recognizing this, international standard-setting organizations have acknowledged the importance of specific measurements—particle size, zeta potential (surface charge), and solubility—as critical predictors of nanoparticle toxicity (74). The biological effects of nanoparticles can vary considerably depending on both their size and the composition of their material. While smaller nanoparticles may induce inflammation and oxidative stress, the relationship between size and effect is complex. For instance, certain nanomaterials, like carbon nanotubes, exhibit carcinogenicity at specific sizes. Relying solely on size-based comparisons between micro and nanoparticles may not accurately assess their biological effects, leading to potential underestimation or overestimation of risks.[61].

5.1.2 Biological effect

The biological impacts of nanoparticles are largely attributed to their enhanced ability to penetrate tissues, which is due to their smaller particle size compared to their bulk counterparts. In fact, these biological effects tend to intensify as nanoparticle size diminishes[64]. The correlation between particle size and the acute toxicity of intravenously administered silica nanoparticles in mice was investigated and the result showed that as particle size decreased, there was a marked increase in acute toxicities, including fatal toxicity and liver damage[64]. Nanoparticles are particularly harmful to fetuses and infants, as their defense systems such as the blood-brain barrier and the immune response are not fully matured. It has been observed that nanoparticles may pose toxicity risks to fetuses and infants at concentrations that are considered safe for adults. For instance, exposure to particles measuring 2.5 μm or smaller during pregnancy or lactation may heighten the risk of children developing autism spectrum disorder[65].

Epidemiological studies suggest that exposure to certain nanoparticles can decrease sperm motility. Furthermore, animal studies have demonstrated that nanoparticles, particularly diesel exhaust particles rich in certain materials, can disrupt sex hormone secretion. Studies also show that silver nanoparticles, with diameters of 20 and 200 nm, can reduce sperm counts, cause sperm abnormalities, and induce DNA damage in germ cells[63].

5.1.3 Immunological challenges of nanomedicines

A significant challenge in translating toxicological data from preclinical models to humans involves immunotoxicity. The immune system may be triggered by various components, particularly when biologics such as proteins, peptides, antibody fragments, or nucleic acids are incorporated into nanoparticles. Alterations in the drug or carrier can lead to conformational changes, increasing their immunogenic potential. For example, in the case of nab-paclitaxel, an immune-type response was noted in pigs with the drug, though not with albumin alone, highlighting the potential immunological risks of such formulations[66].

The conjugation of C60 fullerene derivatives to bovine serum albumin (BSA) has been shown to generate particle-specific antibodies, which were subsequently utilized for immunization. Similarly, polyamide-amine dendrimers conjugated with BSA exhibited heightened antigenic properties, inducing dendrimer-specific antibodies. The intricate production processes involved in nanoparticle-based drugs also provide multiple opportunities for endotoxin contamination, further contributing to immune responses[66]. Nanoparticles exhibit varying degrees of immunogenicity, influenced by factors like size, surface properties, and charge. Certain nanoparticles can trigger the activation of the complement pathway, prompting rapid clearance by macrophages in organs like the liver and spleen. For instance, nanoparticles made of superparamagnetic iron oxide like Ferumoxytol and Ferumoxtran-10 can be swiftly eliminated through this mechanism. [67].

5.1.4 Regulatory Challenges to nanomedicines developments

It may seem obvious that the path to approval for nanomedicines may encounter many obstacles given the complexity and wide range of possible products based on nanoparticles. The Food and Drug Administration, the European Medicines Agency and other regulatory bodies currently review new drugs based on nanoparticles product by product[66]. Standards for evaluating nanomedicines as a distinct class of therapeutic agents are largely lacking. The initial steps in

deciding whether or not nanomedicines will be subject to further regulation are the recent efforts to develop some guidelines and definitions[66]. In contrast to conventional medications, which typically contain solely one active agent and the remaining components primarily function as dormant formulations contributes (excipients), nanoparticle-based medications are complex due to their multiple components, each of which has the potential to influence the pharmaceutical properties of the drug's active ingredient. It is logical to assume that intricate regulatory techniques and considerably more complex processes will result from nanomedicines[66]. The primary drawbacks of nanoparticles are their difficulty in industrial applications and the significant time and expense required for their manufacturing. Simultaneously, delayed release and repeated administrations may be harmful to the cardiovascular system, cause cancer, and induce pulmonary inflammation. Tissue targeting might not be completely accomplished, and therapies cannot be stopped at any point. [68].

5.1.5 Ethical issues

The identification and evaluation of risks and hazards, nonmaleficence (doing no damage), autonomy (making decisions for oneself), justice (distributing risks fairly), privacy (when managing medical data), and respect for people are all ethical concerns[69]. Workers' acceptance of risk, the implementation of controls, their decision to participate in medical screening, the detection and dissemination of risks and dangers by experts, officials, and employers, and making appropriate investments in toxicologic and exposition control research are the ethical issues that most impact individuals in tasks involving nanomaterials[70]. Due to the field's infancy, the tiny number of workers who may have been exposed thus far, and the short timeframe for the development and detection of chronic diseases, there is a dearth of information on the health consequences of nanotechnology on employees[70].

Exposure to ultrafine particles (such as those with diameters less than 100 nm) and fine particles (such as those with diameters less than 2.5 μm) is the most pertinent human experience. Epidemiologic investigations of air pollution and research on occupational cohorts subjected to mineral debris, cellulose, welding smoke, the combustion products, and little-soluble, low-

toxicity particulates such carbon black and titanium dioxide have evaluated both fine and ultrafine particles[70]. Research on animals indicates the dangers of being exposed to modified nanoparticles, highlighting their correlation with lung inflammation and cytotoxicity due to oxidative stress. Accurate interpretation of these findings relative to human exposure levels is imperative. Evidence suggests that increased PM2.5 air pollution is linked to adverse health effects, particularly in susceptible populations, despite ongoing debates regarding concentration thresholds[70].

Animal studies show risks of engineered nanoparticles, correlating surface area with oxidative stress and lung inflammation. Higher oxidative stress heightens inflammation and cytotoxicity risks. Interpretation should account for human exposure doses. Evidence links increased PM2.5 air pollution with health effects, particularly in vulnerable populations like the elderly with respiratory and cardiovascular diseases..[70] Animal studies highlight potential hazards of engineered nanoparticles, including pulmonary fibrosis and translocation to the brain and circulation. Concerns arise over platelet activation and vascular thrombosis, indicating possible health risks for exposed workers.[70].

5.2 FUTURE PERSPECTIVES.

5.2.1 Personalized Nanomedicine

The customized, personalized treatment strategy used to provide the right medication to the right patient at the right dose is known as personalized medicine. The strategy was motivated by a number of considerations, including as the fact that many patients experienced unjustified side effects from drugs and that treatment efficacy varies around 25% to 80% depending on the kind of drug [71]. Proteomic, genomic, and epigenetic research, together with particular patient health issues and environmental factors, are all part of personalized medicine. On the other hand, systems in the 10–100 nm range are included in the broad term of nanotechnology. The phrase also suggests that structures at this nanoscale can be controlled to achieve a desired result[71]. Because of their size, which makes them unable to reach at a wider scale (e.g., larger than 1 μm

scale), molecules in the nano size range can interact with cells at the subatomic and molecular scales. Many of these innovations are employed daily in contemporary clinical practice, and nanomedicine has been linked to the mitigation, tracking, diagnosis, and therapy of disease [4].

There are several places where nanotechnology and personalized medicine converge. First, there is the diagnostic field, where nanotechnology can be very helpful in pharmacogenetic testing, determining the status of certain medication targets, and doing in both vivo as well as vitro testing. Second, the therapeutic field, since nanomedicine can customize a medication to a particular target found for a particular patient's ailment[72]. Furthermore, nanomedicine's ability to target makes it feasible to attain doses significantly higher than the non-formulated drug's maximum tolerated dose. As a result, the dosage can be modified according to each patient's unique circumstances. Last but not least, nanomedicine can get around two important factors that affect each person's unique drug response: the differences in cytochrome-P enzymes (CYP) and drug transporters among various ethnicities. The formulation of medications using nanomedicine may make them both intracellular in the endocytic process, which is independent of the transporter, and stealthy to metabolizing enzymes[73].

5.2.2 Nanotechnology and Artificial Pancreas Development

The therapy of Type 2 diabetes may be revolutionized by nanotechnology, which makes individualized nanomedicine possible for better medication delivery and accurate glucose regulation. Artificial pancreas systems that use nano sensors and nanocarriers have the potential to completely transform diabetes management, improving patient outcomes and well-being[72]. The creation of an artificial pancreas may provide diabetic patients with a long-term remedy. In 1974, the original concept was first explained. Its operation is straightforward: a sensor electrode continuously checks blood glucose levels; the data is fed into a tiny computer that powers an infusion pump, and a tiny reservoir releases the necessary amounts of insulin into the bloodstream[72]. An alternative approach to regulating blood glucose involves utilizing a small silicon container housing pancreatic beta cell derived from animals, encased in a material featuring precisely sized nanopores. These nanopores permit the passage of glucose and insulin while preventing larger immune molecules from entering. Implanted subcutaneously in diabetic

individuals, these containers offer a temporary means of restoring the body's glucose regulation without requiring potent immunosuppressive drugs, thus reducing the risk of infection[72].

CONCLUSIONS

Diabetes Mellitus (DM) encompasses both type 1 and type 2, characterized by symptoms such as hyperglycemia, excessive urination, thirst, and weight loss. Diabetes mellitus type 2 is a global concern, with prevalence expected to rise, particularly in urban areas of Ethiopia. Treatment options range from traditional drugs like metformin and insulin to newer alternatives such as GLP-1 receptor agonists. Non-pharmacological interventions like diet and exercise are crucial, despite challenges in maintaining them. Nanotechnology, focusing on materials at the nanometer scale, presents significant advancements in medical diagnostics and treatments, building upon historical applications. In modern medicine, nanotechnology enhances diagnosis through sensitive sensors and facilitates treatment via gene therapy and targeted drug delivery systems. In T2DM diagnosis, nanotechnology enables highly precise sensors for insulin and glucose monitoring, while in treatment, it revolutionizes insulin delivery with alternatives like oral insulin and nano pump. Challenges include safety concerns, biological effects, immunological challenges, and regulatory hurdles that must be addressed. Looking forward, personalized nanomedicine and advancements in artificial pancreas development hold promise for improving patient outcomes and revolutionizing diabetes management.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

During the creation and editing of this publication, the authors hereby declare that no generative AI tools, including text-to-image generators and large language models (ChatGPT, COPILOT, etc.), were utilized.

REFERENCES.

1. Ayelign, B., et al., *Tnf-α (− 308) gene polymorphism and type 2 diabetes mellitus in ethiopian diabetes patients.* Diabetes, metabolic syndrome and obesity: targets and therapy, 2019: p. 2453-2459.
2. Lin, Y. and Z. Sun, *Current views on type 2 diabetes.* The Journal of endocrinology, 2010. **204**(1): p. 1.
3. Abdul Basith Khan, M., et al., *Epidemiology of type 2 diabetes—global burden of disease and forecasted trends.* Journal of epidemiology and global health, 2020. **10**(1): p. 107-111.
4. Garus-Pakowska, A., *Metabolic Diseases—A Challenge for Public Health in the 21st Century*. 2023, MDPI. p. 6789.
5. Kumar, G.V., N. Usha, and B. Sandyashree, *Risk Assessment for Type-2 DM among the OPD patients attending at JSS Hospital Chamarajanagara.* International Journal of Nursing Education and Research, 2021. **9**(3): p. 297-300.
6. Mushait, K. and S. Arabia, *Predictors and Associated Risk Factors of Development of Type 2 Diabetes Mellitus.* JOURNAL OF HEALTHCARE SCIENCES 2022. **2**(6): p. 100-105.
7. Zeru, M.A., et al., *Prevalence and risk factors of type-2 diabetes mellitus in Ethiopia: systematic review and meta-analysis.* Scientific reports, 2021. **11**(1): p. 21733.
8. Jones, K.L., et al., *Effect of Metformin in Pediatric Patients With Type 2 Diabetes: A randomized controlled trial.* Diabetes Care, 2002. **25**(1): p. 89-94.
9. Serbis, A., et al., *Diagnosis, treatment and prevention of type 2 diabetes mellitus in children and adolescents.* World Journal of Diabetes, 2021. **12**(4): p. 344.
10. Di Figlia-Peck, S., R. Feinstein, and M. Fisher, *Treatment of children and adolescents who are overweight or obese.* Current problems in pediatric and adolescent health care, 2020. **50**(9): p. 100871.
11. Terse, P.P., et al., *Nanotechnology and Nanocapsule-Based Approaches for the Diagnosis and Therapeutics of Diabetes Mellitus: A Concise Survey.* Journal of Drug Delivery and Therapeutics, 2023. **13**(9): p. 151-159.
12. Sahu, M.K., R. Yadav, and S.P. Tiwari, *Recent advances in nanotechnology.* International Journal of Nanomaterials, Nanotechnology and Nanomedicine, 2023. **9**(1): p. 015-023.
13. Mansoori, G.A. and T.F. Soelaiman, *Nanotechnology--An introduction for the standards community*. Vol. 2. 2005: ASTM International. P.21.
14. Gnach, A., et al., *Upconverting nanoparticles: assessing the toxicity.* Chemical Society Reviews, 2015. **44**(6): p. 1561-1584.
15. Thwala, L.N., et al., *Nanotechnology-Based Diagnostics for Diseases Prevalent in Developing Countries: Current Advances in Point-of-Care Tests.* Nanomaterials, 2023. **13**(7): p. 1247.
16. Gordon, N., U. Sagman, and C. Alliance, *Nanomedicine taxonomy*. 2003: Canadian Institutes of Health Research Canada. P. 32.
17. Aeila, A.S.S., T.M. Sai, and A.R. Kumar, *Nanoparticles—the future of drug delivery. J.* Pharmaceutical Res, 2019. **9**(12): p. 631-636.
18. Bayda, S., et al., *The history of nanoscience and nanotechnology: from chemical–physical applications to nanomedicine.* Molecules, 2019. **25**(1): p. 112.

19. Omran, B.A. and B.A. Omran, *Fundamentals of nanotechnology and nanobiotechnology.* Nanobiotechnology: A Multidisciplinary Field of Science, 2020: p. 1-36.
20. Nasrollahzadeh, M., et al., *An introduction to nanotechnology*, in *Interface science and technology*. 2019, Elsevier. p. 1-27.
21. ARILESERE, A.O., *NANOTECHNOLOGY IN MEDICAL SCIENCE.* 2019: p. 50.
22. Isigonis, P., et al., *Risk governance of emerging technologies demonstrated in terms of its applicability to nanomaterials.* Small, 2020. **16**(36): p. 2003303.
23. Reibold, M., et al., *Carbon nanotubes in an ancient Damascus sabre.* Nature, 2006. **444**(7117): p. 286-286.
24. Garnett, E., L. Mai, and P. Yang, *Introduction: 1D nanomaterials/nanowires.* Chemical reviews, 2019. **119**(15): p. 8955-8957.
25. Robertson, J.W., M.L. Ghimire, and J.E. Reiner, *Nanopore sensing: A physical-chemical approach.* Biochimica et Biophysica Acta (BBA)-Biomembranes, 2021. **1863**(9): p. 183644.
26. Lyberopoulou, A., E.P. Efstathopoulos, and M. Gazouli, *Nanotechnology-based rapid diagnostic tests.* Proof and concepts in rapid diagnostic tests and technologies, 2016: p. 89-105.
27. Agarwal, K., S. Mondal, and H. Rai, *Quantum dots: An overview of synthesis, properties, and applications.* Materials Research Express, 2023. **10**: p. 26.
28. Gil, H.M., et al., *NIR-quantum dots in biomedical imaging and their future.* Iscience, 2021. **24**(3): p. 102189.
29. Jackson, T.C., B.O. Patani, and D.E. Ekpa, *Nanotechnology in diagnosis: a review.* Advances in Nanoparticles, 2017. **6**(03): p. 93-102.
30. Reisch, A. and A.S. Klymchenko, *Fluorescent polymer nanoparticles based on dyes: seeking brighter tools for bioimaging.* Small, 2016. **12**(15): p. 1968-1992.
31. Bhatia, D., et al., *Biosensors and their widespread impact on human health.* Sensors International, 2024. **5**: p. 100257.
32. Cavazzana, M., et al., *Gene therapy targeting haematopoietic stem cells for inherited diseases: progress and challenges.* Nature reviews Drug discovery, 2019. **18**(6): p. 447-462.
33. Shomali, N., et al., *Mesenchymal stem cells as carrier of the therapeutic agent in the gene therapy of blood disorders.* Journal of cellular physiology, 2020. **235**(5): p. 4120-4134.
34. Ma, C.-C., et al., *The approved gene therapy drugs worldwide: from 1998 to 2019.* Biotechnology advances, 2020. **40**: p. 107502.
35. Croze, R.H., et al., *Viral Vector Technologies and Strategies: Improving on Nature.* International Ophthalmology Clinics, 2021. **61**(3): p. 59-89.
36. Goswami, R., et al., *Gene Therapy Leaves a Vicious Cycle.* Front Oncol, 2019. **9**: p. 297.
37. Zu, H. and D. Gao, *Non-viral vectors in gene therapy: recent development, challenges, and prospects.* The AAPS journal, 2021. **23**(4): p. 78.
38. Harish, V., et al., *Review on nanoparticles and nanostructured materials: Bioimaging, biosensing, drug delivery, tissue engineering, antimicrobial, and agro-food applications.* Nanomaterials, 2022. **12**(3): p. 457.
39. Hefnawy, A., et al., *Dual-ligand functionalized core-shell chitosan-based nanocarrier for hepatocellular carcinoma-targeted drug delivery.* International Journal of Nanomedicine, 2020: p. 821-837.
40. Bian, X., et al., *Therapeutic angiogenesis using stem cell-derived extracellular vesicles: an emerging approach for treatment of ischemic diseases.* Stem cell research & therapy, 2019. **10**: p. 1-18.
41. Wang, Y., et al., *Is viral vector gene delivery more effective using biomaterials?* Advanced Healthcare Materials, 2021. **10**(1): p. 2001238.

42. Smagul, S., et al., *Biomaterials loaded with growth factors/cytokines and stem cells for cardiac tissue regeneration.* International journal of molecular sciences, 2020. **21**(17): p. 5952.
43. Wagner, A.M., et al., *Quantum dots in biomedical applications.* Acta biomaterialia, 2019. **94**: p. 44-63.
44. Baishya, B., et al., *Enhancing of oral bioavailability of poorly water-soluble antihypertensive drugs.* Int J Curr Pharm Res, 2021. **13**(4): p. 42-7.
45. Afarid, M., S. Mahmoodi, and R. Baghban, *Recent achievements in nano-based technologies for ocular disease diagnosis and treatment, review and update.* Journal of Nanobiotechnology, 2022. **20**(1): p. 361.
46. Nayak, K. and M. Misra, *A review on recent drug delivery systems for posterior segment of eye.* Biomedicine & pharmacotherapy, 2018. **107**: p. 1564-1582.
47. Bors, L.A. and F. Erdő, *Overcoming the blood–brain barrier. challenges and tricks for CNS drug delivery.* Scientia Pharmaceutica, 2019. **87**(1): p. 6.
48. Hartuti, S., A. Nasution, and S. Syafril, *The effect of drug-related problems on blood glucose level in the treatment of patients with type 2 diabetes mellitus.* Open Access Macedonian Journal of Medical Sciences, 2019. **7**(11): p. 1798–1802.
49. Almutairi, E., *Statistical modelling and machine learning for the epidemiology of diabetes in Saudi Arabia*. 2022, Brunel University London. p. 180.
50. Sugumar, V., et al., *Current development of chemical penetration enhancers for transdermal insulin delivery.* Biomedicines, 2023. **11**(3): p. 664.
51. Zhan, Z., et al., *Microliter sample insulin detection using a screen-printed electrode modified by nickel hydroxide.* ACS omega, 2020. **5**(11): p. 6169-6176.
52. Subha, G. and M. Kalaiselvi, *Synthesis and characterization of zinc oxide nanoparticles using Curcuma amada and it's in vitro anti-diabetic activity.* AIJRSTEM, 2019. **26**: p. 149-156.
53. Angelov, G.V., et al., *Healthcare sensing and monitoring*, in *Enhanced Living Environments: Algorithms, Architectures, Platforms, and Systems*. 2019, Springer. p. 226-262.
54. de Souza Marinho, T., et al., *Intermittent fasting benefits on alpha-and beta-cell arrangement in diet-induced obese mice pancreatic islet.* Journal of Diabetes and its Complications, 2020. **34**(3): p. 107497.
55. Mukhopadhyay, P. and P. Kundu, *Stimuli-responsive polymers for oral insulin delivery*, in *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications*. 2019, Elsevier. p. 525-546.
56. Xu, Y., et al., *An overview of in vitro, ex vivo and in vivo models for studying the transport of drugs across intestinal barriers.* Advanced Drug Delivery Reviews, 2021. **175**: p. 113795.
57. Pathomthongtaweechai, N. and C. Muanprasat, *Potential Applications of Chitosan-Based Nanomaterials to Surpass the Gastrointestinal Physiological Obstacles and Enhance the Intestinal Drug Absorption.* Pharmaceutics, 2021. **13**(6): p. 887.
58. Garg, U., et al., *Current Advances in Chitosan Nanoparticles Based Drug Delivery and Targeting.* Adv Pharm Bull, 2019. **9**(2): p. 195-204.
59. Kim, J.U., et al., *Optimization of phytic acid-crosslinked chitosan microspheres for oral insulin delivery using response surface methodology.* International Journal of Pharmaceutics, 2020. **588**: p. 119736.
60. Pethe, A., et al., *Advances in insulin drug delivery systems.* Journal of Pharmacy Research, 2009. **2**(3): p. 534-540.
61. Desai, N., *Challenges in development of nanoparticle-based therapeutics.* The AAPS journal, 2012. **14**(2): p. 282-295.
62. Duvall, M.N. and K. Knight, *FDA regulation of nanotechnology.* Beveridge and Diamond, PG: Washington, DC, USA, 2012: p. 144.

63. Coleman, M.E., et al., *Examining evidence of benefits and risks for pasteurizing donor breastmilk.* Applied Microbiology, 2021. **1**(3): p. 408-425.
64. Garcés, M., et al., *Current understanding of nanoparticle toxicity mechanisms and interactions with biological systems.* New Journal of Chemistry, 2021. **45**(32): p. 14328-14344.
65. N'Dea, S., et al., *Gold nanoparticle biodistribution in pregnant mice following intravenous administration varies with gestational age.* Nanomedicine: Nanotechnology, Biology and Medicine, 2021. **36**: p. 102412.
66. Desai, N., *Challenges in development of nanoparticle-based therapeutics.* Aaps j, 2012. **14**(2): p. 282-95.
67. Wang, Y.X., *Superparamagnetic iron oxide based MRI contrast agents: Current status of clinical application.* Quant Imaging Med Surg, 2011. **1**(1): p. 35-40.
68. Xuan, L., et al., *Nanoparticles-induced potential toxicity on human health: Applications, toxicity mechanisms, and evaluation models.* MedComm (2020), 2023. **4**(4): p. e327.
69. Varkey, B., *Principles of Clinical Ethics and Their Application to Practice.* Med Princ Pract, 2021. **30**(1): p. 17-28.
70. Schulte, P.A. and F. Salamanca-Buentello, *Ethical and scientific issues of nanotechnology in the workplace.* Environ Health Perspect, 2007. **115**(1): p. 5-12.
71. Clack, K., et al., *Toward personalized nanomedicine: the critical evaluation of micro and nanodevices for cancer biomarker analysis in liquid biopsy.* Small, 2023. **19**(15): p. 2205856.
72. Mandal, D., J.K. Sarmah, and J. Gupta, *NanoRevolution: Pioneering Applications of Nanotechnology in Type II Diabetes Care.* Engineering Proceedings, 2023. **56**(1): p. 56.
73. Alghamdi, M.A., et al., *The Promise of Nanotechnology in Personalized Medicine.* J Pers Med, 2022. **12**(5).