RESEARCH ARTICLE

Past, Present and Future Perspective of Application of Nanobiotechnology in Pharmacology and Innovative Therapeutics

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Abstract

Nanobiotechnology, by definition, is a multi-strategic technique that combines nanotechnology and biotechnology to engineer the properties of therapeutic agents, e.g., target delivery of therapeutics by nanoparticles, in a unique way as paradigm shifts from fundamental biological study to clinical pharmacology. The concept was introduced as an effective alternative to conventional drug delivery and targeting method. Nanobiotechnology has several applications in cancerous disease, autoimmunity, inflammation, infectious diseases. Nanoparticles have biomimetic properties and have capability to encapsulate the drug molecule for the safest delivery to the target organ. Nanobiotechnology research is currently progressive and needs extensive exploration and understanding for its potential use in future innovations. The present review studies the concept of nanobiotechnology, its origin, mechanism of drug delivery and targeting, applications to decipher the role of this field in future advanced research.

Introduction

The term *"Nanotechnology"* entails studying the influence of nanoparticles on the technological processes at the atomic and molecular levels. Particles at the nano size exhibit differential and unique properties, including smooth surface texture and the ability to provide a larger surface area for efficient catalyst production.[1] On the other hand, biotechnology is a continuously emerging field of life sciences that has enabled reasonable modifications in biological systems to benefit humans. Since biotechnology has grown into several fields such as medical, agriculture, marine, environmental and so on, it has also introduced a newly trending concept of nanobiotechnology.[1]

Nanobiotechnology is a multi-strategic approach that merges nanotechnology with biotechnology to engineer different properties of therapeutic biological agents at the molecular scale[1]. The nano systems carry small biomolecules, proteins, and genes that can cure in a healthcare system. Nanobiotechnology has already started to impact the healthcare system using nano-based systems. Nanoparticles are small particles with size of 1 to 100 nm in range and are not detectable by the human eye. The particles have extended physicochemical properties and synergistic capabilities, which enhance the functional capacities of solid and active biological agents for the treatment of disease.[2] Nanobiotechnology has a strong application in the form of nanomedicine. The concept of nanomedicines emerged because of the functional strength of nanoparticles to act as a medicinal component. Nanomedicine is basically a refinement of molecular medicine.[3] Technological modulations at the small-scale level can facilitate the appropriate targeting and recovery of the diseases. The field has several opportunities for advancements and can provide accuracy and reliability in the care setting. It can open extended visions in research and investigate more comprehensive phenomena. Based on the previous discussion, present study aims to determine the scope of nanobiotechnology in the pharmaceutical therapeutics and innovation. The review has a potential to describe how the field of nanobiotechnology can address multiple health complexities for the benefit of human health and what opportunities it holds for future advancements.

History of Nanobiotechnology in Pharmacology and Innovative Therapeutics

The foundation of nanobiotechnology was based on physicist scientist Richard Feynman's concepts.[4] He introduced the concept of technology at the nanoscale. According to his theory, nanoscale machinery can manufacture and fabricate [4]. In 1981, Kim Eric Drexler presented his publication *"The Coming Era of Nanotechnology,"* add addressed the molecular manufacturing in his book. He utilized the concepts of Feynman's theory and provided manifesting of small molecules with specific atomic composition using designed proteins.[4] The rise of nanobiotechnology included biomolecules such as genes, proteins, peptides, and other potentially bioactive compounds. The field has expanded to nanogenomics and nanoproteomics and gained therapeutic insights for healthcare concerns. The use of nanosystems in biological treatment identified drug delivery systems that transfer biological macromolecules to their targets with effectiveness and fewer side effects. The approach is specifically significant for complex diseases.[5]

Drug Delivery Systems and Nanotechnology

Nanotechnology's drug delivery systems include nanoparticles, nanoemulsions and nanosuspensions, nano(co)crystals, and lipid-based nanocarriers (Fig. 1). These systems have potentially improved treatment outcomes in part as a consequence of their properties that include but are not limited to the increased surface area, solubility, bioavailability, fast rate of dissolution, drug protection from degradation, and fewer dosage requirements.[6] The niosomes and nano co-crystal are the potential small-sized nanocarrier systems with a validated and optimized design that can improve the bioavailability and target delivery of nevirapine and lamivudine-zidovudine respectively.[7-8] Hence, nanoparticles act as a strong carrier for drugs and exhibit a preference for a specific target or enhance the bioavailability of the API.[9] Also, the nanoparticles have molecular attachments with biorecognition properties that further enhance bioavailability. Metal nanoparticles encapsulate antimicrobial agents and interact with the cellular membrane to exhibit antimicrobial effects. Polymer nanoparticles on the other hand combine nanoparticles with polymers to enhance the capability of drug delivery. Other types of drug delivery system are chitosan-based because of their attachment property to the mucosal surface. Nanoparticles conjugated with chitosan further promotes the drug delivery system and is a great depiction of biotechnology integration in the nanotechnology field.[9]

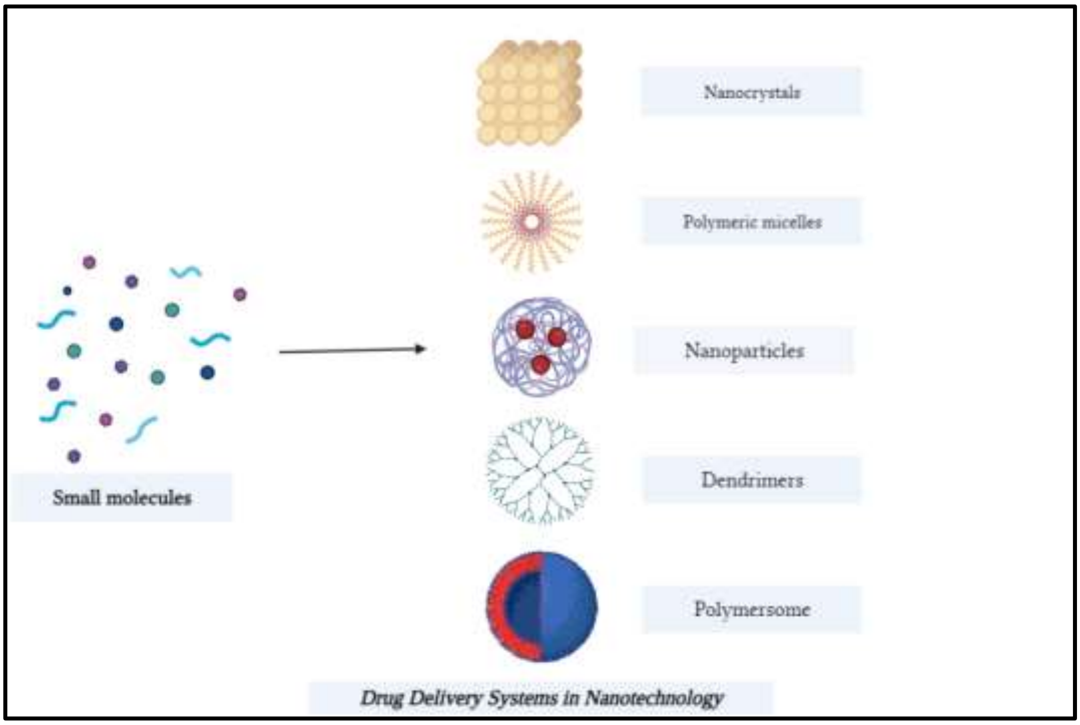

Figure. 1 Different types of nano-based drug delivery systems (Source: Author's Own Creation)

Drug Targeting Methods in Nanotechnology

Nano systems are advantageous compared to conventional systems due to their shown potential to reduce side effects, monitor drug distribution, prolong stay in circulation, prevent organ damage, and avoid administration errors.[10] Furthermore, some of the nanoparticles can inhibit the loss and degradation of drug compounds. Drug targeting can be active or passive.[10] Passive targeting is achieved through passive systems to enhance nanocarrier deposition. The deposition is caused by the enhanced permeability and retention property of passive systems to carry out the drug targeting.[11] One example of passive drug targeting is through creating a tumor microenvironment.[12] Active targeting is achieved using a vector system that increases the interaction between nanocarriers and the target site.[10] Antibodies, peptides, and transferrin proteins can be used as a vector to facilitate the nanocarriers in reducing the side effects of drug.[10]

One of the active targeting techniques is carbohydrate-mediated targeting.[12] Since carbohydrates have strong identification of antigen-specific molecular patterns and infection, nanoparticles can be conjugated with carbohydrate moieties such as lectins to directly recognize the antigen integration and infection.[12] Drug targeting is an essential aspect of nanotechnology in research, therapeutics, and outcomes of nano-based drug interventions.

Present Advancement in Nanobiotechnology in Pharmacology and Innovative Therapeutics

Application of Nanobiotechnology in Management of COVID-19

Nanobiotechnology has a potential implication in the field of pharmaceutical sciences. Recent advancements in this emerging field have shown trends for managing chronic and previously considered incurable ailments.[13] Since COVID-19 is the most immediate area of concern in the present world, nanotechnology trends must address these challenges. COVID-19 is dominating because of the rising mutations producing variants of concerns (VOC) such as alpha, beta, delta, and omicron strains. These mutations result from site-specific variations in the viral proteins.[14] A list of various drugs is under testing for COVID-19 management. For example, tocilizumab is an effective alternative treatment for COVID-19 patients to reduce cytokine-mediated inflammatory responses, but there is a significant uncertainty about its safe long-term effects.[15] Despite this fact, no consensus about safe therapeutics has been found. Nano-based systems can effectively target specific sites through drug encapsulation and reduce drug toxicity.[16] Nanoparticles encapsulate viral proteins to target site-specific mutations are a suitable bio-based formulation for managing the heterogeneity of infections caused by a virus, as shown in Fig 2.

Research collaborations between pharmaceuticals currently developed nano-based vaccine candidates, including TNX-1810, TNX-1820, and TNX-1830. These vaccine agents could deliver nano-sized viral vectors to prevent actual viral infections. The nanoparticles can drive the human immune system to produce antibodies against SARS COV-2 infections quickly. Besides, Entos Pharmaceutical™ has produced a liposome-based formulation with increased efficiency for protein delivery which can suitably transfer the genetic load directly into the cell.[17] Apart from effective delivery, nano biomaterials can be used as an adjuvant to reduce systematic toxicity. Conclusively, nanotechnology can increase drug loading, targeting efficiency, and synergistic effects of drugs to combat the consequences of viral infection.[18] More comprehensive findings show the mechanisms of nanoparticles to block viral entry inside the cell, which is a primer to causing the infection. Proteins such as 3CLpro and PLpro have a significant sequence similarity with viral proteins, which means they can utilize the covalent enzyme inhibition pathway to block viral entry through ACE2 receptors.[19] These nanobiotechnology contributions to diagnosing and managing SARS COV-2 showed its potential applications.

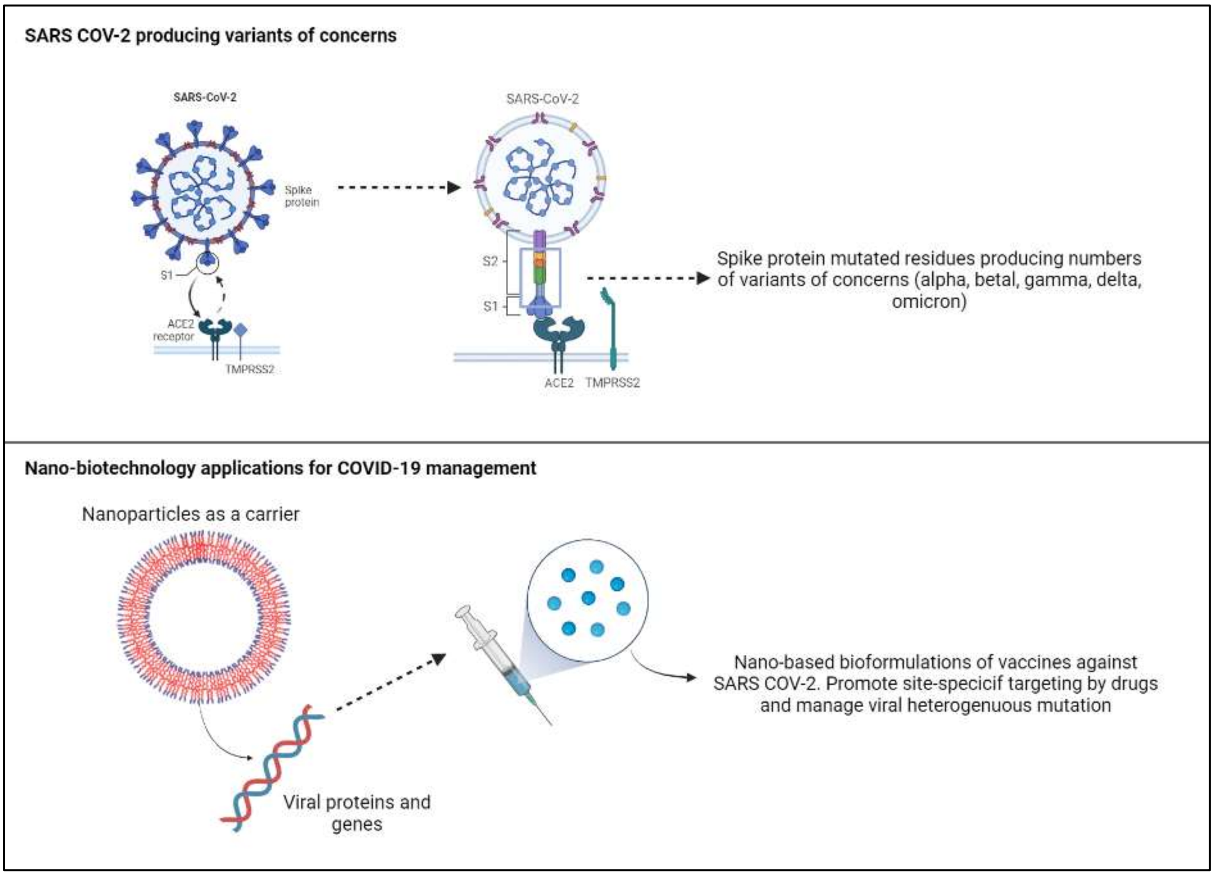

Figure 2. Representing nano-based carriers for viral proteins and bioformulation for COVID-19 infection (Source: Author's Own Creation)

Application of Nanobiotechnology in Treatment of Cancerous Diseases

The concept of nanobiotechnology in cancer research is based on disease imaging and drug delivery. Applications of nanopharmaceuticals are diverse because of a wide range of modifications. Nanoparticles as ligands, polymers, capsules, and adhesive support are important implications of nanobiotechnology .[20] These particles have an exceptional functionality to overcome the most critical cancers such as brain cancer which requires pharmaceutical products to cross the blood-brain barrier (BBB). It is very crucial to cross BBB and reach target site in brain. On the other hand, Nanomedicines have chemical surface modification and electrical properties that can facilitate detection and treatment.[21]

In addition, nanoenzymes can alter the enzyme activity depending on the need for a therapeutic procedure. Coated nanoparticles such as doxorubicin encapsulated in nanoparticles can activate NADPH into oxidases to produce oxygen electron species while promoting the generation of free radical ions to deteriorate cancerous cells.[22] More so, other nanoparticles are conjugated with biopolymers with self-assembled properties. For instance, PEG- PCL (polyethylene glycol with poly copolymers) was used to inhibit the migration of breast cancer cells.

Cancer is a heterogeneous disease with severe complications; therefore, nano-based practical imaging, targeting, and management are the potential pharmaceutical therapeutics. Nanoparticles were used to treat prostate cancer, such as nanoparticles encapsulating the paclitaxel was found effective in research over mice for prostate cancer.[23] However, to enhance the delivery of the drug, a Cremophor® gel (drug suspension as a thick gel) based delivery procedure was explored to directly inject the drug at the tumor site.[23] Research also studied the attachment of phenylboronic acid with chitosan nanoparticles to activate the tumor-targeting and enhance particle penetration at the tumor sites to improve tumor therapy.[24]

Application of Nanobiotechnology in Treatment of Infectious Diseases

Infectious disease is a significant public health problem. World Health Organization proposed a report that demonstrated that infectious disease despite of several treatment options still require a surveillance. 63% of childhood deaths are caused by infectious diseases.[25] Besides, adults are suffering infectious diseases with significant ratio worldwide. Around 25 million adults are living with HIV condition in Sub-Saharan African region followed by Europe and Central Asia. Another type of infection caused by leishmaniasis is endemic to 88 countries.[25] It is one of the most complicated issues because of heterogeneous sources such as bacteria, fungus, parasites, and their resistance against antimicrobials and other medicinal products.[26] Nanobiotechnology advances the therapeutic procedure with an effective way of killing the infection. Liposome-based ensure selective and controlled delivery of drugs to kill out the infection. It reduces the drug toxicity to healthy tissues. Liposome-based encapsulation of amphotericin B, which was used against leishmaniasis infection, reduced the drug toxicity and enhanced effectiveness. The drug is sold under the brand name Ambisome® in the present market.[26]

Moreover, the global implication of nanobiotechnology for infectious diseases is to manage the drug dosing and frequency levels. Numerous infectious diseases are followed by increased dosing and complications of managing the dose to achieve optimum recovery. Therefore, nanoparticles regulate the systemic release of a drug, such as poly-esterase-based drug delivery system and are degraded in the physiological environment to sustain the release and diffusion of drugs in the systems.[27] Such nano-based formulations ultimately enhanced the bioavailability of the API. Amorphous itraconazole nanoparticles in preclinical studies increased the drug concentration inside the lungs against pulmonary infections.[27] This approach is one of the significant applications of nanotechnology in infectious disease treatment.

Application of Nanobiotechnology in Treatment of Metabolic Diseases

Metabolic disorders as defined by the WHO is a syndrome with complex pathological conditions such as abdominal obesity, hypertension, and abnormal lipid accumulation.[28] All types of metabolic diseases such as hyperlipidemia, diabetes, obesity, liver inflammation and others are the leading causes of mortalities.[29] Global survey showed 604 million adults and 108 million children suffering from obesity. Likewise, 8.8% global prevalence of diabetes was also reported.[28] Pharmacotherapeutic products are comprehensively used to diminish their chronic and prolonged persistence. Nanosystems have the potential to accomplish the anticipated results. It was found that nano-based delivery can enhance the liver deposition of berberine (botanical and therapeutic product) against cardio-metabolic disorders.[29]

In addition, the field has been further tailored by its application for personalized medicines. Nanobiotechnology introduced personalized medicines based on the pharmacometabolomic information of the patient.[30] Nanostructured scaffolds can provide a large surface area for the necessary exchange of metabolic waste hence decreasing the chance of metabolic complexities.[31] Metabolic syndromes increase the risk of other types of cardiovascular diseases. Cardiovascular symptoms generate from the disturbances in lipid levels in the blood. However, nanotechnology comprises formulations such as chitosan nanoparticles that can lower the serum lipid levels with no effects of toxicity.[32] Hence, nanobiotechnology provided strategic options for mitigating these complex disorders.

Application of Nanobiotechnology in Treatment of Neurodegenerative Diseases

The blood-brain barrier is also an obstacle and area of concern while addressing all types of neurodegenerative disorders. Most drugs and imaging agents cannot cross it, therefore, restricting treatment approaches for neuronal diseases. Nano molecules can cross the blood-brain barrier at the molecular level without disturbing the normal physical functioning of barriers. A study reported that nanoparticle conjugates with iron chelates protected the neurons that would otherwise be damaged by beta-amyloid peptides accumulation in Alzheimer's disease.[33] Likewise, nano emulsions have been used to reduce the drug's toxicity and improve its targeted delivery in Alzheimer's and Parkinson's. Nanoparticles can also detect Aß levels in the brain, thus fostering the early prevention of Alzheimer's, an incurable illness.[34] A nano-based curcumin formulation was recently reviewed for treating Alzheimer's. The formulation presented an efficacious inhibition of beta-amyloid aggregation and amyloid fibrils formation in invitro and invivo effects[35] (Fig. 3). Since Alzheimer's and Parkinson's are the most ubiquitously found neurodegenerative complexities, research mainly focused on these two diseases. However, other diseases are also being investigated to prove the complete effectiveness of this technology in the present pharmacotherapeutics.

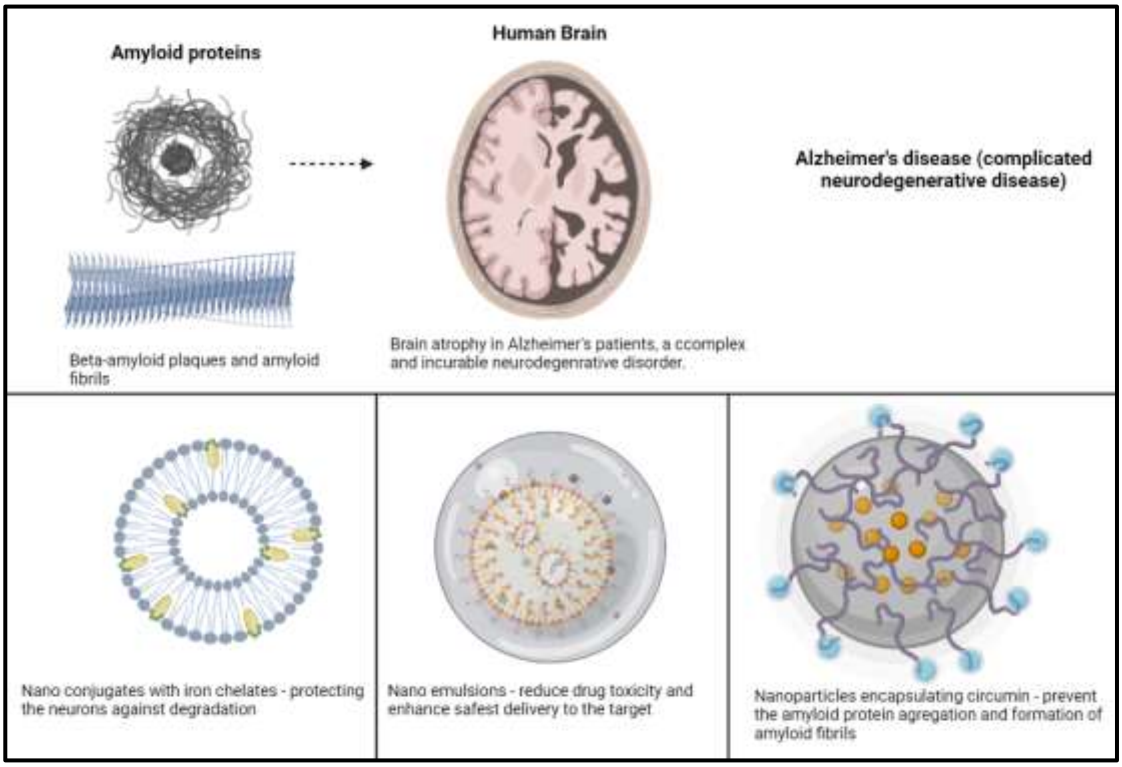

Figure 3. Explicit representation of nanoparticles and their roles against Alzheimer's disease (Source: Author's Own Creation)

Application of Nanobiotechnology in Treatment of Autoimmune Diseases

Nanotechnologies remained a field of interest for identifying solutions for multiple complexities like autoimmune diseases. It emerged as an intelligent design for addressing diseases with an undefined cause.[36] Autoimmune disorders affect the body's response to secondary infections generating complicated causes.[37] Under the concept of nanobiotechnology, substantial indications have been explored that are applicable in the respected field. Biological agents are utilized as immunomodulatory agents to suppress and regulate the immune system. The regulation is achieved by inhibiting cytokine productions and targeting immune cells for suppression.[38] These strategies are beneficial, but drug toxicity has several limitations and less target specificity. Nanomedicines or using nanocarriers to facilitate targeted and safest delivery of biological agents towards the target site is nano-based therapeutics' primary application. For example, cationic liposome encapsulating TNF-α can target small interference RNA to suppress cytokine production, as depicted in Fig. 4. PLGA nanoparticles encapsulating PEG conjugated peptides target T cells to induce the expression of immunosuppressive cytokines.[38]

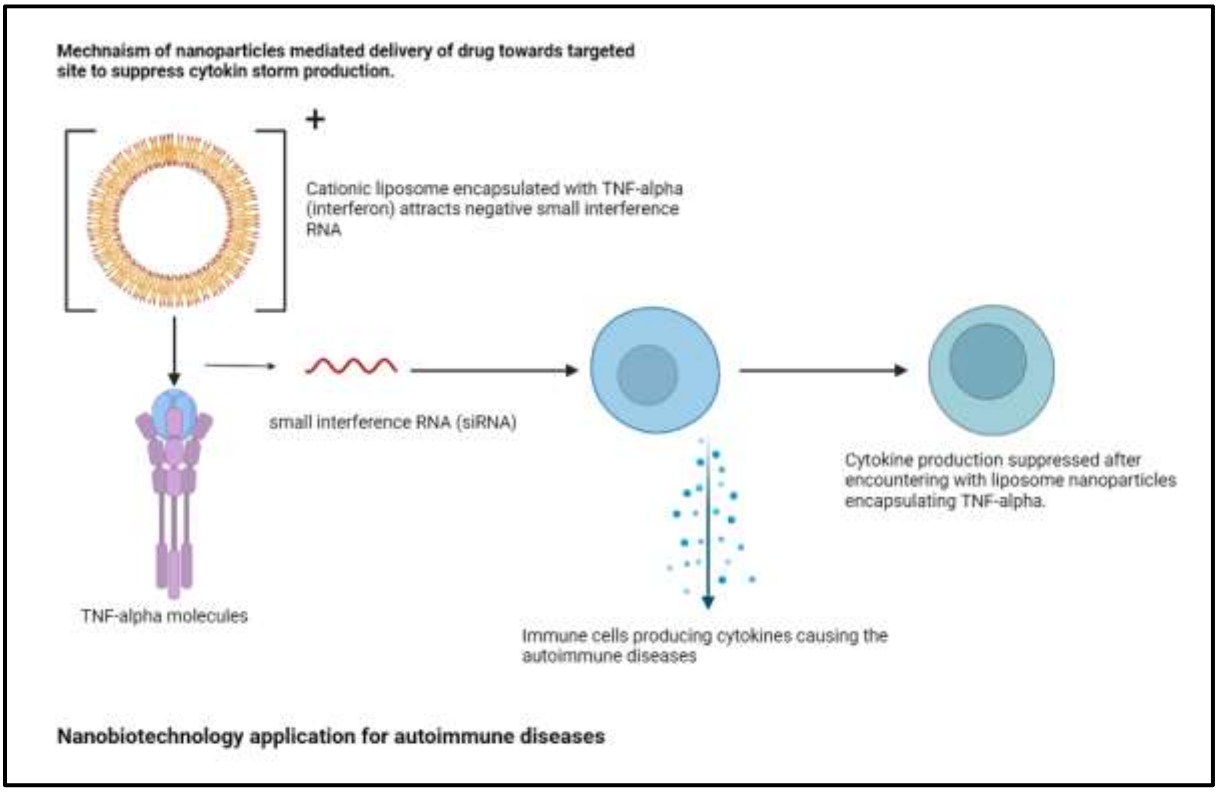

Figure 4. Role of nano-based systems in the suppression of autoimmune responses and associated inflammation (Source: Author's Own Creation)

Furthermore, CAR-therapy was used conventionally for autoimmune-mediated leukemia in patients. It was reported that polymeric nanoparticles loaded with DNA were used to target responsible genes invivo in host cells which showed rapid targeting and improvement compared to the conventional approach.[39] Besides, nanobiotechnology is further progressing to enhance the applicability and dependability of the technology.

Application of Nanobiotechnology in Treatment of Inflammations

Nanobiotechnology has many applications in inflammatory diseases and has overcome inflammatory damage. It offered a new paradigm through innovative drug delivery systems, individual targeting, and detection.[40] Colitis is a chronic inflammation of the colon and small intestines that severely affects the digestive tract's mechanism. Decreased levels of selenium characterize ulcerative colitis. It was proposed in preclinical studies on mice that selenium nanoparticles, when conjugated with *Ulva lactuca* polysaccharide (ULP), can offer a therapeutic potential to overcome hyperinflammation.[41] ULP was found to display solid immune modulation.[41] Other types of treatment involve nanomedicines such as peptide-based anti-inflammatory nanomedicines biomimetic medicines. Biomimetic medicines include liposomes and cell membrane proteins that enhance the circulation of nanoparticles to reach the target sites safely.

Moreover, biodegradable polyester nanoparticles can target atherosclerosis which is the inflammation of arteries.[42] More so, the biomimetic properties of nanoparticles simultaneously reduced the antiviral and anti-inflammation effects associated with COVID-19. When loaded in polymeric nanoparticles, anti-inflammatory drug lopinavir induced macrophage and neutrophil activation.[43] Nanoparticles are very extensive to address the issues of disease-associated inflammations and improve the capacity of the body's cell function.

Future Perspective of Nanobiotechnology in Pharmacology and innovative therapeutics

The future of nanobiotechnology is anticipated based on the diversity of its application. Besides present applications, the field has various opportunities for exploring and improvements. Future research focuses on finding solutions to address other diseases such as neurological disorders since the early focus was on Parkinson's and Alzheimer's. Bonilla et al., (2021) proposed nanoparticles with biodegradable properties for the treatment of epilepsy.[44] These particles have the potential for increased penetration and specific site delivery. In addition, advances are made to improve the effectiveness of nanoparticles. Chitosan is an effective polymeric polysaccharide that must be investigated because it is enriched with antiviral, anti-inflammatory, and anti-tumor properties. Synergistic effects can be induced in nanoparticles for wound management by using the chitosan matrix.[45] Not only these but also nanotechnology and genomics are contributing towards exploring innovative therapeutics for the future advancement of solution-based strategies.[46] Even though nano-based medicines reduce drug toxicity and ease access to a targeted area, drug distribution levels must also be considered. Treatment of neuroinflammation now has possibilities with use of nanotechnology. Current challenges of neuroinflammation are prominent with the high mortality cytokine storms caused by Covid-19.[47] Targeted delivery of nanoparticles promises superior tools to effectively access neuropathological tissue in a controlled manner.[48] Research is also focused on the mechanisms of nano-pharmaceuticals through quantum dot application to analyze their suitable application concerning different diseases.[49] The field of nanobiotechnology is extended and can address the potential issues in pharmacology that are still unresolved.

Conclusion

Nanobiotechnology is a field with a diverse range of scope and applications. One of the most critical areas of its application is in pharmaceutical sciences and innovative therapeutics, where it has shown numerous contributions. Assessing the applications of nanobiotechnology in different areas of the disease characterized by diagnostics and therapeutics can advance the level of understanding about this field which is still very complex. The report showed that nanobiotechnology is potentially active in addressing and managing different healthcare diseases, including neurological diseases, inflammatory diseases, infectious diseases, metabolic diseases, autoimmune diseases, and present COVID-19 management. This review would be helpful and facilitate the researcher in the future to thoroughly investigate the responsible phenomenon and mechanism with a clear understanding of the concept.

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