Review

Nanotechnological advancement in antimicrobial drug designing

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Abstract: The global spread of multidrug-resistant (MDR) microbial infections is currently one of the most severe risks to global public health, with 10 million fatalities expected by 2050 unless action is taken. Nanotechnology has revolutionized science and medicine. The reliance on nanotechnology is growing. Nanoparticles have distinct properties that improve biological, chemical, and physical properties studied for various uses. A significant area of attention in the synthesis of nanoscale modulators is the utilization of crude formulations, retro-synthesized, and pure chemicals, mainly from herbal sources, with fewer adverse effects. Green chemistry has devised a tangential technique for synthesizing metals and metal oxides to produce nanoparticles. Plant extracts (leaves, stems, and shoots) and microorganisms (bacteria, fungus, and yeast) are used as reducing intermediates to make nanoparticles. Studies in microbiology have shown that nanoparticles kill bacteria, fungi, viruses, and protozoa. These green nanoparticles contain antibacterial, antifungal, and anti-inflammatory effects. Most nanoparticles have high antibacterial properties, indicating they may be used to combat diseases and biological contaminants. These nanoparticles have antibacterial action against pathogenic microorganisms that cause serious illnesses, including multidrug-resistant pathogens. The current research will pave the way for future applications and improved methods for producing nanoparticles, paving the way for an innovative route in nano-life sciences with widespread recognition.

Keywords: multidrug-resistant (MDR); nanotechnology; antimicrobial

1. Introduction

The infectious diseases caused by resistant bacteria are a global concern and have received more and more attention from various leading research groups. For instance, only in the United States of America, the methicillin-resistant *Staphylococcus aureus* (MRSA) causes approx 19000 deaths per year to incur, and $3 to $4 billion of health care costs are increasing per year [1]. Most of the MDR infections caused by *Mycobacterium tuberculosis* strains in the developing world is emerging threat that is difficult to cure and often fatal [2-4]. Despite extensive research for drug discovery, the competition for effective antibiotics and therapy is still far from the end. Therefore, the search for advanced, potential and safe medicines has become progressively more critical; and is the need of the hour owing to the devastation caused by bacterial diseases. The traditional drug designing methods involving exhaustive testing of compounds require a lot of workforce efforts, time, and expenses. The high demand for effective drugs provided a better and better understanding of the protein-drug interactions and the development of more sophisticated software required for molecular modeling. We can now save our time, cost, and labor by using these software and computational approaches to shortlist the compounds from substantial compound libraries to be tested in the experimental laboratory. Instead of computational biology, researchers are progressive on nanotechnology advancements and their applications in developing medicines and pharmaceuticals.

Nanostructured materials consist of nanoparticles, dendrimers, micelles, drug conjugates, metallic nanoparticles etc. [5].

These nanostructured materials are important in the formulation and distribution of pharmaceutical drugs. Because of their distinct physical features, nanomaterials such as carbon nanotubes outperform existing medication delivery and diagnostic technologies [6]. They can adsorb or conjugate with medicinal and diagnostic substances such as medicines, DNA, vaccines, antibodies, biosensors, and so on due to their high surface area[7]. Metallic nanoparticles, such as silver and gold nanoparticles, are widely used in medication delivery, particularly in cancer treatment, as well as in biosensors [8,9]. Magnetic nanoparticles are widely used in magnetic resonance imaging as hyperthermia agents, which heat the magnetic particles, treat malignancies, and deliver targeted drugs [10,11].

This article has compiled the correlation between computational biology and nanotechnological advancement in drug or medicine development.

2. Computational approaches to drug designing

The disease progression involves multi-play of a multitude of enzymes and other proteins [12]. Pharmaceutical agents typically act by attaching to a specific protein, and hundreds of proteins have been verified as therapeutic targets for one or more disorders [13, 14]. In today's pharmaceutical research, the aim is to check on a single protein, and generally, the target enzyme is completely blocked. In this regard, a drug molecule that effectively competes with the enzyme-substrate for binding can be provided. The drug molecule, generally the inhibitor of the protein, binds in the protein's active site. Thus, the drug compound will block the enzyme's active site, and the desired reaction will not be catalyzed. Various computational methods are used for drug discovery programs, broadly classified into two types, structure-based and ligand-based approaches (Fig. 1).
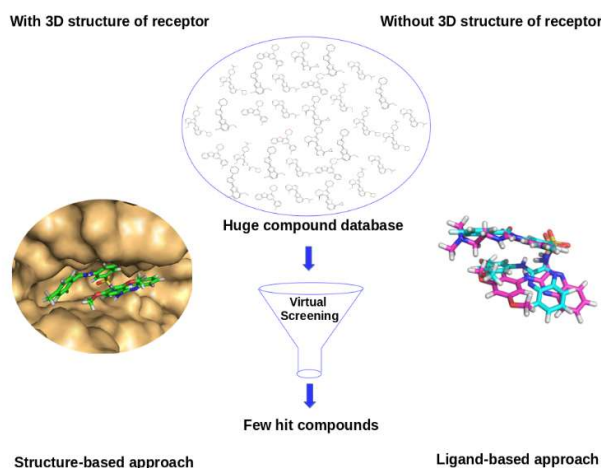

Figure 1. Outline for the drug designing, slection of the compound from the database, observing the binding affinity with a specific receptor and allocating ligand or cofactors for target biological moieties.

Structure-based approaches use the 3D structure of a specific therapeutic target protein to design inhibitors of the protein. Molecular docking is a structure-based approach that predicts the binding mode and affinity of the compounds in the protein's binding site. In addition to the 3D structure of the protein, active site information on the protein's surface is also required. The active site provides the minimal region for docking the ligand. If the functional site information is not available, the whole protein surface is searched for the potential binding sites. Various docking algorithms are available which score the docked pose based on their shape complementarity (steric fit) and the calculated free energy and allow the compounds to rotate and translate in the active site, and the best

scoring pose is considered as the final docked pose for further analysis and interpretation [15]. The docking software in common use is AutoDock, DOCK, FlexX, Glide, Gold, and Surflex [15-19]. The majority of docking tools allow the conformational flexibility of the ligands, whereas only a few, such as FlexX and Glide, also allow flexibility in the protein conformations. Various docking software uses a variety of scoring functions and provides different scores for a protein-ligand complex. The limitations of individual scoring functions are overcome by consensus scoring [20]. Virtual screening is a process of screening huge virtual libraries of compounds for their potential to bind specific sites of the target protein. The combination identified as the best scoring compound which binds the target protein is called a lead.

The benefits of virtual screening over preliminary screening can be realized from an interesting example whereby a group at Eli Lilly used a traditional enzyme and cell-based high-throughput screening to identify a lead compound inhibiting novel transforming growth factor-β1 receptor, which was further improved by structure-activity optimization used in vitro assays [21]. Another group at Biogen Idec, through virtual screening of 200,000 compounds, independently identified the same compound as best hit [22]. Thus, virtual screening could detect the same lead as tedious experimental approaches with low cost and labor in less time. One of the success stories for novel antibiotics targeting the ribosome is Rib-X Pharmaceuticals' structure-based computational design of novel oxazolidinones, Radezolid, which is in Phase II clinical trials[23].

When the target protein information or structure is not available, ligand-based approaches are used. These ligand-based approaches are based on machine learning, where a classification rule or activity prediction rule is formulated from a training-set which that contain known active and inactive compounds [24], and similarity methods which involve ranking combinations in the order of decreasing similarity to a known functional/actives [25]. Based on some scoring scheme, all these methods rank the compounds to reduce being active. Some of these methods include structure similarity-based search, pharmacophore model, SAR, and QSAR, etc. The structurally similar compounds possess interrelated biological activities. The 2D and 3D similarity searches are performed to select combinations for focused libraries. Various descriptors such as fingerprints, 2D and 3D, and other molecular surface properties are exploited for compound similarity or diversity analysis.

Another ligand-based approach uses pharmacophore, which can be understood as an ensemble of spatial and electronic features (hydrogen bonds, ionic interactions, and hydrophobic parts) necessary for optimal interactions of a ligand in the active site of the protein. This pharmacophoric pattern qualifies the compound to be involved as it is crucial for ligand-protein interaction. Screening these electronic features in large compound libraries leads to finding novel scaffolds for developing lead compounds. The pharmacophore model development for receptors without a known 3D structure is achieved by linking ligands' spatial and electronic features that bind to the receptor. The structural alignment of ligands is required for this comparative analysis. Various groups have developed many methods for the structural alignment of compounds [26]. An efficient program Genetic Algorithm for Multiple Molecule Alignment (GAMMA) can access the link (http://www2.chemie.uni- rlangen.de/research/drugdesign/ga.phtm) and perform the alignment incorporating the flexibility of molecules using a combination of Genetic algorithms and Newton optimizer [27]. The pharmacophore models can obtain potential drug leads by 3D chemical database queries. The pharmacophore-based screening of virtual compound libraries can be performed using various software, including Discovery Studio and the Phase module of Maestro suite (Schrodinger Inc.)[28].

When we have some known effective drugs or ligands of a target protein, Structure-Activity Relationship (SAR) is used, which correlates the spatial and chemical features with its biological activity. Quantitative Structure-Activity Relationship (QSAR) / 3D-QSAR models are also developed to link the actions to their quantitative structure properties, called descriptors for a set of compounds having similar biological activity [29,30]. The QSAR application is predominantly in the field of pharmaceutical development. It

became an indispensable part of drug discovery, utilized in various steps from lead discovery to lead optimization. Furthermore, The 3D pharmacophore models can be inferred by molecular modeling and conformational analysis from the SAR models.

Once a promising lead compound is identified, different core scaffolds and side-chain substitutions are checked and enumerated to evaluate the activity (enzyme inhibition/toxicity/disease cure). Efficient docking of the combinatorial library generated around the lead compound and core-hopping methods can accelerate the lead optimization process for the fine-tuning activity.

3. Nanotechnological advancement in drug formulation and synthesis

Nanotechnology and its applications in medicines and pharmaceuticals have made significant advances in the twentieth century. Nanoparticles, dendrimers, micelles, drug conjugates, metallic nanoparticles, and other nanostructured materials are examples of nanostructured materials. These nanostructured materials are essential in the formulation and distribution of pharmaceutical drugs. Because of their distinct physical properties, nanomaterials such as carbon nanotubes outperform other drug delivery and diagnostic systems. They can adsorb or conjugate with medicinal and diagnostic substances such as medicines, DNA, vaccines, antibodies, biosensors, and so on due to their high surface area. Metallic nanoparticles, such as silver and gold nanoparticles, are widely used in medication delivery, particularly cancer treatment. Magnetic nanoparticles are commonly used in imaging for tumor treatment and targeted drug administration. Liposomes have received a lot of attention as nanocarriers for targeted drug delivery. Because of their small size, these nanocarriers have been widely researched and developed for new and targeted drug delivery. They have a wide range of applications, including long circulatory and passive and active gene, protein, and peptide delivery. Figure 1 depicts various fundamental nanocarriers in nanoformulations.
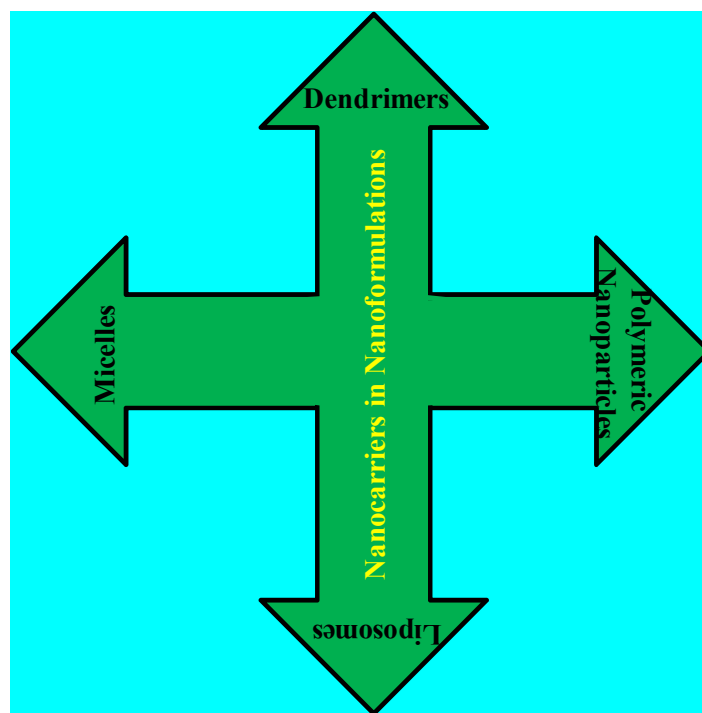

Figure 2. Basic nanocarriers involve in nanoformulation systems.

4. Properties of different types of nanocarriers

The size of the nano-drug formulations is < 100 nm, and the drug is attached to the drug carrier either by dissolving, entrapping or encapsulating it [31]. The significant

features that a nano drugs formulation should possess are that the drug should reach the active site of delivery and be resistant to biochemical degradation, enzymatic attack, pH, temperature, etc. The formulation should also release the drug in its active form at the target sites in quantified amounts [32]. Different types of nanoformulations such as liposomes, polymers, nano-emulsions, dendrimers etc., are generally employed for drug delivery. The dendrimers are polymeric molecules with tree-like structures with large attached side-wise polymer networks [33]. By covalent linking or encapsulation within its core, the dendrimers can carry different drugs. These can also be functionalized by using different chemical techniques to suit the target sites better. Polymeric nanoparticles (PNPs) can be either nanocapsules or nanospheres [34]. The nanocapsules serve as medication reservoirs, retaining active medicinal components in either an aqueous or nonaqueous surrounding fluid. On the other hand, the nanospheres can be regarded as a solid/mass of matrix polymers, with drug molecules confined within the sphere center or adsorbed at the mass surface [35]. Liposomes are sphere-shaped vesicles made up of one or more phospholipid bilayers in an aqueous phase that can be used to encapsulate pharmaceuticals like steroids, vaccinations, and genetic elements [36]. Micelles have a core shell-like shape with an inner hydrophobic core and an outer hydrophilic corona that is used to transport medications and allow for their more prolonged circulation in the body or any other biological system.

5. Synthesis routes of different nanoformulations

The choice of preparation processes is critical in creating nanoformulations with the appropriate characteristics for a specific medication delivery application.

Polymer backbone synthesis is preferably accomplished through three routes: divergent and convergent growth. Third, the hyper core and branching monomers grow as double exponential growth or click chemistry techniques [37]. The dendrimer developed from the core site during divergent evolution. First, the interaction between the core and the reagent occurs, resulting in the formation of a first-generation dendrimer. Similarly, the cycle is continued until dendrimers of the specific width are obtained. Several dendrons react with a multifunctional core to generate a dendrimer during concurrent growth. This synthesis entails the stepwise assembly of building blocks and is often time-consuming for large-scale production.

The polymer is the primary component used in the formulation of PNPs. According to polymer source of origin, natural polymers and synthetic polymers are the two principal polymers employed in creating polymeric nanoparticles [38].

The synthesis of dendrimers is done by preferably three routes, i.e., divergent growth, convergent growth, and thirdly the hyper core and branched monomers growth, double exponential growth, and click chemistry approaches. In the divergent evolution, the dendrimer's development originated from the core site. Firstly, the reaction between the core and reagent takes place to form first generation dendrimer. Similarly, the process is repeated to get dendrimers of the desired size. In the concurrent growth, several dendrons react with a multifunctional core to form a dendrimer. This synthesis involves the stepwise assembly of building blocks and is often time-consuming for production on a large scale.

The main component utilized for PNPs formulation is the polymer. According to the polymer source of origin, two major polymers are used for polymeric nanoparticles formulation; natural and synthetic polymers. PNPs can be prepared by different techniques such as solvent evaporation, emulsion polymerization, etc. In the solvent evaporation method, the emulsion of polymers is designed in a solvent such as carbon tetrachloride, tetrahydrofuran, ethyl acetate, etc. The emulsion is transferred into PNPs by the evaporation of the solvent. The PNPs can also be collected by ultracentrifugation, followed by washing to remove unwanted additives, and then lyophilized. The emulsion polymerization prepares PNPs from monomers as starting materials. The monomers are polymerized in liquid media using oxidants, which initiate polymerization. The emulsion

polymerization is also performed by using surfactants, which prevent the aggregation of the PNPs and act as a stabilizing agent.

The preparation of liposomes includes mechanical procedures, organic solvents, or detergent removal from phospholipid/detergent micelle mixtures. The water-in-oil emulsion of phospholipids and buffer is first prepared, followed by removing the organic phase at reduced pressure. This process leads to the entrapment of drug molecules (~60-65%) into the formed liposomes. In the detergent removal technique, the phospholipid and detergent are mixed to get a micellar structure, followed by detergent removal to get a micellar system mainly composed of phospholipid arranged in a single bilayer vesicle. The High-pressure extrusion technique involves passing multilamellar vesicles through a polycarbonate membrane of the tiny pore sized at high pressure to get a unilamellar liposome. Then microfluidizer is used to force the material through a narrow orifice, which helps remove bilayers. This technique works best for liposomes with a size greater than $70\mu m$.

In this method, copolymers are dissolved in aqueous media above the critical micelle concentration, giving a micellar structure with a center core. The drugs are inserted inside the core of the micelle for delivery purposes.

6. Metal oxide and its medical application

As of late, the synthesis of metal and metal oxide nanoparticles has been acknowledged in nanotechnology. Green chemistry and biological synthesis has inspired a thoughtful consideration of the analysts to investigate the environmentally friendly methodologies for the synthesis of nanoparticles as a more secure other option to the conventional physical and chemical techniques, which includes the toxic and risky chemicals, outrageous conditions, for example, hoisted temperature, high pressure, and necessity of costly instrumental facilities and so on. In this manner, natural resources such as fungi, yeast, actinomycete, bacteria, and primarily medicinal plants have been misused for practical and eco-friendly nanoparticle synthesis. The advancement of reliable, eco-friendly procedures for nanomaterials synthesis is a vital part of nanotechnology due to the developing need to limit or kill the utilization of environmental risk substances while green chemistry. Antibacterial activity relates to compounds that locally eliminate microbes or back off their growth without being lethal to the surrounding tissue. Most current antibacterial agents are chemically modified natural compounds, for example, β-lactam, cephalosporins, and carbapenems. Also, purely natural products and purely synthetic antibiotics are often used. Also, nanomaterials have risen as a novel antibacterial agents. There are a lot of reports accessible for the synthesis of metal nanoparticles, for example, as metals and their bimetallic nanoparticles and they are talked about underneath:

The authors detailed the biosynthesis of utilizing Aspergillus flavus as a reducing agent for the preparation of TiO_2 nanoparticles observed the morphology by SEM. It revealed the spherical and oval shape of the nanoparticles with the size of 62-74nm. The minimum inhibitory concentration (MIC) estimation of the TiO2 nanoparticles was observed to be 40 μg/ml toward Escherichia coli. The biosyntheses of TiO_2 nanoparticles demonstrated great antibacterial activity towards Escherichia coli among the other tried bacteria, in particular S.aureus, P.aeruginosa, K.pnemoniae, B.sublitis with the MIC of 40 μg/ml [39]. Synthesis of Iron nanoparticles utilizing Aspergillus oryzae TFR9 has been published and shown the particle size in 10-25 nm by Dynamic Light Scattering (DLS) [40]. Antimicrobial activity of ZnO nanoparticles using Ochradenus baccatus leaf extract. The biogenic chemically synthesized ZnO nanoparticles have been subjected to antimicrobial activity to determine their proficiency against different pathogens [41]. They have acquired different sizes of the zone of inhibition according to the type of pathogens. The synthesis and concentration of ZnO nanoparticles showed a maximum antimicrobial activity towards to S.aureus comparison to other pathogens [42].

In contrast, ZnO nanoparticles synthesized by the green approach demonstrated a more prominent massive zone inhibition when compared to chemically synthesized ZnO

nanoparticles [43]. Jayaseelan et al. created ZnO nanoparticles using a unique microbial approach, employing the Aeromonas hydrophila as an environmentally friendly reducing and capping agent. They said that at a dose of 25 ug/ml, the highest zone of inhibition was seen against the tested bacteria Pseudomonas aeruginosa (221.8mm) and the fungus Aspergillus flauor (191.0mm)[44]. Researchers have established the role of Ag nanoparticles in the regulation of microbial infections [45,46]. Since their discovery, carbon nanotubes have become a focus of advanced study. One of their main applications is antibacterial activity, which is a hot topic of research right now [47]. It is hypothesized that the cell wall is harmed as a result of interaction with pure SWNTs. Antimicrobial activity has also been demonstrated for multi-walled carbon nanotubes. The role of Cu nanoparticles in antibacterial activity has gradually been investigated [48]. The polypyrrole/Cu-doped ZnO nanocomposite for sensor development and antibacterial investigations was recently reported [49]. They have demonstrated superior antibacterial activity against *B. subtilis* than the common antimicrobial drug amoxicillin. It is critical to creating composites of these materials for a synergistic action against microbes in the current situation. On *Escherichia coli*, a large portion of the work on the use of copper nanoparticles as antibacterial agents has been performed [50]. Metal particles must be studied as antimicrobial agents due to their broad spectrum of antimicrobial activity and lack of cross-reactivity with anti-infection drugs [51]. Because of their increased survivability, new generation medications are nanoparticles of polymers, metals, or ceramics that can combat illnesses such as cancer [52,53] and human infections such as different microscopic organisms [54].

7. Computational biology application in nano-drug formulation and delivery

A nanoparticle not only demonstrates medication delivery but also confirms target delivery, which is crucial. There are numerous colorific markers available; nevertheless, nanoparticles have a favored position of exhibiting a change in fluorescence markers for medicative imaging and diagnostic applications and imaging of cancers and other diseases in vivo. Lee et al. showed, for example, that Fe_3O_4 nanoparticles on uniform color doped nanomaterials may be used as a complexity operator in appealing reverberation imaging and layered doxorubicin in the pores. This framework has tremendous promise as evidenced by tests in attractive reverberation and fluorescence imaging, and doxorubicin was effectively conveyed to tumor locations, and its anticancer movement was observed [55]. In addition, a histidine-labeled cyan fluorescent protein-topped appealing mesoporous silica nanoparticles framework for sedate conveyance and fluorescent imaging was developed [56]. Quantum peaks are small (1– 10 nm) semiconductor nanocrystals composed of a main inorganic center (e.g., Cd and Se) surrounded by a metallic shell (ZnS). They are commonly used in organic chemistry and can also be used as medicine carriers or fluorescent markers for other pharmaceutical transporters. Among the wide range of nanoparticles, press oxide and gold nanoparticles have received the most attention [57]. Because of the proximity of surface plasmons, gold, copper, and silver nanoparticles retain light in the visible region, allowing us to consider their size-dependent light assimilation via surface plasmon reverberation (SPR). Gold nanoparticles and nanorods offer a variety of unique features that have been studied for possible uses in bio-subatomic identification. [58] outlined a method for mixing gold nanoparticles with regular gellan gum to deliver doxorubicin hydrochloride and demonstrated the successful stacking of doxorubicin onto gold nanoparticles. Similarly, Gibson et al. [59] described an extremely precise assessment of organic activity by describing the readiness of the gold medicine nanoparticle framework. Hwu et al. [60] used Fe_3O_4 and gold as the center to combine three paclitaxel-conjugated nanoparticles. As anticancer treatments, these conjugated nanomaterials compete with another class of rivals. Regarding biocompatibility and non-cytotoxicity, gold nanoparticles, as approved by the FDA, have evident advantages over other metallic particles and could also be utilized as a favorable carrier for medicine conveyance. Nanoparticles are rapidly becoming the focal point of most undertakings aiming at targets and site-specific pharmaceutical conveyance. The capacity of nanoparticles is

determined by specific characteristics such as molecular estimation, surface charge, surface modification, and hydrophobicity. Nonetheless, various concerns associated with particular officials' directed conveyance and toxic quality must be avoided. The scarcity of information about the dangers of nanoparticles is a significant worry that deserves to be addressed. Suppose these nanoparticles are cautiously meant to deal with challenges identified with the target and course. In that case, they may stimulate another more fruitful viewpoint in the realms of treatments and research. The most promising research in nanoparticle production involves using supercritical liquids, which are environmentally friendly and free of hazardous solvents. Much research is currently being conducted to overcome these difficulties, establishing nanoparticle-based medicine conveyance as the most excellent quality level for site-specific treatments.

8. Conclusion

Research teams are working on site-specific medicine delivery and update and linked with nanocarrier based on nanomaterials. The ability of a nanocarrier to be a target is influenced by particle surface modification, size and charge, and the nature of hydrophobicity. The main concern over the nanocarrier and nanomaterials' selective binding, distribution, and toxicity with the prolonged released state in a nonaqueous and aqueous medium. Assume that these nanocarrier and nano drugs have been meticulously designed to solve difficulties such as target and administration routes and toxicity. They may pave the door for a new, more successful therapeutic and research approach in this situation. In the most promising nanomaterial research, supercritical fluids, which are environmentally benign and free of toxic solvents, are being used. Many studies are being performed to overcome these barriers, with nanoparticle-based medication delivery the benchmark for site-specific treatments.

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