ADVANCES IN NANOTECHNOLOGY FOR CREATING ANTIBACTERIAL DRUGS

Abstract

One of the greatest threats to global public health today is the growth of multidrug-resistant (MDR) microbial diseases, with 10 million deaths predicted by 2050 if nothing is done. Science and medicine have been changed by nanotechnology. Nanotechnology is becoming more and more important. The unique characteristics of nanoparticles enhance the biological, chemical, and physical qualities investigated for numerous applications. The use of simple formulations, pure molecules that have been retro-synthesized, primarily from herbal sources, and have fewer side effects is receiving major attention in the synthesis of nanoscale modulators. In order to create nanoparticles, green chemistry has developed a tangential method for synthesizing metals and metal oxides. As reducing intermediates, bacteria, fungi, and yeast are combined with plant extracts (leaves, stems, and shoots) to create nanoparticles.Microbiology research has demonstrated that nanoparticles can eliminate bacteria, fungus, viruses, and protozoa. These antibacterial, antifungal and anti-inflammatory properties are present in these green nanoparticles. The majority of nanoparticles have strong antibacterial characteristics, indicating they could be employed to fight biological pollutants and illnesses. These nanoparticles have an antimicrobial effect on pathogenic microbes, including pathogens that are multidrug-resistant and cause significant diseases. The current study will open the door to enhanced nanoparticle production techniques and future applications, opening the door to a novel path in Nano-life sciences that will gain general acceptance.

Keywords: global public health, nanotechnology, retro-synthesized, bacteria, antimicrobial

Authors

Shiwali Bisht
Assistant Professor
Motherhood University
Roorkee, Uttarakhand, India.
shivibisht17@gmail.com

Lovely Tyagi
Assistant Professor
Motherhood University
Roorkee, Uttarakhand, India.
tyagilovely29@gmail.com

I. INTRODUCTION

Globally, infectious disorders brought on by resistant bacteria are a problem that has drawn increasing attention from eminent research organizations. For instance, the methicillin-resistant Staphylococcus aureus (MRSA) causes over 19000 fatalities annually in the United States alone, with an annual increase in health care spending of $3 to $4 billion. The majority of Mycobacterium TB MDR infections in developing countries represent an increasing concern that is hard to treat and frequently lethal. Despite intensive drug discovery research, there is still a long way to go until there are efficient antibiotics and treatments.Because of the destruction brought on by bacterial infections, the search for cutting-edge, potentially life-saving, and safe medications has become increasingly urgent. Traditional drug creation techniques that involve extensive compound testing demand a lot of labour, money, and resources. A growing understanding of the interactions between pharmaceuticals and proteins and the creation of more complex software needed for molecular modeling were made possible by the high demand for effective medications. By employing this software and computational methods to choose the compounds from large chemical libraries that should be examined in the experimental laboratory, we can now save time, money, and labour.Researchers are moving forward with nanotechnology developments and their applications in creating medications and therapies rather than computational biology. Nanoparticles, dendrimers, micelles, drug conjugates, metallic nanoparticles, and other components make up nanostructured materials.

These nanostructured materials are crucial for the production and delivery of pharmaceuticals. Nanomaterials, such as carbon nanotubes, function better than current medical delivery and diagnostic methods because of their unique physical characteristics. Due to their large surface area, they can absorb or conjugate with a variety of therapeutic and diagnostic chemicals, including drugs, DNA, antibodies, vaccinations, and biosensors. Metallic nanoparticles, such as silver and gold nanoparticles, are frequently utilized in biosensors and drug delivery, especially in the treatment of cancer. In order to heat magnetic nanoparticles, treat cancer, and deliver specific drugs, magnetic nanoparticles are frequently used in magnetic resonance imaging (MRI).The relationship between computational biology and nanotechnology advances in the creation of drugs or medicines has been gathered in this article.

II. METHODS FOR CREATING DRUGS USING COMPUTATION

A large number of enzymes and other proteins interact to advance the disease. Hundreds of proteins have been confirmed as therapeutic targets for one or more illnesses. Pharmaceutical drugs normally work by binding to a particular protein. Today's pharmacological research focuses on a particular protein and typically completely inhibits the target enzyme. In this case, a therapeutic molecule can be made that successfully competes with the enzyme-substrate for binding. The medication molecule binds to the protein's active site, which is typically where the protein's inhibitor interacts. As a result, the drug ingredient will obstruct the enzyme's active site and prevent the desired reaction from occurring. Drug discovery programs employ a variety of computational techniques, which can be broadly divided into two categories.Designing protein inhibitors using structure-based techniques takes advantage of the 3D structure of a specific therapeutic target protein. The binding mechanism and affinity of the substances in the protein's binding site are predicted by the

structure-based technique known as molecular docking. Information about the protein's surface active sites is also necessary for addition to the 3D structure of the protein. The ligand can dock in the smallest possible area at the active site. If there is no information on the functional sites, putative binding sites are looked for along the entire protein surface.There are several docking algorithms that allow compounds to rotate and translate within the active site while scoring the docked pose based on their shape complementarity (steric fit) and calculated free energy.

The best scoring pose is then taken into consideration as the final docked pose for further analysis and interpretation. Among the most popular docking programmes are Auto Dock, DOCK, Flex X, Glide, Gold, and Surf Lex. Few docking techniques, like Flex X and Glide, also offer flexibility in protein conformations, but the majority of docking tools allow the conformational flexibility of the ligands. Different docking programmes employ various scoring functions and offer various scores for a protein-ligand combination. Consensus scoring overcomes the constraints of individual scoring functions.Virtual screening involves examining enormous virtual libraries of substances for their ability to bind particular locations on the target protein. A lead is a mixture that was found to be the most effective compound at binding the target protein.

A group at Eli Lilly used conventional 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. This example illustrates the advantages of virtual screening over preliminary screening.

Ligand-based techniques are employed when the target protein's information or structure is unavailable. These ligand-based methods are based on machine learning, where a classification rule or activity prediction rule is created from a training set of known active and inactive compounds and similarity methodologies, which rank combinations in decreasing order of similarity to known functional/actives. All of these strategies rank the compounds to lessen their activity based on some scoring system. Structure similarity-based search, pharmacophore models, SAR, QSAR, and other techniques are a few of them. The biological activities of the structurally related substances are connected. For the purpose of choosing combinations for targeted libraries, 2D and 3D similarity searches are carried out.For compound similarity or diversity analysis, many descriptors, including fingerprints, 2D and 3D images, and other molecular surface features, are used.Another ligand-based strategy makes use of pharmacophore, which is a collection of spatial and electronic properties (hydrogen bonds, ionic interactions, and hydrophobic portions) required for a ligand's successful interactions with a protein's active site. The molecule is eligible to participate because of its pharmacophoric pattern because it is essential for ligand-protein interaction. Finding innovative scaffolds for creating lead compounds comes from screening these electronic properties in huge compound libraries. It is possible to create pharmacophore models for receptors without a known 3D structure by connecting the spatial and electrical properties of the ligands with the receptor. This comparison study requires the structural alignment of the ligands. For the structural alignment of compounds, numerous approaches have been developed by different groups. By using 3D chemical database searches, the pharmacophore models can find possible drug leads. Virtual chemical libraries can be screened utilizing pharmacophores using a variety of programs, such as Discovery Studio and the Phase module of the Maestro suite (Schrodinger Inc.).Structure-Activity Relationship

(SAR), which links the physical and chemical characteristics of a target protein with its biological activity, is used when we have some known efficient medicines or ligands of a target protein. For a group of chemicals with comparable biological activity, quantitative structure-activity relationship (QSAR) / 3DQSAR models are also built to connect the actions to their quantitative structure features, known as descriptors.

III. ADVANCES IN NANOTECHNOLOGY FOR MEDICATION FORMULATION AND SYNTHESIS

The twentieth century has seen tremendous advancements in nanotechnology and its uses in healthcare and pharmaceuticals. Nanostructured materials include, but are not limited to, nanoparticles, dendrimers, micelles, drug conjugates, metallic nanoparticles, and others. Pharmaceutical medications must be created and distributed using these nanostructured materials. Nanomaterials, such as carbon nanotubes, outperform existing drug delivery and diagnostic systems due to their unique physical characteristics. Due to their large surface area, they can adsorb or conjugate with a variety of therapeutic and diagnostic chemicals, including drugs, DNA, antibodies, vaccinations, and biosensors. Metallic nanoparticles, such as those made of silver and gold, are frequently utilized in drug delivery, especially in the treatment of cancer. Magnetic nanoparticles are frequently utilized in imaging for the administration of targeted drugs and the treatment of tumours.As nanocarriers for the delivery of specific drugs, liposomes have attracted a lot of interest. These nanocarriers have undergone extensive research and development for the novel, targeted drug delivery due to their small size. They can be used for a variety of things, such as long-distance passive and active genes, protein, and peptide delivery.

IV. CHARACTERISTICS OF SEVERAL NANOCARRIER TYPES

The drug is connected to the drug carrier either by dissolving, entrapping, or encapsulating it in nano-drug formulations, which are about 100 nm in size. The important characteristics that a nano drug formulation should have are the ability for the medication to reach the active site of delivery and be resistant to enzyme attack, pH, temperature, and other factors. Additionally, the formulation should deliver a precise amount of the medicine in its active form to the target areas. Drug delivery typically uses a variety of nanoformulations, including liposomes, polymers, nano-emulsions, dendrimers, etc. Dendrimers are polymeric molecules with enormous connected side-by-side polymer networks and tree-like topologies. The dendrimers can transport various medications by encapsulating them inside their core or covalently attaching them to them.To better fit the target areas, they can be functionalized utilizing various chemical processes. Nanospheres or nanocapsules are two different types of polymeric nanoparticles (PNPs).

By holding active pharmaceutical ingredients in either an aqueous or nonaqueous surrounding fluid, the nanocapsules act as drug reservoirs. Contrarily, the nanospheres can be thought of as a solid or mass of matrix polymers, with drug molecules either confined within the sphere's interior or adsorbed at the mass surface. Liposomes are sphere-shaped vesicles that can be used to encapsulate drugs like steroids, vaccines, and genetic material. They are made up of one or more phospholipid bilayers in an aqueous phase.Micelles are utilized to transport drugs and enable their longer circulation in the body or any other biological system.

Micelles have a core shell-like form with an inner hydrophobic core and an outer hydrophilic corona.

V. METHODS FOR VARIOUS NANOFORMULATIONS' SYNTHESIS

In order to produce nanoformulations with the proper properties for a certain drug delivery application, the choice of preparation techniques is crucial. Divergent and convergent growth are the preferred methods for synthesizing polymer backbones. Third, click chemistry or double exponential growth procedures are used to grow the hyper core and branching monomers. During divergent evolution, the dendrimer emerged from the core location. A first-generation dendrimer is first formed as a result of the interaction between the core and the reagent. The cycle is repeated in a similar manner until dendrimers of the desired width are obtained. During concurrent growth, many dendrons interact with a multipurpose core to produce a dendrimer. For large-scale manufacture, this synthesis necessitates the sequential assembly of building pieces and is typically time-consuming.The primary ingredient in the creation of PNPs is the polymer. The two main polymers used in the production of polymeric nanoparticles are natural polymers and synthetic polymers, depending on the source of the polymer. Dendrimer synthesis can be accomplished by three preferred methods: divergent growth, convergent growth, hyper core and branching monomer growth, double exponential growth and click chemistry. The core location was where the dendrimer evolved through divergent evolution. The first-generation dendrimer is created by the reaction between the core and reagent. To obtain dendrimers of the desired size, the procedure is repeated in a similar manner. A dendrimer is created when numerous dendrons react with a multipurpose core during concurrent growth.

This synthesis, which is time-consuming for large-scale production, includes the sequential assembly of building pieces. The polymer is the primary ingredient used in the formulation of PNPs. Two main types of polymers—natural and synthetic polymers—are employed in the creation of polymeric nanoparticles, depending on the source of the polymer. PNPs can be made using a variety of methods, including emulsion polymerization and solvent evaporation. The emulsion of polymers is created in a solvent, such as carbon tetrachloride, tetrahydrofuran, ethyl acetate, etc., in the solvent evaporation process. The solvent evaporates, transferring the emulsion into PNPs. Additionally, PNPs can be obtained by ultracentrifugation, washed to eliminate impurities, and then lyophilized. PNPs are made from monomers, which are the starting components, using emulsion polymerization.

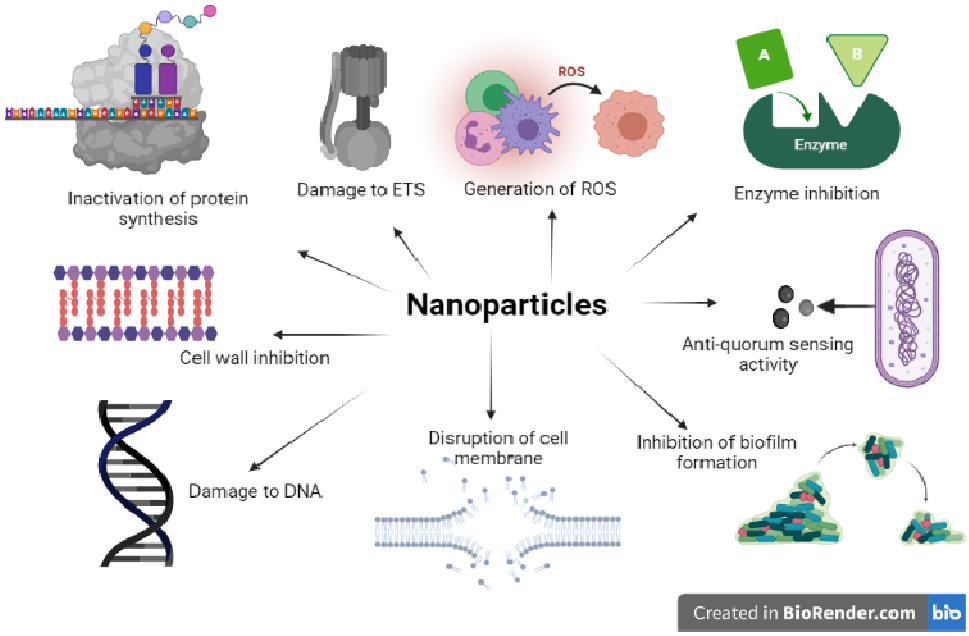

Figure 1: Antimicrobial Mechanisms of NPs

The oxidants that start polymerization are used to polymerize the monomers in liquid media. Surfactants, which serve as a stabilizing agent and stop PNPs from aggregating, are also used in the polymerization of the emulsion. Liposomes can be created mechanically, with organic solvents, or by removing detergent from phospholipid/detergent micelle combinations. The phospholipids and buffer water-in-oil emulsion are first created, and then the organic phase is extracted under reduced pressure. In the liposomes that are created as a result of this procedure, drug molecules are trapped to a degree of 60–65%. The phospholipid and detergent are combined in the detergent removal method to create a micellar structure, which is then removed to reveal a micellar system primarily made up of phospholipid organized in a single bilayer vesicle.In order to create a unilamellar liposome, the high-pressure extrusion approach requires pushing multilamellar vesicles through a polycarbonate membrane with a narrow pore size at high pressure. The substance is then forced through a small aperture using a microfluidizer, which aids in the removal of bilayers. The best results from this method are obtained with liposomes larger than 70 nm. This approach results in a micellar structure with a central core when copolymers are dissolved in aqueous solutions above the critical micelle concentration. For delivery purposes, the medications are placed into the micelle's center.

VI. APPLICATIONS FOR METAL OXIDE IN MEDICINE

Recently, nanotechnology has recognized the creation of metal and metal oxide nanoparticles. Green chemistry and biological synthesis have motivated analysts to carefully consider investigating environmentally friendly methodologies for the synthesis of nanoparticles as a more secure alternative to the traditional physical and chemical techniques, which include the use of toxic and risky chemicals, outrageous conditions, such as elevated temperature, high pressure, and the requirement of expensive instrumental facilities, among others. Natural resources including fungi, yeast, actinomycete, bacteria, and particularly medicinal plants have been abused in this way for the purpose of producing useful and

environmentally friendly nanoparticles.Due to the growing necessity to restrict or eliminate the use of environmental risk compounds while practicing green chemistry, the development of dependable, environmentally friendly methods for the synthesis of nanomaterials is an essential component of nanotechnology. Antibacterial substances are those that kill localized microorganisms or slow down their growth without harming nearby tissue. The majority of today's antibacterial drugs are natural substances that have undergone chemical modification, such as -lactam, cephalosporins, and carbapenems. Additionally, antibiotics that are entirely synthetic and only natural are frequently employed. The biosynthesis of creating TiO2 nanoparticles using Aspergillus flavus as a reducing agent was described by the authors, who used SEM to examine the shape. In the current circumstances, it is essential to make composites out of these materials for a synergistic action against microorganisms.

The use of copper nanoparticles as antibacterial agents has been studied extensively on Escherichia coli. Due to their wide range of antibacterial action and lack of cross-reactivity with anti-infection medications, metal particles must be investigated as antimicrobial agents. New generation medicines, which are nanoparticles made of polymers, metals, or ceramics and have increased survival, can treat diseases including cancer and human infections caused by various tiny organisms.

VII. BIOMEDICAL APPLICATIONS OF NPS

Nanotechnology has a significant impact on many aspects of our life and has recently seen an increase in utilization in the biomedical industry. Nano-engineering materials are created by altering the surfaces of implants and medical devices to inhibit bacterial adherence and biofilm formation. Next-generation nanomaterials are inexpensive and biocompatible medical implants and gadgets.

Antibacterial film-based composite materials allow for a variety of applications, including wound dressings and coatings for implants or catheters. Due to their biocompatibility, natural polymers like cellulose and collagen are preferred when creating composite films. Contrarily, synthetic polymers including polyurethane, polycaprolactone, and polyethylene are employed to create antibacterial composite films due to their processing simplicity and durability. Numerous investigations have been conducted on materials produced with NP that have antibacterial characteristics. AgNPs are often associated with polyethylene, which boosts the polymer's antibacterial characteristics and decreases wear on the polymer surface. AgNPs and polyethylene nanocomposites have the potential to be exploited as antibacterial and antibiofilm inhibiting agents in the food and health industries. Injectable AgNP/methylcellulose nanocomposite hydrogel was created by Kim et al. for topical antibacterial treatments that can be applied to burn sites. Numerous antibacterial nanocomposites, including collagen-dextran-ZnO-NPs, poly(vinyl alcohol)/ZnO , and -chitin/ZnO NPs, have been found to be effective in treating infected wounds. Polyvinyl alcohol (PVA)-based antibacterial contact lenses with AgNPs and CuNPs were created by Kharaghani et al. .

NPs can be created by engineering and coupled with other antimicrobial substances to increase their effectiveness against resistant microbes. Nanoparticles' chemical characteristics enable long-term antibiotic binding to their target sites and enzyme protection. Higher

antibiotic requirements are thus prevented. Antibiotic nanoparticle conjugates must be developed in order to stop multidrug-resistant harmful microbial infections.

Based on physical (hydrophobic, host-guest, and electrostatic contacts) and chemical (with amine, trans-cyclooctene, hydrazide, isothiocyanate, sulfhydryl, azide groups of medication) interactions, conjugated NPs are prepared . The following list of related potential processes describes the synthesis of several antibacterial nanoparticle-drug conjugates.

- The combination of nanoparticle antibiotics offers significant advantages for poorly soluble drug solubility, drug half-life, systemic circulation, and drug release.
- The combination of nanoparticle antibiotics offers significant advantages for poorly soluble drug solubility, drug half-life, systemic circulation, and drug release.Teichoic acid, lipopolysaccharides, and the peptidoglycan layer's negative charge encourage NP attachment and increase bacterial sensitivity to antimicrobial therapy.
- By adhering to the negatively charged surface of the bacterial cell, hydrogenation of NPs makes them more stable and reduces their capacity to perform their intended function.The NPs improve the permeability of the bacterial cell membrane by attaching to the proteins there, which allows more antibiotics to enter the bacterial cell.
- The active surface of NPs damages cell membranes, interferes with protein-protein interactions, and alters metabolism.
- NPs interact with sulfhydryl (-SH) groups in the cell wall to form R-S-S-R bonds and inhibit respiration resulting in cell death. When NPs enter bacteria, they can affect cell membrane functions (permeability, respiration).

VIII. APPLICATION OF COMPUTATIONAL BIOLOGY TO THE FORMULATION AND ADMINISTRATION OF NANOMEDICINE

A nanoparticle proves target delivery in addition to pharmaceutical delivery, which is important. Although there are several colorific markers accessible, nanoparticles have a preference for changing the fluorescence markers for medical imaging. Press oxide and gold nanoparticles have drawn the greatest interest among the diverse variety of nanoparticles. Gold, copper, and silver nanoparticles are able to absorb light via surface plasmon reverberation because of the close closeness of their surface plasmons, which keeps light in the visual range (SPR). Gold nanoparticles and nanorods have been researched for potential applications in bio-subatomic identification due to their range of distinctive properties.described how to administer doxorubicin hydrochloride using a combination of gold nanoparticles and normal gellan gum, and they showed how to successfully stack doxorubicin on gold nanoparticles. Similarly, by defining the readiness of the gold medicine nanoparticle framework, Gibson et al. reported an incredibly accurate assessment of organic activity. Three paclitaxel-conjugated nanoparticles were combined by Hwu et al. using Fe3O4 and gold as the center. These conjugated nanomaterials compete with another class of competitors as anticancer therapies. According to FDA approval, gold nanoparticles are clearly superior to other metallic particles in terms of biocompatibility and noncytotoxicity. They could potentially be used as an effective drug delivery system. The majority of projects aimed at targeting and site-specific pharmacological delivery are increasingly centered on nanoparticles.Specific properties of nanoparticles, such as molecular estimate, surface charge, surface modification, and hydrophobicity, determine their capacity. But numerous worries about directed conveyance and harmful quality by specific officials must be avoided. The

lack of knowledge regarding the risks posed by nanoparticles is a serious concern that has to be addressed.

IX. CONCLUSION

Teams of researchers are striving to update and link a nanocarrier based on nanomaterials with site-specific medication delivery. The degree of hydrophobicity, particle size and charge, and particle surface modification all have an impact on a Nano carrier's capacity to act as a target. The key issue is the prolonged released state's preferential binding, distribution, and toxicity of the nanocarrier and nanomaterials in an aqueous and no aqueous medium. Assume that the target, administration, and toxicity of these Nanocarriers and Nano drug formulations have all been carefully considered in their design. They might open the way for a fresh, more fruitful therapeutic and research strategy in this circumstance. Supercritical fluids, which are non-toxic and environmentally friendly, and free of harmful solvents, are being used in the most promising nanomaterial research.To get around these obstacles, numerous research is being conducted, with site-specific medicine delivery based on nanoparticles serving as the gold standard.

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