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Review Article

Nanotechnology in Herbal Medicine: A Promising Approach for Enhanced Drug Delivery and Therapeutic Efficacy

Prachi S. Tajne*, Vaishnavi S. Kalamb, Pavan N. Girhe, Ravindra L. Bakal, Pooja R. Hatwar

Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangaon Rly, Dist. Amravati (444709) Maharashtra, India

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*Address for Correspondence:

Prachi S. Tajne, Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangaon Rly, Dist. Amravati (444709) Maharashtra, India

Abstract

Nanotechnology has revolutionized the field of herbal medicine by providing a platform for enhanced drug delivery and therapeutic efficacy. The use of nanocarriers and nano formulations has improved the bioavailability and solubility of herbal extracts, allowing for targeted and controlled release of active compounds. This review highlights the potential of nanotechnology in herbal medicine, including the types of nano formulations, methods of preparation, and applications in various diseases. The advantages of nano formulations, such as improved pharmacokinetics and pharmacodynamics are also discussed. Furthermore, the role of computational tools and artificial intelligence in nanotechnology is explored, including their potential to transform drug delivery and disease monitoring. Despite the promising benefits, the drawbacks of nanotechnology, including biocompatibility and toxicity concerns, are also addressed. Overall, nanotechnology has the potential to enhance the therapeutic efficacy and safety of herbal medicines

Keywords: Nanotechnology, Herbal medicine, Nano formulations, Artificial intelligence, Drug delivery

Introduction:

The Greek prefix "nano," which means "dwarf" or extremely little. It is important to differentiate between nanotechnology and nanoscience. The study of molecules and structures 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 [1]. The topic of nanotechnology has attracted the attention of the whole scientific community. Nobel Laureate Richard Feynman introduced the concept of nanotechnology in a December 1959 lecture at the California Institute of Technology. The processing of material separation, consolidation, and deformation by a single atom or molecule is known as nanotechnology [2].

Two key areas of research can be used to summarize the intersection of nanotechnologies and plant derivatives:

1. Utilizing plant extracts for the production of nanomaterials and
2. Integrating them into nano systems [3].

Plant actives and extracts are among the promising prospects in nanotechnology, a multidisciplinary scientific endeavor that is making strides on several fronts. Numerous valuable phytochemicals and herbal medications have been successfully developed as a result of the significant attention paid to nanocarrier systems for plant active ingredients and extracts [4]. Nanotechnology is a rapidly developing topic with a wide range of uses in medical science, including medicine delivery, cosmetics, food ingredient packaging, and many more [5]. Solid, liquid, or gaseous substances of nanoscale dimensions typically 1–100 nm are referred to as nanomaterials. They have special chemical and physical characteristics, including as size effects, quantum effects, and large surface area [6]. Extracts, concentrated fractions, or biomarker components of herbal treatments are examples of nanoscale pharmaceuticals known as herbal nanomedicines. Herbal nanomedicines have several benefits since they are less toxic and have a better bioavailability [7]. Making a nanoformulation of the extract could potentially be helpful [8]. To optimize the synergistic phytochemical agents based on the nano delivery system, the propolis nano formulation is connected to the oral administration delivery system [9]. Due to the synergistic effects of the various phytochemical combinations available, it has been demonstrated that plant extracts, in particular, can target the underlying pathophysiology of diseases and have several modes of action [10]. Because of their many pharmacological characteristics, natural products which have long been a source of therapeutic agents offer great potential. These natural substances can be further enhanced when paired with nanotechnology [11]. To guarantee their effectiveness, accessibility, and safety in the control of the wound healing process, numerous formulations and research have examined the function of herbal extracts [12]. These nano-based formulations can also help herbal medicines overcome pharmacological challenges, such as instability and poor water solubility and bioavailability [13]. Herbal medication delivery methods at the nanoscale may be used in the future to improve plant medicine's efficacy and solve its drawbacks [8].

Among the many benefits of a medicine delivery system based on nanostructure are the following:

1. Because of their incredibly small capacity, they can fit through the tiniest capillary veins.
2. They can reach target organs such the liver, spleen, lungs, spinal cord, and lymphatic system by penetrating cells and tissue gaps.
3. They can offer a prolonged time of regulated release [11].

Classification based on Dimensions of Nanoparticles

Nanomaterials are divided in our types based on their size: 0D, 1D, 2D, and 3D.

- Zero-dimensional (0D): height, breadth, and length are all 0D. The corresponding author is stationed in one location, such as Nano dots. Single-dimensional nanoparticles: For many years, one-dimensional systems like thin films or artificial surfaces have been used in engineering, chemistry, and electronics.
- One-dimensional (1D) : Nanofibers, nanotubes, nano horns, nanorods, thin films, and nanowires are examples of nanomaterials.
- Two-dimensional (2D) nanoparticles: These materials have two dimensions that go beyond the nanoscale. Three examples are nanosheets, nanofilms, and nanolayers.
- Three-dimensional (3D): Bulk nanomaterials are another name for nanoparticles. In every way, these nanoparticles are not small by nature. Stated otherwise, their three-dimensional size exceeds 100 nm. These include several nanolayers, core shells, bundles of nanowires, bundles of nanotubes, and nanocomposites [14].

Types of nano formulation

The pharmaceutical industry uses a variety of nano formulations to deliver drugs. Nanomaterials and nanostructures, either inorganic or organic, make up nano formulations.

1. Inorganic Nanocarriers: Quantum dots, Metal Nanoparticles
2. Lipid Based Nanocarriers: Liposomes, Solid-Lipid Nanoparticles, Nanosuspensions, Nano emulsions.
3. Polymeric Nanocarriers: Dendrimers, Nanogels, Polymer-drug conjugates, Micelles, Polymeric Nanoparticles etc [15,16].

- **Inorganic nanoparticles -** The many kinds of inorganic particles metal, ceramic, magnetic, and nanoshells as well as their size, description, benefits, drawbacks, and uses are created. Inorganic Nanoparticles far smaller in size than organic nanoparticles It encompasses size ranges of 1-100 nm with enhanced loading effectiveness [17].
- **Organic nanoparticles -** The benefits and drawbacks of the different kinds of organic nanoparticles such as carbon nanotubes, quantum dots, dendrimers, liposomes, and polymers are discussed [18].
- **Lipid Based Nanocarriers:** Lipid-based nanocarriers are a versatile and exciting platform for gene therapy, drug delivery, and diagnostics. These nanocarriers encapsulate pharmaceutical compounds in naturally occurring lipids, improving stability, bioavailability, and targeting capabilities [19].

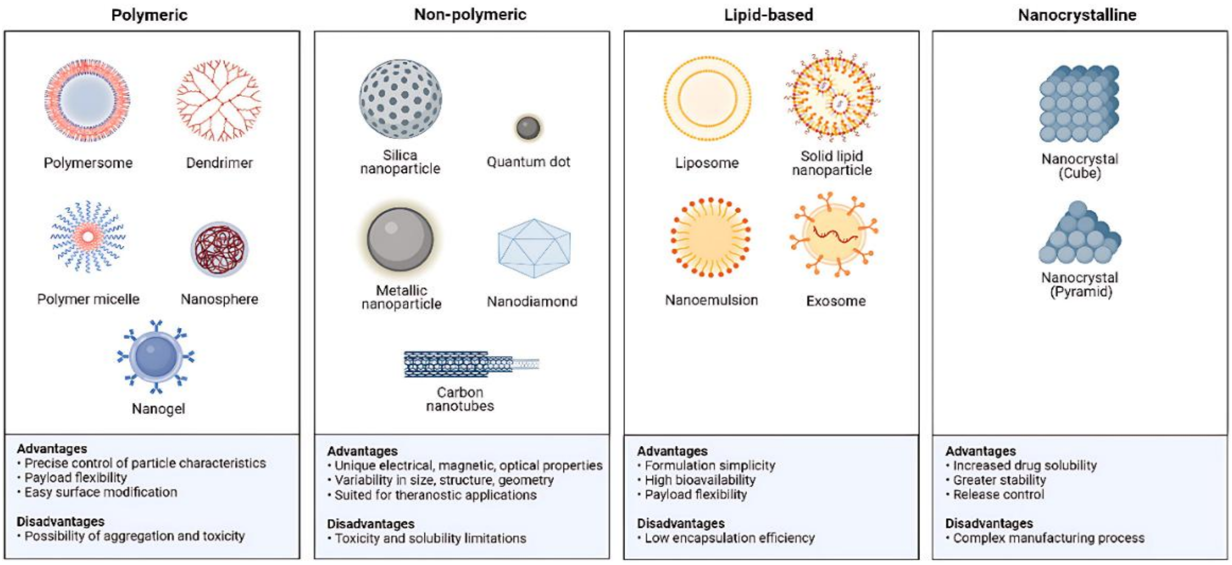

Figure 1: Classes of nanoparticles are employed in the pharmaceutical industry to facilitate drug delivery [20].

- **Polymeric Nanoparticles**:

Polymeric nanoparticles are extremely small (10^{-9} m) polymeric colloidal spheres that can either adsorb or conjugate at their surface or entrap the medication within the matrix. Diffusion and erosion from the matrix cause the medication to be released from the nanoparticles [21]. From polymeric nanoparticles, biodegradable natural and manmade polymers are created. They are very stable and are known to release medications gradually depending on the enclosed molecule [15].

Carbon nanotubes (CNTs):

Fullerenes are a cylindrical set of carbon allotropes that comprise CNTs with unique physicochemical properties that facilitate surface modification. Polyvalent CNTs are rapidly being developed as cancer treatment methods. Targeted medication administration, which aims to target the therapeutic treatment exclusively for tumors, is the most promising approach [22].

Liposomes and Lipid-Based Systems:

Liposomes are tiny bubble-like structures with a hydrophilic head and a hydrophobic tail, like phospholipid. Additionally, lipids are arranged into water, with hydrophilic tails aggregating to form a core and hydrophilic heads freely pointing outward [21]. Because of their superior flexibility and biocompatibility, lipid nanocarriers were chosen [15].

Solid Lipid Nanoparticles:

The particle size of solid lipid nanoparticles (SLN) ranges from 50 to 1000 nm. Particulate systems known as SLN contain stabilizers and physiological lipids that decompose naturally. These are room-temperature melting emulsified nanoparticles made of solid lipids. Mitoxantrone was used to prepare SLN for breast cancer and its lymph node metastases [21]. Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC), which are stable in both lipophilic and hydrophilic environments and safe for transporting and releasing active substances to the skin, release the liposome micelle structure [23].

Nanosuspensions:

Colloidal dispersions of submicron drug particles are known as nanosuspensions (NSs), and they are typically described as biphasic, highly finely dispersed colloids that contain solid drug particles smaller than 1µm [24].

Dendrimers:

A macromolecule with a well-defined molecular mass, the dendrimer is a symmetric, spherical, highly branching, monodispersive polymeric molecule in three dimensions. The Greek words dendron (tree) and meros (part) are the roots of the word dendrimer. Arborols and cascades are additional synonyms for dendrimer. However, the dendrimer is the most widely accepted term. High levels of surface functionality and adaptability are offered by the dendrimers. Encapsulation or conjugation of bioactive substances on the surface of dendrimers can further enhance the functionality of these nanostructure dendrimers [25].

Nanogels:

Originally, the word "nanogel" was used to describe bifunctional cross-linked networks that transmit polynucleotides using a polyion and a non-ionic polymer. Nanogels with a diameter between 100 and 200 nm. Another name for nanogels is hydrogel nanoparticles or nanoparticle-based nanogels. Gels are networks of three-dimensional, nanoscale polymers that are cross-linked chemically or mechanically [26].

Nano emulsion:

Nanoemulsion as a System of Colloids Nano emulsion, which ranges in size from 20 to 500 nm, is also referred to as a mini emulsion, sub-micron emulsion, or ultrafine emulsion. It is possible to modify the nano emulsion structure to suit the requirements of different applications. Oil in water (O/W), water in oil (W/O), and bi-continuous are the three different forms of nano emulsion. In the latter, the interfacial tension induced by the surfactant separates the phases that are present in a nano capsulation system [27].

Nanocrystals:

Common concerns with NPs, liposomes, or solid lipid NPs (SLNs) include high manufacturing costs, platform instability, loading problems, and scaling-up challenges. On the other hand, drug nanocrystals can be administered intravenously without the need for any carrier materials for encapsulation and/or solubilization; however, in order to stabilize pure drug crystals and reduce aggregations, surfactants or polymers are typically needed. Nanocrystals are drug crystals that have a particle size of a few hundred nanometres [22].

Different Methods of Herbal Nano-formulation:

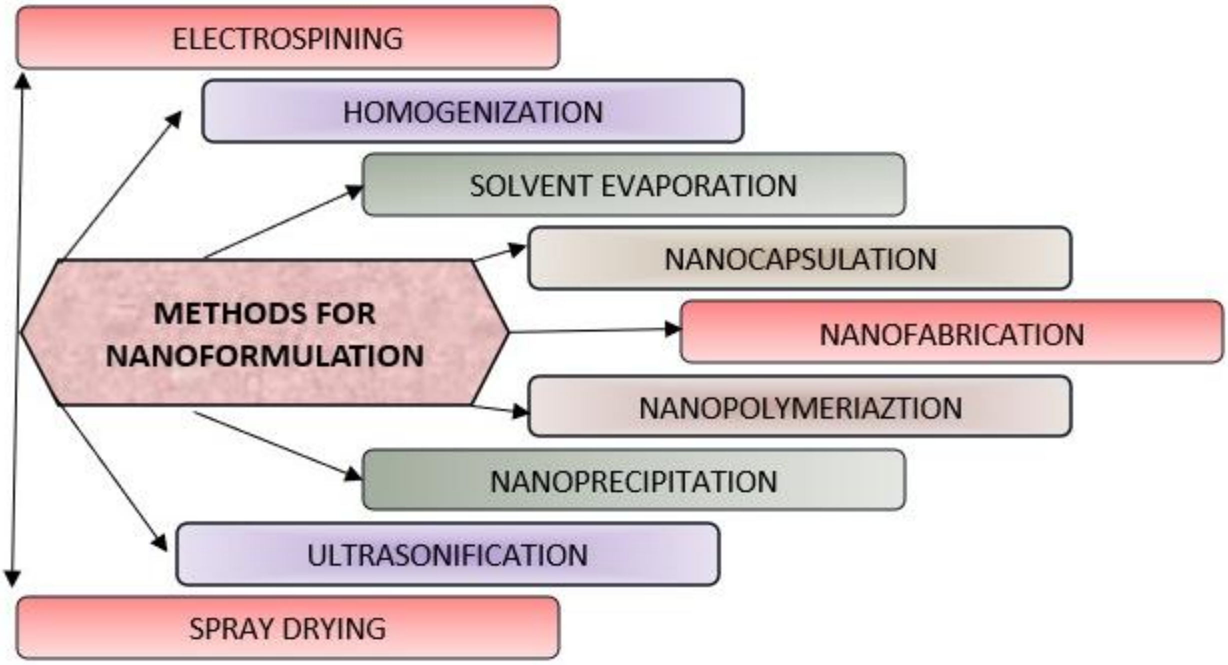

Figure 2: Schematic representation showing the methods for preparation of herbal nano-formulations [15, 28].

Electrospinning:

An efficient, cost-effective, and adaptable technique for creating nanofiber layers with diameters ranging from 3.0 to more than 5.0 nm is electrospinning, which uses a high-voltage electric field to elongate droplets of injected polymer solutions. The high voltage encourages the interaction between charged polymer precursors and external electrical fields, resulting in the formation of polymer nanofibers. The high voltage power source, which can deliver several tens of kilovolts, enables the resulting nanofibers to have unique characteristics like increased surface areas and both intra- and inter-fibrous porosity. This technology is widely used to create one-dimensional (1D) continuous polymeric materials, 1D nanocomposites, or inorganic materials [29].

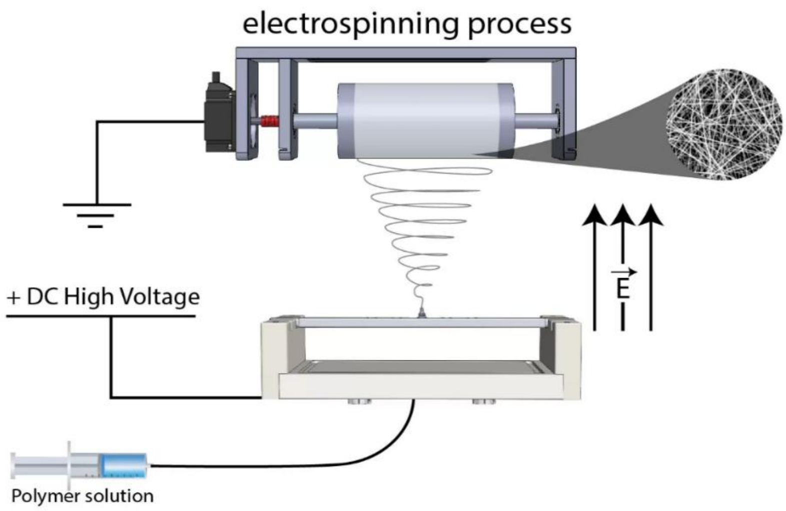

Figure 3: Systematic Representation of Electrospinning Methods [30]

High Pressure Homogenization:

There are two methods for producing Solid Lipid Nanoparticles (SLN) using high pressure homogenization, which are as follows:

a. Hot Homogenization Technique (HHT): This method involves dispersing the drug loaded in melted lipid in an aqueous surfactant solution at the same temperature using a high shear device.

b. Cold Homogenization Technique (CHT): CHT was formed to avoid temperature-induced drug degradation, the partitioning of hydrophilic drugs from the lipid phase to the aqueous phase, and the intricacy of the nano emulsion's crystallization step, which can result in multiple modifications and/or supercooled melts [31].

Solvent Evaporation technique:

Copolymers and medications are dissolved in a common solvent or miscible solvents as part of the solvent evaporation process. This is the preferred technique for PM manufacturing when both polymers dissolve in the solvent and are soluble in water. The solvents evaporate, forming a thin film of drug copolymer. Drug-loaded PMs are created spontaneously when water or buffers are added. Additionally, the size of the micelles is distributed during processing using a sonicator or high-pressure extruder. Likewise [32].

Nanoencapsulation:

The word "nanoencapsulation" describes the potential applications of materials that are encased at nanoscale levels, including layers, films, coatings, and even straightforward micro dispersions. More encapsulation-friendly features are provided by the nanoparticle-based encapsulation technique. More efficiently and with better encapsulation-related characteristics, nanoparticles release bioactive compounds [28].

Nanofabrication:

Nanofabrication creates elements that are 100 nm or less in size. This is a group of techniques, and depending on the direction of the removed material, the etching process creates isotropic or anisotropic features by selectively removing the reactive agents. Sodium carbonate is used to create hollow mesoporous silica nanoparticles, which have been shown to have good biological compatibility and are widely used as drug nanoreactors or nanocarriers [15].

Nano polymerization

These procedures can be classified as either direct polymerization or polymerization reaction, depending on the requirements of the formulation. Other forms of polymerizations include interfacial and emulsion polymerization. Based on the continuous phase, emulsion polymerization is further separated into organic and aqueous polymerization [33].

Nanoprecipitation

Precipitation techniques, in which a drug containing solution is subjected to particular conditions to cause the drug to precipitate into nanoparticles, can be used to create nanoparticles [34]. When a semi-polar solvent that is miscible with water is dislocated from a lipophilic solution, the interfacial tension between the two phases decreases, increasing the shell area and resulting in a configuration of tiny organic solvent droplets even without mechanical stirring This process is based on the interfacial accrual of a polymer [35].

Ultrasonication:

One innovative technological method for the accurate implementation of nanoencapsulation procedures is ultrasonication. Ultrasonication uses mechanical forces to enable nanoscale encapsulation by taking advantage of the phenomenon of high-frequency sound waves propagating in a liquid media. This provides a new and sophisticated way for accomplishing this complex operation. Ultrasonication uses ultrasonic waves as part of its emulsification process to create ultrafine emulsions. It helps disperse solid particles in a liquid medium and break up clusters [28].

Spray Drying Method:

This process is employed in the manufacturing of tablets and powder. After containing API and excipients in the appropriate solvent, a macro suspension is first produced. This suspension is then passed through a homonizer to form a nanosuspension. Eliminating the solvent is the second stage. Two techniques, such as freeze drying and spray drying, are employed for solvent removal. The dryer works on a simple concept. Initially, the heater applies the drying gas into the system through laminar air flow. Fine suspension droplets are sprayed by the spray head, and after the droplets dry, they solidify into particles. This kind of powder can be used as a medication carrier for suspension, for encapsulation, for inhalation, and more [36].

Natural herb used in nanoformulations for the treatment of different diseases

1. **Curcumin:** Curcumin possesses several pharmacological properties, including anti-hyperlipidemic, immunomodulatory, chemo-protective, antineoplastic, antiulcer, and neuro-protective properties [5].
2. **Licorice:** Glycyrrhiza glabra L. and Glycyrrhiza uralensis, or licorice, have anti-inflammatory qualities.
3. **Turmeric:** Turmeric is essential to both Ayurvedic and Traditional Chinese treatment. In vitro, turmeric's primary active ingredient, curcumin, exhibits anti-inflammatory, antibacterial, and antioxidative properties [7].
4. **Propolis:** A product of bees, propolis has several pharmacological properties, including antiviral, antifungal, antibacterial, anti-inflammatory, anti-parasite, and wound-healing properties [9].
5. **Ficus trijuja:** Ficus trijuja is a member of the moraceae family's genus ficus. Due to its high phenolic content, the acetone extract of f. Amplissima leaves exhibited strong wound-healing capabilities through anti-inflammatory and antioxidant actions [4].
6. **Berberis:** The extract has a naturally occurring synergistic blend of components that have the ability to heal wounds. Among its many other biologically beneficial properties, it is a multicomponent anti-infective and, more specifically, an antibacterial agent [4].
7. **Trigonella foenum graecum:** Trigonella foenum graecum restored normoglycemia and normalized the experimental diabetic rats' reduced levels of creatine kinase in the liver, skeletal muscle, and heart [37].

8. **Capsaicinoids:** Capsaicinoids have a significant biological activity and may be used pharmacologically and clinically to treat inflammatory and oxidative disorders, as well as neurological and musculoskeletal discomfort [38].

9. **Hura crepitans L.:** This species is a member of the euphorbiaceae. These substances are secondary metabolites that help plants defend themselves and are essential in lowering oxidative stress, a major contributor to a number of human illnesses, including diabetes, obesity, cancer, and neurodegenerative diseases [39].

10. **Quercetin:** Quercetin known for its neuroprotective and anti-inflammatory properties, quercetin is a bioflavonoid that may be found in a variety of fruits, vegetables, and oils derived from herbs [40].

Advantages of novel formulations of herbal extracts

Herbal remedies and phytoconstituents are believed to be safer and more efficient than allopathic drugs. Globally, the use of natural medicines is increasing. Principles of nanoscience and technology have been applied to these naturally occurring drugs in order to improve their bioavailability and attain tailored distribution [41]. Worldwide, herbal remedies are in widespread use and are acknowledged by both doctors and patients as having superior therapeutic value due to their lower side effects when compared with modern medications. By decreasing toxicity and raising bioavailability, novel drug delivery systems that employ a scientific approach not only reduce the need for repeated administration to overcome non-compliance but also contribute to an increase in therapeutic value [42].

Pharmacokinetic And Pharmacodynamic Enhancement in Nano formulation-

Delivery techniques using nanoformulations could significantly enhance medication PK. However, nano formulation distribution can also have a detrimental impact on therapeutic efficacy and toxicity, whereas excessive buildup of nano formulations may result in tissue-specific toxicity, inadequate absorption and diffusion into tissues may impair pharmacological activity [43]. These consist of metallic nanoparticles, solid lipid nanocarriers, nanoparticles, and nanocapsules. The biodistribution, pharmacokinetics, bioavailability, and specificity of drug delivery to the site are all improved when these methods are chosen for nano formulation [44]. One important pharmacokinetic metric that shows the concentration of a nonvascular medication that can enter the systemic circulation via a nonvascular pathway is bioavailability. Another crucial PK parameter that is assessed by figuring out the values of Cmax and Tmax is the adsorption rate [45].

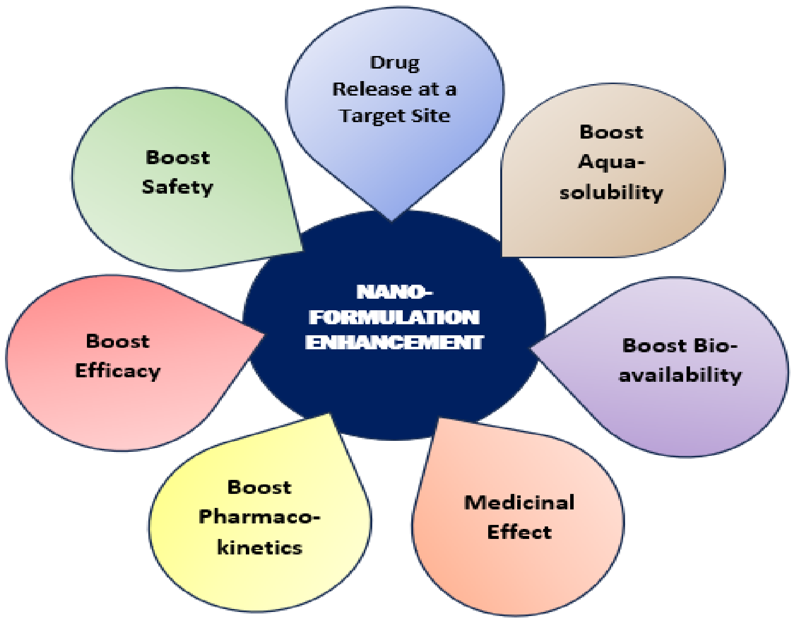

Figure 4: Benefits of nano delivery systems [44].

Three-Dimensional Printing in Nano pharmacy (Nano Printing):

The use of 3D printing in a variety of medical applications has grown significantly. Known as Three-Dimensional Printing (3DP), this technology offers many benefits, including on-demand device creation, complex geometries, and affordable prototyping. Because it allows for personalized production, 3D printing (3DP) is posing a challenge to traditional mass manufacturing processes in the pharmaceutical business for fixed-dose medications. 3D printing technology is acknowledged as an additive manufacturing process since it uses computers to manipulate material layers to create 3D items [46]. Because of their extremely small size and narrow size distribution, a variety of nanotechnologies, such as nanoparticles (lipid, polymer, and metallic nanoparticles), dendrimers, nanodiamonds, nanocrystals, quantum dots, carbon nanotubes, nanogels, nanoemulsions, etc., are being investigated for the creation of different nanomedicines. Through the use of apparent surface functional design, bioconjugation, and exceptional biocompatibility, these nanomedicines are also being produced utilizing 3D printing technology as precision medications to meet the unique needs of each patient [47]. Through individualized drug delivery methods, the use of 3D printing in pharmaceuticals offers innovative breakthroughs in customizing drug compositions to patients' demands, potentially improving therapeutic outcomes. Complicated drug delivery systems and formulations can be precisely created using a variety of 3D printing technologies, such as powder-based, extrusion-based, inkjet-based, and laser-based techniques [48]. Layer-by-layer material deposition onto a substrate is one of the additive manufacturing processes used in 3D printing procedures. Computer software is used to build the final 3D product. Two basic steps are involved in all 3D printing techniques. One is about utilizing computer software to create products, while the other is about using a 3D printer to deposit stuff. Oral administration of solid dosage forms is the most often used medication administration technique. Accurate dosing, chemical and microbiological stability, controlled release properties, and ease of administration are all offered by oral tablets [49].

Use of Computational Tools and AI

Significant advancements in computational modeling techniques are quickly closing the gap between multi-supra molecular structures at the nanoscale, such as nanoparticles and other nano-engineered nanomaterials (ENMs), including nanocarriers, and atomistic levels of description of both organic and inorganic molecular systems [50].

- By enabling precise, tailored therapies at the nanoscale, artificial intelligence has transformed drug delivery. Drug distribution is safer and more efficient thanks to this accuracy, which also reduces adverse effects and improves therapeutic efficacy.
- To fully realize the potential of personalized medicine, AI and nanotechnology must be integrated [51].
- Artificial Intelligence (AI) in nanotechnology is transforming illness monitoring and detection by offering ongoing surveillance and early diagnosis [52].
- The incorporation of AI into nanomanufacturing procedures is making it easier to precisely and efficiently assemble nanoscale structures, which is resulting in ground-breaking developments across a range of industries.
- A new era of environmental monitoring and remediation is being ushered in by the combination of AI and nanotechnology.
- Energy conversion processes are greatly improved by nanomaterials, which are carefully designed at the nanoscale [51].
- Groundbreaking advancements in healthcare are being made possible by the convergence of nanorobotics and medicine [53].

Nanotechnologies Applications

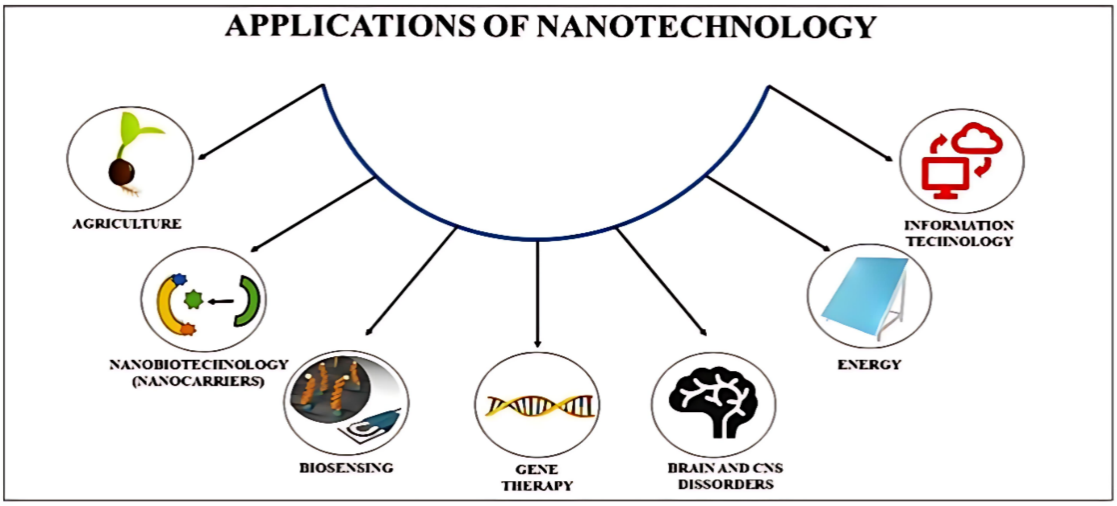

Figure 5: Applications Of Nanotechnology [54]

Applications of nanotechnologies include tissue engineering, medication and gene delivery, protein detection, fluorescent biological labeling, pathogen detection, DNA structural probing, and more. Other methods used in medicine for cancer diagnosis and treatment include phagokinetic investigations, MR imaging contrast enhancement, isolation and purification of biological molecules and cells, and tumor killing by heating (hyperthermia). Advanced medicines with less invasiveness and cost-effective diagnostic equipment that are quicker, smaller, and more sensitive are both made possible by nanotechnology.

Drawbacks of Nanotechnology

The main cause for concern is the nano formulations' biocompatibility. The most important factors are how easily nanotechnology-based treatments have been offered globally at the most basic levels (government hospitals, primary healthcare, etc.) and how much they cost. Furthermore, further research is required to fully understand its toxicity and effects on the environment, human body, and biochemical pathways. Researchers are seriously concerned about the ethical application of nanomedicine in society and the associated safety concerns [55].

Conclusion

Nanotechnology has emerged as a promising approach for enhancing the therapeutic efficacy and safety of herbal medicines. The use of nano formulations and nanocarriers has improved the bioavailability and solubility of herbal extracts, allowing for targeted and controlled release of active compounds. With the integration of computational tools and artificial intelligence, nanotechnology has the potential to transform drug delivery and disease monitoring. However, further research is needed to fully realize the potential of nanotechnology in herbal medicine and to address the concerns related to biocompatibility and toxicity. As the field continues to evolve, it is expected that Nanotechnology will play a significant role in the development of novel and effective herbal medicines. Ultimately, the combination of nanotechnology and herbal medicine may provide a new concept for the treatment.

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