

HERBAL NANOFORMULATION: A NOVEL DRUG DELIVERY SYSTEM

Abstract

Herbal medicine is presently used in many different forms such as whole plants, plant parts, extracts, tinctures, teas, capsules, creams, and other formulations for the treatment of various disorders, from minor illnesses to chronic diseases like cancer and cardiovascular diseases. The bioactive molecules present in medicinal plants play a significant role for imparting therapeutic values of herbal medicines. The limited permeability and low solubility of plant extract play a vital role in the drug delivery system. Many bioactive substances have low bioavailability and cannot reach the desired organ or cell due to their limited solubility in water and lipophilic solutions. To overcome these problems and to improve bioavailability and therapeutic effectiveness of the extract, new drug delivery systems have been developed. Herbal nanomedicines are nanosized medicinal products that include extracts, concentrated fractions, or biomarker elements from herbal remedies. The herbal nanotechnology entails utilization of nanoscale materials and procedures that improve herbal component's medicinal features, enhancing their effectiveness, bioavailability, and targeted delivery. Small particle size, high surface area, hydrophilic and lipophilic nature, and surfactant effects are the important characteristics of nanoformulations which collectively improve the solubility and tissue/membrane permeation of drugs. Due to their small size and high surface area-to-volume ratio, nanoparticles exhibit distinctive characteristics and behaviors. In the present topic, author has described the different types of herbal nanoformulation, preparation, characterization and their application in various diseases with suitable examples.

Key words: Herbal medicine, herbal nanoformulation, types, methods of preparation, limitation.

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I. INTRODUCTION OF HERBAL MEDICINE

Herbal medicine, also called botanical medicine or phytomedicine, where plants or plant parts are used for therapeutic purposes. It is an ancient form of traditional medicine that has been utilized by numerous civilizations all over the world. Herbal medicine uses plant-derived compounds such as leaves, flowers, roots, bark, and seeds that have therapeutic characteristics to heal different ailments. Herbal medicine has a long history in which plants were used as the primary source of cures for numerous illnesses and based on their observations and interactions with plants, multiple indigenous cultures, such as ancient China, India, Egypt, Greece, and Native American tribes, developed extensive herbal knowledge and healing traditions. The use of herbal medicines was recorded in ancient texts and formalized into comprehensive healthcare systems, such as Traditional Chinese Medicine (TCM) and Ayurveda, in ancient civilizations like China and India, respectively [1-2]. The strategy for treatment included dietary changes, lifestyle adjustments, and other therapeutic techniques that utilized herbal remedies. Even when new types of medicine developed throughout history, herbal therapy remained a popular healing method in numerous civilizations. The practice of herbal therapy has decreased worldwide due to modern medicine and pharmaceutical developments. However, as more individuals look to natural and alternative treatments for illness, interest has risen in recent decades. A scientific study is currently being conducted on herbal medicine, and recognized as a complementary and alternative medicine (CAM), to confirm its efficacy, comprehend its mechanisms of action, and explore potential uses. Herbal medicine is presently used in many different forms and areas. Utilizing whole plants, plant parts, extracts, tinctures, teas, capsules, creams, and other formulations is readily available. Herbal medicines are employed to treat a variety of medical disorders, from minor illnesses like colds and digestive problems to chronic diseases like cancer and cardiovascular diseases [3].

It is crucial to remember that medicinal plants frequently have numerous active constituents that combine to provide therapeutic effects. Different plant species and portions of the same plant can have varying combinations and ratios of these chemicals. Certain active substances present in medicinal plants are typically linked to the therapeutic capabilities of herbal medicines. The efficacy and safety of medicinal plants might vary, so it is essential to keep this in mind and utilize them with care [4].

II. LIMITATIONS IN THE HERBAL DRUG DELIVERY

Plant extracts are very much sensitive to climatic condition (light, temperature, heat) and change in pH. Bioactive substances are easily oxidized and destroyed by oxygen and light. As a result the bioactive principles of drug are destroyed. Reaching to the target cells and organ in active form by penetration through cell wall is the major disadvantages of plant extract. The limited permeability and low solubility of plant extract play a significant role in the drug delivery system. Many researchers have been carried out to look into the permeability and solubility problems of plant extracts. Many bioactive substances have low bioavailability and cannot reach the desired organ or cell due to their limited solubility in water and lipophilic solutions. To overcome these problems and to improve bioavailability and therapeutic effectiveness of the extract, new drug delivery systems have been created [5].

III. NEED FOR NOVEL DRUG DELIVERY SYSTEM

Before entering the bloodstream, many bioactive principle of the extract are demolished in the extremely acidic stomach juice, while other constituents may be metabolized by the liver. Therefore, herbal drug may not enter the blood in appropriate quantity. If the drug is not administered to the affected area in the proper amount at the most minimum effective level, it will be difficult to demonstrate its therapeutic effects. Due to their small size and ability to pass through barriers like the stomach's acidic pH and liver metabolism, nanocarriers used with herbal medicines and carry the maximum amount of the drug to its site of action [6]. Herbal nanomedicines are nanosized medicinal products that include extracts, concentrated fractions, or biomarker elements from herbal remedies. Small particle size, high surface area, hydrophilic and lipophilic nature, and surfactant effects are the important characteristics of nanoformulations. Collectively, these characteristics improve the solubility and tissue/membrane permeation of drugs that are not readily soluble, such as curcuminoids from *Curcuma longa*, triterpenoids from *Ginkgo biloba* extracts, bacosides from *Bacopa monnieri* extract, and polyphenols from green tea extract [6]. Due to the following reasons the nanosized new drug delivery system (NDDS) was chosen.

1. Due to their distinct size and high loading capacity, the NDDS can transport a noticeable amount of bioactive principle to the targeted area.
2. Deliver the medicinal product in small particles to increase the drug's surface area and facilitate faster absorption in the blood.
3. The drug concentration remains higher at the site of specific disease locations.
4. Increased permeability and penetration through the barriers due to small size.
5. It target to the perticular disease site without using specific ligand molecules.
6. Side effects have been reduced.
7. The dose of the formulation is decreased.

IV. INTRODUCTION TO NANOTECHNOLOGY

Modern science and engineering focus on altering and controlling matter at the nanoscale. It entails understanding and using the particular characteristics of nanoscale materials, which can display different behaviors and properties from their bulk counterparts. Fabricating and describing nanostructured resources, understanding them, and putting them to use are all aspects of nanotechnology. Nanoparticles, which have dimensions ranging from 1 to 100 nm, are the precursors to nanotechnology. The surface area-to-volume ratio is the main characteristic of nanoparticles that makes it easier for them to mix with other particles. Additionally, it is assumed that nanoparticles work with targeting molecules to transport specific biomolecules where they are needed. Consequently, nanoscale particles are now widely used in creating innovative formulations to treat various ailments [7]. The core concept of nanotechnology is that materials exhibit higher reactivity, increased strength, improved electrical and thermal properties, and distinctive optical behavior when their surface area grows considerably as they are reduced to the nanoscale. Nanoscale materials are substances with particular characteristics and functions due to their nanoscale dimensions. These substances may exist naturally, be created synthetically, or be synthesized using various techniques [8]. Nanoparticles, nanotubes, nanofibres, and surfaces with nanostructures are some common types of nanoscale materials. Nanomaterials are used in medicine for targeted drug delivery and modern diagnostic procedures. Due to their small

size and high surface area-to-volume ratio, nanoparticles exhibit distinctive characteristics and behaviors. These qualities, which are helpful for various applications, result from quantum phenomena and increased surface interactions. Due to their greater surface area per mass, nanoparticles offer additional locations for chemical reactions, adsorption, and interactions with other substances. Since they may move more quickly and freely than larger particles, nanoparticles are helpful in nanofluidics and drug delivery systems. By encapsulating drugs, shielding them from deterioration, and enabling targeted administration to particular tissues or cells, they also increase bioavailability in medicine. Since nanoparticles may move more quickly and freely than larger particles, they help to repair nanofluidics and drug delivery. By encapsulating drugs, shielding them from deterioration, and enabling targeted administration to particular tissues or cells [9]. They also increase bioavailability in medicine. Key features and properties of nanoscale materials are described as below [10].

- 1. Increased Surface Area:** Nanomaterials have a greater surface area than their volume. This makes them highly reactive and improves their ability to interact with other substances or molecules.
- 2. Quantum Effects:** The behavior of electrons is affected by quantum effects, which are stronger at the nanoscale and give rise to remarkable optical, electrical, and magnetic properties.
- 3. Mechanical Properties:** Comparing nanoscale materials to their bulk substitutes, it is common to see improvements in mechanical strength and hardness. This qualifies them for manufacturing lightweight, durable materials and reinforcing composites.
- 4. Electrical and Thermal Conductivity:** Due to their improved thermal and electrical conductivity at the nanoscale, certain materials are advantageous for electronic and temperature control applications.
- 5. Self-Assembly:** The intrinsic characteristics of many nanomaterials allow them to self-assemble into desired structures. The ability to self-assemble is essential for developing precise nanostructures and nanodevices.

V. INTRODUCTION TO HERBAL NANOTECHNOLOGY

Herbal nanotechnology is an evolving field that develops novel methods for synthesis, characterization of herbal nanoparticles by fusing the concepts of herbal medicine with nanotechnology. The process entails utilizing nanoscale materials and procedures that improve herbal component's medicinal features, enhancing their effectiveness, bioavailability, and targeted delivery. However, nanotechnology focuses on manipulating and controlling materials at the nanoscale, usually between 1 and 100 nanometers. Materials can display distinct characteristics and behaviors in this size range, which can be used for a variety of purposes. In the area of herbal nanotechnology, scientists attempt to overcome the drawbacks of conventional herbal medicines by utilizing the advantages of herbal medicine and nanotechnology. The surface area available for interaction with the body is considerably increased by reducing the size of the herbal preparations or isolating active components into nanoparticles. The enhanced surface area facilitates better absorption, targeted delivery, and

magnified therapeutic results. Herbal nanoparticles are produced using a variety of processes, including emulsion, sol-gel, co-precipitation, and green synthesis processes [11].

VI. HERBAL NANOPARTICLES FROM AN AYURVEDIC PERSPECTIVE

Nanomedicine originates from the ancient tradition of Ayurveda, which uses metal nanoparticles like Bhasma for therapeutic purposes. The process of preparing Bhasma (ash) is called "Bhasmikaarana," in which herbal medicines and metal ions are transformed into metal ion nanoparticles with a higher oxidative state. These metal nanoparticles are excellent because of their enhanced stability, superior absorption, and body compatibility. The Dhatu (Metal) Bhasma is usually prepared with metals such as silver (Rajata), mercury (Parada), zinc (Yasada), iron (Loha/Aayasa), tin (Vanga), lead (Naga/Sisaka), copper (Tamra), and gold (Swarna). The examination of Bhasma is carried out by Transmission Electron Microscopy (TEM) and Scanning Electron Microscope (SEM) which revealed decrease in particle size to 5-50 nm. The medicinal substance may be more effectively absorbed and targeted to specific tissues when using metal nano particles (NPs) comprising various phytoconstituents. These preparations work better because of their micro size. Swarna Bhasma (Gold NPs) is used to treat tuberculosis, anemia, asthma, and other respiratory disorders; Parada Bhasma (Mercury NPs) is used to treat skin disorders; Loha Bhasma (Iron NPs) is used to treat abdominal tumors, inflammation, coughs, and intestinal disorders; Tamra Bhasma (Copper NPs) is used to treat skin disorders, inflammation, and coughs; Rajata Bhasma (Silvers NPs) is used to treat respiratory diseases; Sisaka Bhasma (Lead NPs) is used to treat abdominal tumors, piles, and intestinal disorders; Yasada Bhasma (Zinc NPs) is used to treat diabetes, conjunctivitis, wound healing, jaundice, and gonorrhoea; and Vanga Bhasma (Tin NPs) is used to treat gastrointestinal and genitourinary disorders. Bhasma can be an excellent paradigm for the advancement of nanomedicine and has significant relevance to current nanomedicine overall. Various herbal medications and/or their active ingredients have been employed to create and improve various nanoformulations [12].

VII. TYPES OF HERBAL NANOPARTICLE

There are about 16 different types of herbal nanopreparations are being used in novel drug delivery. These include (1) polymeric herbal nanoparticles, (2) solid lipid nanoparticles, (3) phytosomes, (4) nanomicelles, (5) self-nano emulsifying drug delivery system, (6) nanofibers, (7) liposomes, (8) dendrimers, (9) ethosomes, (10) nanoemulsion, (11) nanosuspension, (12) carbon nanotubes, (13) nanoniosome, (14) Nanocomposites, (15) Nanocapsules and (16) Transferosomes (Figure 1).

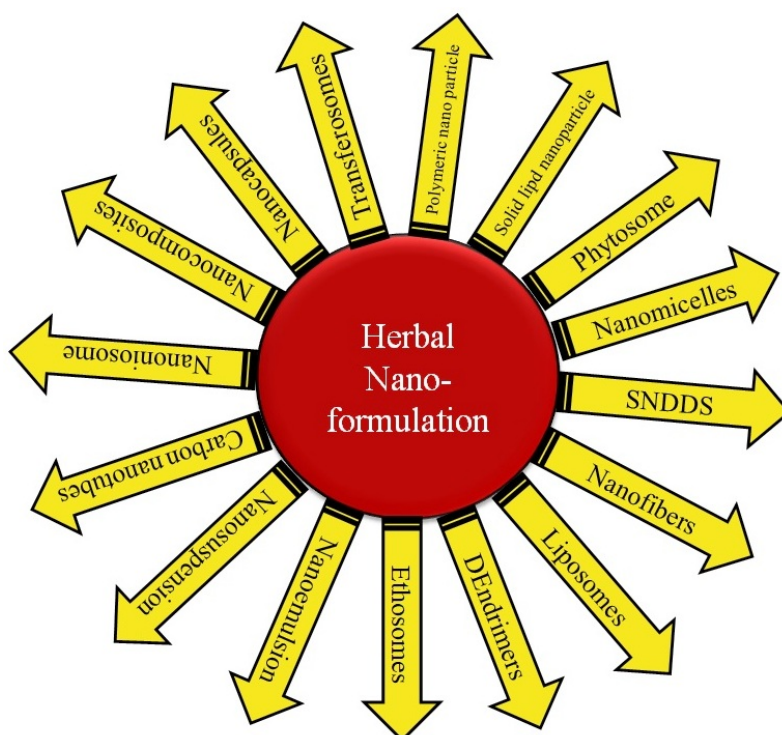


Figure 1: Different types of herbal nanoformulations

- 1. Polymeric Herbal Nanoparticles (NPs):** The bioactive molecules are enclosed inside a biocompatible and biodegradable polymeric matrix to form polymeric nanoparticles. The most often used polymers are Poly-D, L-lactic acid, L-lactic-co-glycolic acid, Poly (ϵ -caprolactone). Certain naturally occurring polymers, like alginates, albumin, and chitosan, are also utilized to synthesize nanoparticles. Herbal nanoparticles are commonly prepared via solvent evaporation, coacervation, or polymeric dispersion methods. The herbal nanoparticle is prepared for poorly soluble and poorly bioavailable drugs. Additionally, this herbal nano formulation helps to increase the stability of drugs that are entrapped and to deliver drugs with sustained release. As an example, at 200-300 nm particle sizes, hypericin showed better solubility, which is used in photochemotherapy. At a particle size of 100 nm, the stability of catechins has increased, which are used to treat cancer and as anti-obesity, antiviral, and anti-inflammatory agents. At a particle size of 228 nm, the bioavailability of quercetin has increased [12].
- 2. Solid Lipid Nanoparticles (SLNPs):** Solid lipid nanoparticles (SNPs) are spherical dispersions of herbal drugs confined inside the solid lipid core with average particle size from 10 to 1000 nm. Using herbal medicines in nanocarriers provides targeted and regulated drug delivery, which helps to reduce the medicine's adverse effects. High-pressure hot or cold homogenization, emulsification/evaporation, supercritical fluid extraction of emulsions, ultra-sonication, high-speed homogenization are some techniques used to prepare. The SLNPs comprise lipid carriers such as triglycerides, partial glycerides, waxes, fatty acids, steroids, and stabilizers, including biocompatible surfactants like polysorbate and poloxamer sodium glycocholate, and the herbal medicinal extract or active phytoconstituents. The lipid carrier enhances drug permeability through the lipid bilayer. With solubility and permeability being the two main points of contention, this drug administration is most appropriate for BCS Class-II

drugs (Biopharmaceutical classification System, class II pharmaceuticals: high permeability and low solubility). At particle sizes of 123.1 nm, a decrease in the harmful effects of podophyllotoxin has been found. At 447 nm particle size, curcuminoids have shown increased stability. To increase memory enhancer, bacoside's in vitro release has been raised at a particle size of 56 nm. For the treatment of diabetes, berberine's bioavailability has been enhanced at a particle size of 76.8 nm [13].

- 3. Phytosomes:** The combination of the terms "phyto" (plant) and "some" (cell-like) results in the word "phytosomes," which refers to "small cell-like structures." The polar (water-soluble) phytoconstituents in phytosome drug delivery combine with the phospholipids to generate a lipid-soluble complex. The preparation of the phytosome formulation was frequently carried out so as to enhance the lipophilicity of the corresponding drugs, hence improving their permeability and bioavailability. Phytosomes are a unique formulation for extract and fractions containing polar biomolecules. In this formulation, the polar phytoconstituents form hydrogen bonds with the polar head of phospholipids. Due to the amphiphilic nature of the phospholipids, herbal medicines are more bioavailable and permeable across cell membranes. At 50 μm particle size, there was an improvement in the lipid solubility and sustained release profile of catechin. At a particle size of 684 nm, the skin permeability of rutin has increased. Gingerol's antimicrobial activity has increased at 254.01 nm particle size [14].
- 4. Nanomicelles:** Nanomicelles are colloidal amphiphilic dispersions with particle sizes between 10 and 100 nm. When the amphiphilic molecules are put into the solvent, they display a particular self-assembly property because of hydrophilic and hydrophobic groups in structure. Researchers term this combination of nanomicelles. Amphiphilic molecules assemble in a hydrophilic solvent with the hydrophilic portion outside and the hydrophobic part inside the inner core. Normal micelles are those that have the same orientation, and reverse micelles are those that have the opposite direction. A few benefits of the nanomicelles drug delivery system include easy manufacturing, increase in solubility of drug, circulatory and tissue permeability, decreased toxicity, and targeted drug delivery. Formulation of nanomicelles can significantly enhance the stability, bioavailability, and cell permeability of hydrophobic compounds such as steroids, terpenoids, and others. To treat hepatotoxicity, the bioavailability of glycyrrhizin has been enhanced at a particle size of 82.99 nm. At a particle size of 2.7 nm, berberine's liver-healing ability has been enhanced [15].
- 5. Self-nano Emulsifying Drug Delivery System (SNEDDS):** The SNEDDS an anhydrous type of nanoemulsion where a spontaneous oil/water nanoemulsion with droplet size less than 100 nm is formed by combining the drug, oil, and surfactant. Hydrophilic co-surfactants such as PEG-200, PEG-400, Labrafil CS 1499, Transcutol, and surfactants such as Tween-20, Tween-80, Span-80, Labrasol, and Chremophor EL, and lipids/oils such as Capmul PG12, Captex 170, Captex 300, and Capmul MCM EP are the most often employed in SNEDDS. Most herbal drugs and extracts have been associated with poor solubility and permeability. Because they contain hydrophilic phytoconstituents like polyphenolics, glycosides/bacosides, etc., and lipophilic phytoconstituents like terpenoids, steroids, etc. It is possible to successfully manufacture these herbal formulation/extracts as SNEDDS to improve their biological activity, permeability, solubility, and bioavailability. At particle size 38.4 nm, the oral bioavailability and

pharmacokinetic profile of oleanolic acid have been improved for treating both acute and chronic hepatitis. At 73 nm particle size, curcumin's bioavailability as a cancer treatment has increased [16].

- 6. Nanofibres:** Researchers have recently become interested in nanofibres because of their exceptional qualities, which include their lighter weight compared to standard fibers, increased surface area and porosity, and fine diameter of 50-1000 nm. To avoid the first-pass metabolism, the drug is mainly delivered through the buccal route using a nanofibre composed of water-soluble polymer. When the nanofibres come into touch with saliva in the buccal cavity, they quickly dissolve or disintegrate; this releases the drug, which is then instantaneously absorbed to provide a quick response. Water-soluble polymers, including polyvinyl alcohol, poly- ϵ -caprolactone, chitosan, and polyvinyl pyrrolidone, have been widely employed in the production of drug-delivery nanofibres that possess specific characteristics. The ability of Hyaluronic acid to heal wounds has been enhanced at 410 μm thickness. Also, the power of Thymol to heal wounds has been enhanced at thicknesses between 267 and 356 nm [17].
- 7. Liposomes:** Liposomes are spherically shaped, bi-layered lipid medicine carriers of natural biocompatible phospholipids and cholesterol. The size of the particle ranges from 0.05-5.0 μm . It arises from the drug enclosed in the hydrophilic core by a self-assembling lipid. The ability of the liposome to pass across biomembranes is unique. Liposomes can also have specific targeting ligands, including membrane proteins bonded to their surface, making liposomes a target-specific drug delivery vehicle. Usually, the thin-film hydration approach was used to prepare liposomes. It is preferable to develop herbal medicines with high permeability and poor lipid solubility properties as liposomal delivery systems. At particle sizes of 77 nm, vincristin has been shown to have reduced neurotoxicity and increased therapeutic efficacy. The oral bioavailability of Silymarin has risen to 3.5 times at 329 nm particle size [18].
- 8. Dendrimers:** Dendrimers are symmetrical molecules that are nanoscale. They consist of a tiny atom or group of atoms encircled by symmetric branches called dendrons. The most significant influence on dendrimer's chemical and physical characteristics comes from their structure. From the core shell, they extend outward and then react with monomers that contain either two dormant or one reactive molecule. Due to their distinct properties, high compatibility with biological systems, well-defined spherical structure, and hyperbranching, dendrimers have extensive use in various fields, including medicine and biomedicine. In particular, a wide range of drugs can be incorporated into the three-dimensional structure of dendrimers to generate biologically active drug conjugates. Dendrimers can trap high molecular weight hydrophobic and hydrophilic phytoconstituents through covalent bonds and host-guest interactions. Moreover, it offers a large surface area advantageous for drug release and trapping. Taken together, these unique qualities make it the perfect carrier for delivering herbal extracts to specific areas. However, because of some toxicity-related problems, its potential uses in biological fields are restricted. Dendrimers are created using two most popular methods: divergent and convergent. The enhanced anti-inflammatory properties of Quercetin have been noted at 59.72 nm particle sizes [19].

- 9. Ethosomes:** Ethosomal systems are new lipid vesicular carrier types with comparatively high ethanol content. These nanocarriers are specifically made to carry therapeutic substances through the skin and into deep skin layers with varying physicochemical features. New compounds were added to the original formula and producing various types of ethosomal systems. The preparation of such novel formulation involves the application of many approaches. Due to their ease of application and stability, ethosomal dispersions are added to gels, patches, and creams. Besides clinical trials, highly different *in vivo* models are employed to assess their effectiveness in dermal/transdermal distribution. Due to some distinctive properties, such as high entrapment efficiency, high deformability, and better transdermal absorption of both lipophilic and hydrophilic phytoconstituents into the skin to treat various skin infections, it has attracted a lot of attention as an alternative liposome carrier in the last ten years. The cold and hot methods are two ways to prepare ethosomes. At a particle size of 67.09 nm, there is an increased skin deposition of apigenin both *in vitro* and *in vivo*. At particle sizes of 139.7-231.8 nm, a better stability profile of the topical formulation of *Sesamum indicum* seed ethanol extract was observed [20].
- 10. Nanoemulsion:** This is a heterogeneous mixture of lipid and aqueous phases that is thermodynamically stable. The lipid is distributed as droplets in the continuous aqueous phase, which is stabilized by appropriate emulsifying agents. These spherically shaped droplets have dispersed particle sizes ranging from 100 to 600 nm. Because of its lipophilic interior, nanoemulsion can transport lipophilic components more readily than liposomes. It offers additional advantages over other administration methods because it may be administered transdermally, orally, or by eyes. This method is frequently employed for the preparation of herbal nanoemulsion using plant extracts or phytoconstituents. This will increase the stability, solubility, cell permeability, and oral bioavailability due to the presence of hydrophilic and lipophilic phytoconstituents. The most widely used processes for preparing nanoemulsions are solvent evaporation, microfluidization, and high-pressure homogenization. For example, at particle sizes of 19.97 nm, increased stability of capsaicin was noted. Better intestinal membrane permeability of colchicin was noted at 41.2 nm particle size [21].
- 11. Nanosuspension:** The nanosuspension can be defined as the biphasic colloidal dispersion of solid drug particles in an aqueous medium that is stabilized by a surfactant. The size of the nanosuspension particles ranges from 100 to 1000 nm; however, for drug delivery, the particle size between 100 and 200 is most preferable. This dosage form is most appropriate for water-insoluble constituents with greater log p value. Therefore, it is possible to administer nonpolar compounds more effectively using this method. This dosage form can enhance the bioavailability of lipophilic of drugs by decreasing the particle size and improving cell permeability, and absorption. Due to its flexibility in administering medications through several routes, including oral, ophthalmic, cutaneous, parenteral, and pulmonary, this approach has recently been widely utilized in drug delivery. The enhanced solubility and dissolution rate of Rodonin were seen at particle sizes of 322.7 nm. At 300-500 nm, there was an increase in the bioavailability of myricetin, which is poorly soluble in water [22].

- 12. Carbon Nanotube:** Carbon nanotubes are cylindrical nanostructures formed by the hexagonal arrangement of hybridized carbon atoms. These are buildings with one or more walls made from graphene sheets that have been rolled. It is utilized from the twenty-first century to treat the disease. Because of their high surface area, rich electronic polyaromatic structure, and exceptional chemical stability, carbon nanotubes (CNTs) can conjugate with a wide range of medicinal molecules, including proteins, drugs, enzymes, and antibodies. Numerous investigations have shown that the delivery of therapeutic compounds into cells is safer and more successful when coupled with CNTs than when provided using other techniques. They have also demonstrated exceptional efficacy as a drug delivery vehicle due to their direct cellular penetration and ability to preserve the medicine throughout the body. CNTs were initially used to bind antibiotics and antineoplastics, which are used to treat infections and cancer, respectively. For example, it was found that captothecin's cytotoxicity increased at particle sizes between 20 and 700 nm [23].
- 13. Nanoniosome:** Niosomes can entrap hydrophilic drugs in the core cavity and hydrophobic drugs in the non-polar area of the bilayer. The term "niosomes" refers to the amphiphilic character of the substance, in which the drug is enclosed in a vesicle made of a non-ionic surfactant. The size of niosomes is small (10-1000 nm). These formulations resemble liposomes in many ways, but they are more flexible because the non-ionic surfactants are included in their bilayer. Compared to liposomes, the bilayer has more excellent chemical stability due to non-ionic surfactants. Chemical stability, biodegradability, biocompatibility, low production costs, simple storage and handling, and minimal toxicity are the primary goals in developing niosomal systems. Niosomes can be administered orally, parenterally, and topically. Niosomes are employed as a delivery system for a variety of drugs, including synthetic and natural antigens, hormones, and other bioactive substances [24].
- 14. Nanocomposites:** Nanocomposite refers to the material consisting of several phases, at least one of which exhibits a dimension of one, two, or three nanometers (1-1000 nm). This improves the material's mechanical qualities, molecular permeability, and drug release control, as well as its thermal stability, flame retardancy, chemical resistance, surface finish, electrical conductivity, and optical clarity. The controlled drug release obtained from the nanocomposite allows for the long-term distribution of the ideal therapeutic dosage, improving overall patient compliance and drug effectiveness [25]. The nanocomposites of *Angelica gig*'s ethanolic extract showed a lower IC₅₀ than the silver nanoparticle of the ethanol extract group, indicating improved antiproliferation activity. They also showed that the silver nanocomposite group had a higher percentage of apoptosis than the silver nanoparticle of the ethanol extract group, demonstrating improved *in vitro* anticancer activities.
- 15. Nanocapsules:** Nanocapsules (NCs) at particle range of 10-1000 nm are vesicular systems made up of one or more active ingredients in the core (aqueous or oily) and concealed within a polymeric wall (protective matrix). Due to its various benefits, including improved poor water solubility, stabilizing drugs by shielding the molecule from the environment, providing the proper pharmacokinetic profile, permitting controlled release, and simplifying oral delivery, it has enormous promise as a drug carrier. The increased water solubility of lipophilic therapeutic molecules, improved

bioavailability, and controlled drug release are the benefits of this approach. This core is made of either natural or synthetic polymers and is encircled by a distinctive polymeric membrane [26]. Honokiol-loaded Nanocapsules significantly inhibited the growth of breast cancer cells in vitro compared to free Honokiol, and they also effectively inhibited the growth of Solid Ehrlich Carcinoma (SEC) tumors by a factor of 2.3 when compared to Honokiol alone (free drug). The NCs also showed a decrease in the levels of biomarkers for cancer growth, and their safety in animals was confirmed.

- 16. Transferosomes:** A transferosome has a bi-layered structure that can encapsulate lipophilic, hydrophilic, and amphiphilic drugs with higher permeation efficiency than conventional liposomes. Due to their elastic nature, transferosomes can deform and squeeze through tiny pores much smaller than their own size. It has the tendency to aggregate and penetrate via intracellular pores and channels within the skin and pass through the stratum corneum driven by osmotic pressure. Therefore, it serves as promising systems for the transdermal delivery of drugs. Transferosomes that contained vincristine increased the drug's lymphotargeting, improving its antimetabolic effects, and minimizing side effects [27].

VIII. DIFFERENT METHODS USED IN THE FORMULATION OF HERBAL NANOMEDICINES

For the preparation of nanophytomedicines, different approaches have been used. These methods include a supercritical fluid method, solvent emulsification-diffusion method, complicated coacervation method, salting out method, nanoprecipitation, co-precipitation method, and self-assembly method. The high-pressure homogenization method, the solvent emulsification-evaporation technique, and the solvent emulsification-diffusion technique are the most often used and are described in more detail below.

- 1. Complex Coacervation Method:** Electrostatic interactions between positively and negatively charged biopolymers result in a complex coacervation that traps active constituents. The two polysaccharides most frequently utilized for making complex coacervates are gelatin and gum Arabic. The complex coacervation method has been utilized to encapsulate d-limonene using pectin-whey protein, sodium caseinate-gum Arabic, eicosapentaenoic acid, and docosahexaenoic acid, as well as palm oil with chitosan-pectin and chitosan-xanthan complexes [6].
- 2. Co-Precipitation Method:** Precipitation is a process where, precipitate's carrying down of soluble substances under specific circumstances. In most cases, a nucleation suddenly arises in solution when the components' concentration reaches supersaturation. Diffusion occurring on the surface of the nucleation will cause it to expand, resulting in the formation of nanoparticles. To obtain homogenous nanoparticles, the nucleation must be slowed down during the growth process. It is a solvent displacement method and is a wet chemical procedure. Ethanol, acetone, hexane, and nonsolvent polymers are examples of polymer solvents. Polymer phases can be either synthetic or natural. The rapid diffusion of polymer-solvent into a nonsolvent polymer phase by mixing the polymer solution at last leads to the formation of nanoparticles. The complex coacervation method is modified by this technique to produce nanoscale core-shell particles. It has been claimed

that this technique will help poorly water-soluble drugs to maintain good dispersion and stability [28].

- 3. Salting-out Method:** This method is based on the finding that the presence of an electrolyte reduces the solubility of a non-electrolyte in water [29]. Another technique for the preparation of Poly (lactide-co-glycolide) PLGA NPs is salting out. First, the PLGA is dissolved into the commonly water-miscible organic solutions (oil phase). Tetrahydrofuran (THF) and acetone are common solvents. The surfactant and saturated electrolyte solution make up the aqueous phase. The organic solvent shouldn't be able to dissolve the electrolytes. The two salts typically used are magnesium acetate tetrahydrate and magnesium chloride hexahydrate (60 % w/w), which have a ratio of 1:3 (polymer to salt). Under intense shearing force from an overhead mechanical stirrer, the oil phase is emulsified in the aqueous phase. The salting-out method differs from the emulsion diffusion approach in that no solvent diffusion stage is required due to the salt's presence. Distilled water is added to the created O/W emulsion while being stirred magnetically to reduce the electrolyte's ionic strength. NPs are produced due to the hydrophilic organic solvents migrating from the oil phase to the aqueous phase simultaneously. Finally, the samples are purified, and the salting out agent is removed by centrifugation.
- 4. Nanoprecipitation method or Solvent Displacement method:** This technique relies on the displacement of a semipolar solvent miscible with water from a lipophilic solution followed by the interfacial deposition of a polymer. Even without mechanical stirring, this reduces the interfacial tension between the two phases, increases the surface area, and results in the production of subsequent tiny droplets of organic solvent [30]. Interfacial deposition process or solvent displacements are other names for nanoprecipitation. The oil phase is gradually mixed with the aqueous phase while moderately stirred, the colloidal suspension in the nanoprecipitation process produces nanoparticles. The parameters influencing the nanoprecipitation method include:
 - The organic phase injection rate.
 - Aqueous phase agitation rate.
 - The oil phase/aqueous phase ratio.

Due to the absence of shearing stress, particle sizes with very narrow distributions can be synthesized. This technique is frequently used to entrap hydrophobic drugs but is also sometimes utilized to include hydrophilic drugs. The polymer and drugs are dissolved in a water-miscible organic solvent, such as acetone or methanol. Then the solutions are added into an aqueous solution containing surfactant. The rapid formation of the NPs occurs through fast solvent diffusion. The solvents are subsequently removed at reduced pressure.

- 5. Supercritical Fluid Methods:** Submicrometer and nanometer-sized formulations can be produced with this technique. A supercritical fluid (SCF) is used above its thermodynamic critical point of temperature and pressure, and can either be a liquid or a gas. Carbon dioxide and water are the most prevalent SCFs [31].
- 6. Self-assembly Methods:** Self-assembly is a physical process in which preexisting disordered components, such as atoms or molecules, arrange themselves into precise

nanoscale structures through physical or chemical interactions without the aid of any outside source [32].

7. **High Pressure Homogenization:** High pressure (100-200 bars) and a microfluidizer are used in high-pressure homogenization (HPH), which pushes a coarsely formed emulsion containing the "drug" through a microscopic window. This high-energy stream then enters the disruption unit, where it collides. Due to impact and cavitation, the "drug" particle size is reduced to the submicron unit in the disruption unit. Pressures, cycle counts, and drug concentration are some factors that affect the outcome. Reproducibility, homogeneous particle size distribution, quicker production periods, and continuous manufacturing are just a few advantages of this technique. A lipid that has been melted at a temperature range of 5-10 °C above the melting point acts as a solvent medium for the drug throughout both hot and cold homogenization operations [33].
8. **Solvent Emulsification-Evaporation Technique:** This method is benefit for thermolabile "drugs" because no heat stress is involved in this process. However, using an organic solvent makes lipids less soluble since it interferes with the drug molecules. The hydrophobic and lipophilic drugs are dissolved using an organic solvent completely immiscible in water. The production of solid lipid nanoparticles follows the removal of the organic solvent by evaporation by mechanical stirring at room temperature and reduced pressure. After that, the mixture is emulsified in an aqueous phase using a high-speed homogenizer [34].
9. **Solvent Emulsification-Diffusion Technique:** The process starts when water and the solvent, partially soluble in water, are saturated. The drug and lipid are then dissolved in an aqueous phase that has been saturated with the solvent, and using a mechanical stirrer, the solvent and water are emulsified. Water is introduced in a 1:5 to 1:10 ratio to the continuous phase to facilitate solvent diffusion, which also causes the nanoparticle lipids to aggregate. During the process, the stirring is kept continuously. Finally, lyophilization or vacuum distillation is utilized to remove the diffused solvent [34].

IX. CHARACTERIZATION OF HERBAL NANOFORMULATIONS [35]

1. The shape and size distribution of nanoparticles are characterized by high-resolution scanning electron microscopy (SEM).
2. Atomic-scale resolution and structural data on nanoparticles are provided by transmission electron microscopy (TEM).
3. The crystal structure and phase of nanoparticles can be determined by X-ray Diffraction (XRD)
4. The size distribution of nanoparticles in solution can be measured by Dynamic Light Scattering (DLS).
5. The functional groups on the surfaces of nanoparticles are identified using Fourier Transform Infrared Spectroscopy (FTIR).
6. The information about the electronic properties of the nanoparticle can be obtained by measuring the absorption of light using UV-visible spectroscopy.
7. The elemental composition of nanoparticles can be analyzed by using Energy-Dispersive X-ray Spectroscopy (EDS)

8. High-resolution surface topography and mechanical property investigations of nanoparticles are possible with atomic force microscopy (AFM).
9. Zeta potential measurement can determine the surface charge and stability of nanoparticles in a solution.
10. The stability and surface modifications of nanoparticles can be analyzed by measuring changes in mass as a function of temperature using Thermogravimetric Analysis (TGA)

X. ADVANTAGES OF HERBAL NANOFORMULATION

Besides impressive *in vitro* effects, most herbal medications and extracts have poor *in vivo* results because the active phytoconstituents they contain are not readily soluble, have poor permeability, and are not as bioavailable. These limitations restrict the use of herbal medicines. However, nanoformulations have recently shown the ability to overcome these limitations by offering several advantages over conventional herbal drugs [36].

- 1. Solubility Enhancement of Phytoconstituents:** Herbal medicines contain many compounds with different levels of water and lipid solubility. Terpenoids and steroids primarily dissolve in lipids, while their glycosides can dissolve in water. The considerable variance in the solubility of multiple phytoconstituents makes it challenging to formulate them in a single compatible dosage. Here, nanotechnology significantly impacts the drug's solubility by reducing the drug's particle size and increasing its surface area [37].
- 2. Augmented Permeability:** Cell permeability and systemic accessibility determine the drug's effectiveness. The P-glycoprotein efflux pump is one of the unique mechanisms in the human body responsible for eliminating xenobiotics, drugs, and poisonous or hazardous substances. These efflux pumps may recognize foreign substances based on their physicochemical properties, such as particle size, ionizability, and hydrophobicity. Particles smaller than 200 nm are unlikely to achieve the maximum quantity of drug release inside the cell membrane [38].
- 3. Enhanced Bioavailability:** The phytoconstituents found in herbal medicine have a range of molecular weights, solubilities, and permeabilities, which limits their *in vivo* efficacy. Nanotechnology promotes the bioactivity and bioavailability of herbal medicine by reducing the size of drug particles, increasing surface area, and allowing targeted and sustained distribution of active phytoconstituents [39].
- 4. Improved Stability of Herbal Medicines:** Herbal medicines are susceptible to degradation during storage, which can cause them to lose their effectiveness or produce dangerous metabolites. Offering enough stability is essential for the patient's safe use and long-term storage. These stability-related issues can be considerably reduced with improvements based on nanotechnology [40].
- 5. Reduced Adverse/Side Effects:** The fundamental advantage of nanoformulation is that it increases the permeability and bioavailability of active components, increasing the efficacy of the corresponding drug. The nanoformulation technology observed the same or better therapeutic outcomes at lower doses, which would help reduce toxicities and dose-related side effects. In solid lipid nanoparticle form, podophyllotoxin's harmful effects were significantly reduced [41].

6. **Targeted Drug Delivery:** Targeted drug delivery is the most desirable yet challenging assignment for an effective therapy. With the recent advancement of nanoformulation, specific drug delivery is now possible. Cancer and other related ailments are successfully being treated. These techniques include pH-sensitive self-assembled nanoparticles, cancer microenvironment-sensitive, intelligent nanomicelles, monoclonal antibody-coupled liposomes, and nanoscale therapeutic particles [42].
7. **Controlled or Sustained Drug Delivery:** The size and surface characteristics of nanoparticles substantially impact drug encapsulation and sustained/controlled drug release. Drug release can still be maintained if the particle size is reduced from the micrometer to the nanometer range. The optimal particle size for prolonged release with circulation periods up to 160 h and decreased renal drug clearance was therefore found to be between 50 and 200 nm. Additionally, recent advancements in biodegradable polymer and PEGylation of hydrophobic biopolymer might make it possible for the drug to be administered for a more extended period of time [43].

XI. APPLICATIONS OF HERBAL NANOTECHNOLOGY FOR DIFFERENT DISEASES

Herbal nanotechnology has a wide range of uses, including treating cancer, diabetes, hepatic disorders, and wounds. Herbal nanoparticles can be delivered specifically to particular cells or tissues to minimize adverse effects and maximize therapeutic results. Herbal nanoparticles can have synergistic effects when combined with other nanomaterials or drugs, which increases their medicinal potential. The lists of herbal nanoformulations and their uses in various diseases are described in Table 1.

Table 1: Different type of herbal nanoformulations and their applications

Extract / compound	Type of nano particle	Particle size	Diseases	Application	Ref
Ethanol extract of <i>P. senega</i> root	Polymeric herbal nanoparticles	147.7 nm	Anticancer	The anticancer effective of nanoparticle has increased than <i>P. senega</i> root extract	[44]
Curcumin	Polymeric herbal nanoparticles	200 nm	Anticancer	The aqueous solubility and bioavailability has been increased	[45]
Andrographolide	Polymeric herbal nanoparticles	226 nm	Anticancer	The biopharmaceutical properties was increased	[46]
<i>B. serrata</i>	Solid lipids nanoparticles	178 nm	Anticancer	Anticancer activity was increased	[47]
Andrographolide	Solid lipids nanoparticles	120-170 nm	Anticancer	Anticancer activity was increased	[48]
Pomegranate extract	Solid lipids nanoparticles	407.5-651.9 nm	Anticancer	Anticancer activity was increased	[49]
Methanol extract of <i>Allium sativum</i>	Phytosomes	500 nm	Anticancer	Anticancer activity was increased	[50]
Aqueous extract of <i>Carica papaya</i>	Phytosomes	135.8 nm	Anticancer	The bioavailability of the extract was increased	[51]
Cucurbitacin	Nanomicelles	35.2 nm	Anticancer	The bioavailability of the extract was increased	[52]
Curcumin	Self-nano emulsifying drug delivery system	73 nm	Anticancer	The bioavailability of the extract was increased	[53]
<i>Pandanus conoideus</i> Lamk oil	Self-nano emulsifying drug delivery system	193.1 nm	Anticancer	The bioavailability of the extract was increased	[54]
Vincristine	Liposomes	77 nm	Anticancer	The therapeutic efficacy was	[55]

				increased	
Artemisinin	Liposomes	455 nm	Anticancer	The therapeutic efficacy was increased	[56]
Malloapelta B	Dendrimers	146.8–194.5 Nm	Anticancer	The anticancer activity was increased	[57]
<i>Sophora alopecuroides</i>	Ethosomes	142 nm	Anticancer	The anticancer efficacy was increased	[58]
Colchicine	Nanoemulsions	41.2 nm	Anticancer	Bioavailability was increased	[59]
Oridonin	Nanosuspension	322.7 nm	Anticancer	The anticancer efficacy was increased	[60]
Camptothecin	Carbon nanotubes	20-700 nm	Anticancer	Cytotoxicity activity was increased	[61]
Curcumin	Polymeric herbal nanoparticles.	200 nm	Anti-inflammatory	The aqueous solubility and bioavailability was Increased	[62]
Tetrandrine	Solid lipids nanoparticles	80 - 200 nm	Anti-inflammatory	Solubility and encapsulation was enhanced	[63]
Rutin	Phytosomes	684 nm	Anti-inflammatory	Permeability of skin was enhanced	[64]
Celastrol	Nanomicelles	117.3 nm	Anti-inflammatory	Drug release profile was increased	[65]
Methanol extract of <i>P. lanceolata</i> Leaf	Self-nano emulsifying drug delivery system	141.51 nm	Anti-inflammatory	Anti-inflammatory activity was increased	[66]
Thymol	Nanofibers	267-356 nm	Anti-inflammatory	Improved therapeutic efficacy	[67]
Baicalin	Liposomes	373 nm	Anti-inflammatory	Bioavailability was increased	[68]

Quercetin	Dendrimers	59.72 nm	Anti-inflammatory	Anti-inflammatory activity was increased	[69]
Apigenin	Ethosomes	67.09 nm	Anti-inflammatory	Enhanced therapeutic efficacy	[70]
Dried gum resin extract <i>B. serratta</i>	Nanoemulsions	11.2 - 34.78 nm	Anti-inflammatory	Enhanced permeation	[71]
Myricetin	Nanosuspension	300-500 nm	Anti-inflammatory	Bioavailability was increased	[72]
Quercetin in green tea	Carbon nanotubes.	0.48 nm	Anti-inflammatory	Enhanced therapeutic efficacy	[73]
Eugenol and cinnamaldehyde	Polymeric herbal nanoparticles.	200 nm	Antimicrobial	Increased in antimicrobial activity	[74]
Aqueous ethanol extract of <i>G. biloba</i>	Solid lipids nanoparticles.	119 nm	Antimicrobial	Increased in efficacy	[75]
Sinigrin	Phytosomes.	153 nm	Antimicrobial	Enhanced activity	[76]
Alcoholic extract of <i>H. perforatum</i>	Nanofibers	245 nm	Antimicrobial	Increased in therapeutic efficacy	[77]
Alcoholic extract of Neem leaf	Liposomes	3.2 μ m	Antimicrobial	Efficacy of topical activity was increased	[78]
Quercetin and Catechin	Polymeric herbal nanoparticles	399.67 nm; 410.59 nm	Antioxidant	Enhanced in scavenging property	[79]
Umbelliferone	Solid lipids nanoparticles.	173.4 nm	Antioxidant	Significant increased in antioxidant property	[80]
Luteolin	Phytosomes	122.72 nm	Antioxidant	Bioavailability was increased	[81]

Silymarin	Nanomicelles	247 nm	Antioxidant	Significant increased in activity	[82]
Zedoary essential oil	Self-nano emulsifying drug delivery system	68.3 nm	Antioxidant	The increased in oral bioavailability, stability and aqueous dispersibility	[83]
<i>M. oleifera</i> kernel oil	Nanofibers	22-40 nm	Antioxidant	Stability increased	[84]
Thymoquinone	Liposomes	100 nm	Antioxidant	Increased in efficacy and bioavailability	[85]
Ethanol extract of <i>Hippophae rhamnoids</i> leaf	Ethosomes	96.98-395 nm	Antioxidant	Increased in permeability	[86]
Catechin	Nanoemulsions	98.6 nm	Antioxidant	Increased in permeability and bioavailability	[87]
Zerumbone	Nanosuspension	211 nm	Antioxidant	Increased in solubility and dissolution rate	[88]
Quercetin in green tea	Carbon nanotubes	0.48 nm	Antioxidant	Increased in activity	[73]
Vitamin E	Polymeric herbal nanoparticles.	130-350 nm	Wound healing	Improved in activity	[89]
<i>Tecomella undulate</i> Bark	Nanofibers	100-300 nm	Wound healing	Enhanced in therapeutic efficacy	[90]
Shikonin	Liposomes	169.4 nm	Wound healing	Enhanced in stability	[91]
<i>A. vera</i> Gel	Nanosuspension.	163.0 nm	Wound healing	Increased in wound healing	[92]
<i>Cassia fistula</i> leaf extract	Polymeric herbal nanoparticles.	32.8 nm	Antidiabetic	Increased in efficacy	[93]
Berberine	Solid lipids	76.8	Antidiabetic	Increased in bioavailability	[94]

	nanoparticles.	nm			
<i>Casuarina equisetifolia</i> Extract	Phytosomes	295 nm	Antidiabetic	Increased in stability of the formulation	[95]
Silymarin	Nanomicelles	247 nm	Antidiabetic	Significant increased in activity	[82]
Ethyl acetate extract of <i>Eugenia polyantha</i> leaves	Self-nano emulsifying drug delivery system	84.5 nm	Antidiabetic	Increased in antidiabetic activity	[96]
Aquous extract of <i>Salvia officinalis</i>	Liposomes	<80 nm	Antidiabetic	Increased in activity	[97]
Ethanol extract of <i>P. amarus</i>	Nanoemulsions	213 nm	Antidiabetic	Increased in solubility	[98]
Berberine	Nanosuspension	73.1 nm	Antidiabetic	Increased in bioavailability	[99]
Silibinin	Solid lipids nanoparticles	178.9 nm	Hepatoprotective	Enhanced in therapeutic efficacy	[100]
Catechin	Phytosomes	50 μ m	Hepatoprotective	Increased in lipi solubility and drug release profile	[101]
Glycyrrhizin	Nanomicelles	82.99 nm	Hepatoprotective	Increased in bioavailability	[102]
Oleanolic acid	Self-nano emulsifying drug delivery system	38.4 nm	Hepatoprotective	Improved in bioavailability	[103]
Silymarin	Liposomes	329 nm	Hepatoprotective	Increased oral bioavailability	[104]

XII. CHALLENGES AND OPPORTUNITIES IN HERBAL NANOFORMULATIONS

Herbal nanotechnology requires more investigation to realize its potential and guarantee its efficacy. The development and commercialization of herbal nanotechnology products face several difficulties, including regulations, ethical issues, and standardization of production techniques.

- 1. Complex Chemical Nature of Herbal Extracts:** The phytoconstituents found in plant extracts frequently have various molecular weights, solubilities, therapeutic potentials, and chemical classes. While some compounds, like monoterpene, sesquiterpene, diterpene, and tri-terpenoids, are non-polar and lipid-soluble, others, such as polyphenolics, glycosides, etc., are polar and aqueous soluble. Other compounds, like flavonoids, alkaloids, etc., may have a medium polarity and only partially dissolve in water or lipids. These differences make it challenging to create and characterize a nanoformulation strategy. By fractionating these extracts based on bioassays, these issues can be overcome. The resulting fraction would only consist of a variety of phytoconstituents with similar chemical classes and solubility profiles, which could increase the synergistic effect of the fractions [105].
- 2. Challenges of Biological Barriers:** Every drug delivery system must get pass a few biological barriers to get to the site of action. For example, oral nanoparticles must pass through the gastro intestinal tract narrow epithelial junction and acidic environment of the gastrointestinal tract. Therefore, it is imperative to create a new class of biodegradable polymer that can survive an acidic environment and prevent the destruction of the drugs by peptidase enzymes [106].
- 3. Target-Specific Drug Delivery:** The targeting of drug delivery is affected by many variables, including biological barriers like the blood-brain barrier (BBB), which prevents large or hydrophilic drug molecules from entering the brain, environmental factors like dense stroma, which results in poor drug perfusion and distribution inside solids, leaky microvasculature, which limits the transport of drug molecules into the interstitial space, etc. Therefore, a variety of improved nanoformulation approaches should be researched to deliver the medicine to specific targets [107].
- 4. Cost of Analysis and Characterization of Nanoformulations:** For the development and optimization of nanoformulation, a variety of high-priced tools are required, such as TEM, AFM, and SEM for surface morphology and particle size analyzer, zeta-sizer for zeta potential, particle size and polydispersity index (PDI) analysis, ultra-high-pressure homogenization for adjusting particle/droplet size, HPLC/UPLC for determining entrapment efficiency, drug loading, and in vitro drug release. Furthermore, the addition of excipients and additives, such as biodegradable polymers, surfactants, co-surfactants, cryoprotectants, etc., increases the price of nanoformulation. It decreases the number of nanoformulations that are available on the market [108].
- 5. Physical Stability of Nanoformulation:** The nanoformulations are intended for pulmonary, ocular, parenteral, and cutaneous administration; the stability of each drug delivery system is essential in ensuring its effectiveness and safety. For example, self-

aggregation or a particle size increase of more than 5 micron in a nasal nanosuspension may cause nasal blood capillary obstruction, drug leakage from nanoparticles, and nanoemulsion cracking may affect drug loading and efficacy. Nevertheless, these problems can be substantially managed by employing the proper preparation method and maximizing zeta-potential, etc [109].

- 6. Pharmacology and Safety Challenges:** Nanoformulation has some toxicity-related issues despite its numerous advantages. Most are pseudoallergy or non-Ig-E mediated hypersensitivity reactions, which can cause life-threatening circumstances like cardiac distress, anaphylactic shock, face swelling and flushing, headache, etc. Therefore, before preclinical or clinical research, it is required to undertake relevant *ex vivo* or *in vitro* assays such as cytotoxicity, immunotoxicity, and genotoxicity. Furthermore, to assess the long-term toxicity and biocompatibility difficulties with nanoscale drug delivery devices, specialized *in vivo* toxicology studies in appropriate animal models should be carried out [110].

XIII. NEW APPROACHES AND CHALLENGES

Nanosized drug delivery methods for herbal treatments can potentially improve biological activity and resolve issues with plant-based therapies. Implementing clinically effective remedies in this field still faces many obstacles. Evaluating novel methods to regulate how nanomaterials interact with biological systems is one of the significant difficulties in translating this technology into treatments. The development of nanotechnology-based drug delivery systems challenges new obstacles, including the potential for producing multifunctional systems that address multiple biological and therapeutic requirements and the viability of scale-up methods that quickly bring revolutionary therapeutic techniques to market. Toxicology and biocompatibility of nanoparticles, as well as achieving international standards, are two new issues [40].

XIV. FUTURE PROSPECTIVE

There has been extensive research on herbal medicines and natural products. Many institutes are developing herbal remedies for use in drug delivery systems at the fundamental and clinical trial levels. The only demand is to develop more effective ways to provide these formulations in the body's various parts in doses that will not interfere with the current therapy. The idea of employing herbal nanoparticles to treat multiple disorders could attract the attention of future research teams. As a result, using "herbal remedies" in nanocarriers will increase the possibility of treating various chronic diseases and bringing about health advantages. Herbal medicines are a rich source of healthy compounds that contain antioxidants and chemicals that have specific uses in food. This form of collaborative research between traditional "herbal remedies" and more modern approaches to the present drug delivery system, i.e., "Nanotechnology," has already been established. According to estimations, the significance of the current drug delivery system would expand if nanocarriers were used along with natural products and herbal remedies [111]. In conclusion, the promising combination of herbal medicine with nanotechnology presents new opportunities for improving the efficacy of herbal treatments. By utilizing the unique properties of nanoscale materials, researchers are attempting to develop new methods for targeted drug delivery, enhanced bioavailability, and improved therapeutic outcomes in herbal medicine.

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