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Drug Delivery Systems Designed to Maximize the Therapeutic Efficacy of Herbal Medication: A Review Article

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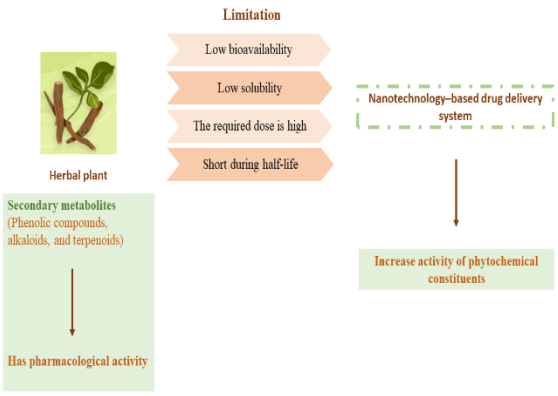
Abstract

Herbal medicines have been used for centuries to treat a variety of ailments. However, their efficacy can be limited by their poor bio-availability and solubility. Nano-technology offers a promising new approach to improving the delivery of herbal medicines. Nanoparticles can be used to encapsulate herbal ingredients, making them more soluble and bio-available. This can lead to improved therapeutic efficacy and reduced side effects. There are a number of different types of nanoparticles that can be used to deliver herbal medicines. Some of the most promising include liposomes, micelles, and nanoparticles made from bio-degradable polymers. These nanoparticles can be tailored to target specific tissues or cells, which can further improve the efficacy of herbal medicines.

Keywords Nano-technology, Nano-carriers, Herbal medicines, Drug delivery

1. Introduction

The goal of the discipline of applied science and technology known as "Nano-technology" is to create devices and dosage with a size between 1 and 100 nm [1] . Nano-medicine is the term used recently to explain how nano-technology is used in the diagnosis, treatment, monitoring, and control of biological systems [2]. The lipids, polysaccharides, and synthetic bio-degradable polymers used to create the nanocarriers are all safe materials [3]. Since all of the active ingredients work together synergistically, to increase the therapeutic value, the effectiveness of herbal medicines is determined by how well they function overall. Each active component has a vital job to perform, and they are all connected to one another. However, the majority of medications made from herbs have an insoluble nature that causes reduced bio-availability and greater systemic clearance, requiring repeated administration or larger doses, rendering the medication an unsuitable option for therapeutic usage. In phyto-formulation research, creating forms of nanodosage such as liposomes, proliposomes, solid lipid nanoparticles, and polymeric nanoparticles (Nanospheres and Nanocapsules). Polymeric nanoparticles (Nanospheres and Nanocapsules) have many benefits for herbal drugs, including: improved solubility, and bio-availability, protection from toxicity, increased pharmacological activity, increased stability, and improved tissue macrophag. As a result, herbal pharmaceuticals with nano-sized drug delivery systems may one day be used to improve activity, and address issues with plant-based therapies. As a result, incorporating nanocarriers as novel drug delivery systems (NDDS) into the traditional medicine system is critical in combating more chronic diseases such as diabetes, asthma, cancer, and others [4].



Graphical abstract

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2. Herbal medications

One of the earliest types of health care systems was a curative system based on herbal drugs. Formulations made from plants could be crucial for a person's healthcare. Alternative plant-based natural medicines for a wide range of diseases have emerged as a result of the dramatic rise in the world's population, inadequate access to expensive allopathic medications with unwanted side effects, and issues like multidrug resistance in dangerous pathogens. A complex mixture made from plant sources that is used as a medicine or pharmaceutical is known as a "Phyto-medicine or Phyto-pharmaceutical". Most functional drugs roughly 50% of them are made from natural materials [5]. Some examples of herbs with medicinal benefits including *lavender, which* exhibits anti-inflammatory, anti-oxidant, sedative, spasmolytic, anti-depressant, anti-cholinesterases, anti-bacterial, and anti-fungal properties [6]. *Allium sativum* L. (Garlic), exhibits hypoglycemic, anti-oxidant, anti-inflammatory, anti-cancer, anti-hyperlipidemic, anti-microbial, and hepatoprotective activities [7]. *Cucurbita pepo (Pumpkin)*, has benefits such as wound healing, improving spermatogenesis, anti-inflammatory, anti-microbial, anti-oxidative, anti-ulcerative properties, and benign prostatic hyperplasia treatment [8]. The *Ginkgo biloba*, extract EGb 761 contains terpene lactones, flavonoids, and various other constituents. Egb 761 improves cognitive and neurological function through anti-oxidant action, anti-inflammatory action, anti-apoptotic action, enhancing neuroplasticity, modulation of amyloid-aggregation, and defense against mitochondrial dysfunction, all of which confer neuro-protective properties [9]. *Crataegus (Hawthorn)*, has been used in Chinese medicine for centuries to possess therapeutic effects on tonifying the spleen, regulating blood glucose, prompting appetite, and lipid metabolism because it contains a lot of biologically active substances, such as flavonoids, terpenoids, phenolics and pectin [10]. *Zingiber* (Ginger), possesses anti-inflammatory, anti-oxidant, anti-microbial, and anti-cancer properties, as well as outstanding antiviral activity due to its high anti-viral compound concentration [11]. *Matricaria recutita* (Chamomile), contains volatile oils, flavonoids, coumarins, organic acids, terpenes, sterols, and polysaccharides, among other compounds. Having a wide array of compounds, chamomile exhibits various pharmacological activities such as anti-cancer, anti-inflammatory, anti-infective, anti-oxidant, hypotensive, hypoglycaemic, hypolipidaemic, anti-depressant, anti-allergic, and neuroprotective effects, and others [12]. Novel glycosidic derivatives isolated from *ashwagandha* (*Withania somnifera*), such as withanosides I-XI, have been reported to have anti-Alzheimer's, anti-stress, and neuroprotective activity. Anti-viral withanolide glycosides have also been shown to be potential COVID-19 therapeutic agents [13]. *Serenoa repens* (Saw palmetto), seeds contain essential phenolic compounds that provide anti-inflammatory, anti-oxidant, anti-microbial, and anti-diabetic benefits when mixed into food [14]. *Curcuma longa* L. (*syn. Curcuma domestica*), commonly known as turmeric. Turmeric has been used to treat hepatic and gastrointestinal disorders, rheumatism, arthritis, skin diseases, inflammation, fever, amenorrhea, and sepsis, as well as ~~as~~ a laxative and an anthelmintic [15].

3. Disadvantages of herbal drugs

The bulk of traditional herbal remedies have low solubility due to the presence of hydrophobic compounds. The ineffectiveness of herbal medications due to poor oral administration, solubility, and bio-availability is a significant barrier to their use. Traditional herbal preparations are not preferred for the development of novel medication formulations because they lack chemical characterization, standardisation, validation, and scientific justification of their therapeutic potential. Traditional herbal medicines are frequently used orally, which results in low drug concentrations at the site and a restricted therapeutic impact since large volumes of these treatments waste away due to their body-wide dispersion based on physicochemical and biochemical characteristics. Many herbal components may degrade in the stomach's acidic environment, while others may be metabolized by the liver, which prevents enough phyto-compounds from reaching the blood. A poor or nonexistent therapeutic effect might be observed if the indicated dose or amount of the medication is administered (minimum effective dose level). Due to their poor solubility and bioavailability, several phytochemicals have a constrained therapeutic range. Researchers are always looking for ways to improve patient compliance and therapeutic efficacy through targeted medication delivery and controlled drug release. Multidisciplinary approaches are proposed for targeted administration to enhance their pharmacokinetics, bio-recognition, pharmacodynamics, and effectiveness due to different limitations of herbal medications and the low efficacy of the treatment of persistent disorders. Such innovative delivery systems require such interdisciplinary contributions from polymer chemistry, nanotechnology, pharmacology, bio-conjugate chemistry, etc. [5].

4. Toxicity of herbal medications

Toxicological issues related to the use of herbal medicines have frequently been linked to serious adverse fatalities, including cardiovascular issues, psychiatric issues, neurological effects, liver toxicity or malfunction, and hematologic and renal toxicity.

The diagnosis of herbal toxicity is often made by ruling out alternative causes, and taking into account the temporal link between exposure to the herb and the onset of the adverse event. The metabolic activation of herbal ingredients via phases I and II reactions, within the human body may also produce reactive intermediates, contributing to the toxicity of herbs. The subsequent reactive intermediates can form covalent bonds with DNA and proteins, which can be harmful to organs, mutagenic, or even cancerous. Medicinal plant products contaminated with pesticides and microbial contaminants, heavy metals, toxic substances, and adulterants that can be toxic to consumers are some additional factors, that compromise safety. Herbs harvested from polluted sites, or through subpar farming techniques may also be at risk [16].

5. Herb-Drug interaction

Herbal medicines frequently have a wide range of pharmacologically effective substances, which considerably raises the likelihood of interactions. Herb-drug interactions may frequently be more likely than drug-drug interactions to occur. The pharmacokinetic interactions of herb-drug that result from one medication interfering with the elimination, metabolism, or absorption of another medication and the pharmacodynamic herb-drug interactions that result from two different medications working in the same or opposite directions and ultimately affecting the dose response and any mechanisms of therapeutic or toxic effects are two examples of how interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects as show in **Fig. 1** [16]. When cardiovascular drugs with a limited therapeutic horizon, such as digoxin and warfarin, are coadministered with herbs, herb-drug interactions have been discovered. For instance, taking warfarin and St. John's Wort concurrently lowers prothrombin time, which may lessen the anti-coagulant action and necessitate taking more warfarin [17].

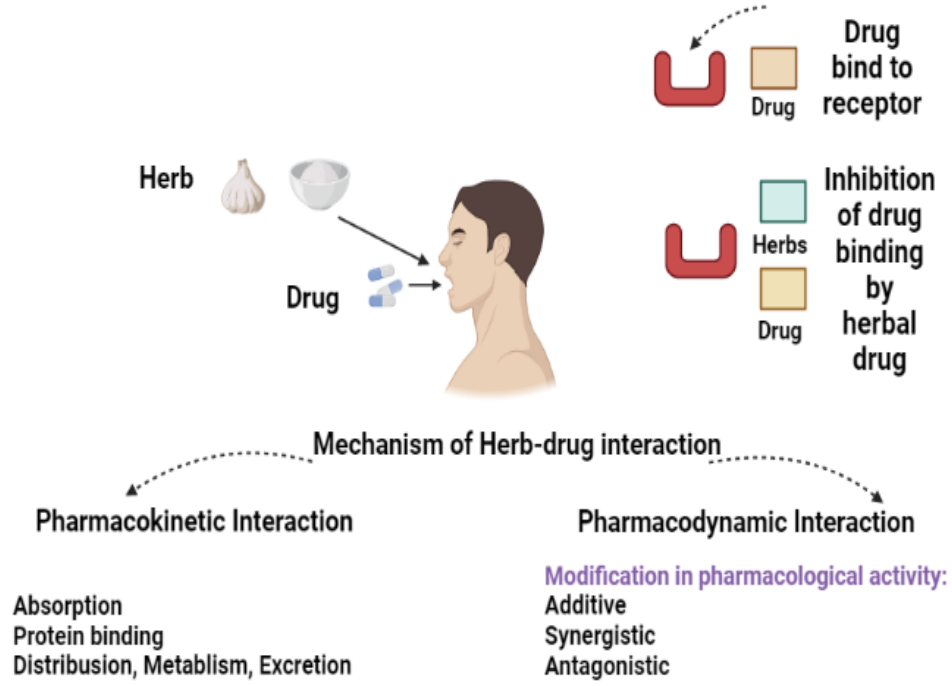

Fig. 1 Two mechanisms of the Herb-Drug interaction

6. COVID-19 and herbal medicine

For the purpose of informing public health measures during pandemics, and epidemics, access to trustworthy information, sources is crucial. The corona-virus disease, 2019 (COVID-19) pandemic has been complicated by an excess of information, which has made it difficult to implement effective public health interventions. After the new disease's global announcement at the start of 2020, COVID-19 had been the subject of over 2000 publications in scholarly

journals by mid-March 2020 [18]. It is anticipated that more systematic reviews (SRs) on COVID-19 than any other disease will be published as a result. As COVID-19 spreads throughout nations, researchers and scientific organizations have begun to consider the use of herbal medicine in the management of the disease [19,20]. Numerous studies, have shown that using herbal medication can reduce COVID-19 symptoms, enhance test results, and boost the clinical cure rate. However, due to their complex chemical makeups and potential herb/drug interactions, herbal medicines may have some unintended side effects, necessitating a more complete analysis. The data supporting the effectiveness and safety of herbal remedies has also been comprehensively compiled in SRs [20,21]. The quality, emphasis, and intervention used in these SRs, however, have made it difficult to evaluate data on the effects of herbal medicines accurately. Herbal products are recognized by the WHO (World health organization) as an essential component of the healthcare system [22].

7. Cancer and herbal medicine

Several clinical trials, have shown that various herbal medications can have a variety of anti-cancer effects. According to their ability to inhibit certain cancer kinds, a variety of herbal medications, have been categorized and arranged in this area for therapeutic usage as demonstrate in **Table 1**.

8. Nano-medicine

Nano-medicine employs tiny instruments, to diagnose, prevent, and cure disease, as well as better understand the intricate pathophysiology of disease. The ultimate objective is to raise the standard of living. It involves the three branches of nano-technology, diagnostics, imaging tools, and nanoparticle-based medication delivery. The term "theranostics," which involves using the same nano-pharmaceuticals for both diagnosis and therapy, is more pertinent and recent. Although colloidal gold has been used since ancient times, Metchnikov and Ehrlich (winners of the Nobel Prize in Medicine in 1908) are considered the modern pioneers of nano-medicine, for their work on phagocytosis and, respectively. Liposomes, polymer-drug conjugates, DNA-drug complexes, antibody-drug conjugates, polymer-protein conjugates, polymer nano-capsules, albumin-drug conjugates, block-copolymer micelles, anti-arthritis gold nanoparticles, and anti-microbial silver nanoparticles are just a few of the seminal works on nanoparticles for nano-medicine, that emerged in the last 30 years of the twentieth century. These nano-medicines, come in a variety of sizes that frequently go outside the realm of the 1-100 nm narrow definition of the nano-world [23].

9. Types of nano-carriers

Nano-carriers have variable types, polymeric nanoparticles, magnetic nanoparticles, quantum dots, phospholipids micelles, colloidal nano-liposomes, metal and inorganic nanoparticles, dendrimers, polymeric micelles, and solid lipid nanoparticles as show in **Fig. 2**. The most common formulation techniques are the complex coacervation method, high-pressure homogenization method, co-precipitation method, nanoprecipitation method, solvent displacement method, salting-out method, solvent emulsification–diffusion method, self-assembly methods and, supercritical fluid methods [4].

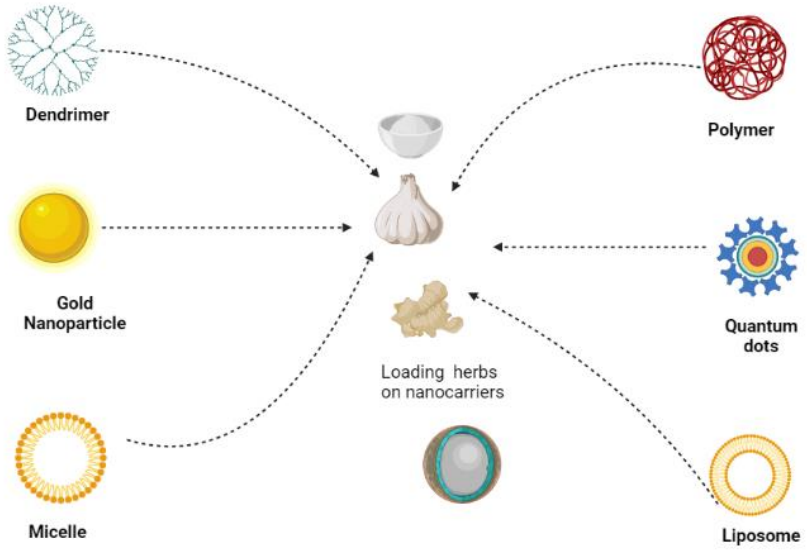

Fig. 2 Types of nanocarriers can be used in drug delivery system of herbs to increase the its effect. The best to be used magnetic nanocarriers to target the herb to the site

10. Nano-technology-based herbal medicine

The benefits of nanoparticles as nano-carriers for a drug delivery system are particle size and surface characteristics of nano-carriers can be manipulated to actually achieve both the two ways passive and active drug targeting after parenteral administration, controlled release and the particle degradation , enhance shelf life of product, the specific site targeting can achieve by using of magnetic nan-carrier [24,25], control the release of the drug during the transportation, modifying the drug's organ distribution and subsequent clearance in order to improve drug therapeutic efficacy and reduce side effects, it used in a variety of methods of administration including oral, nasal, parenteral, intra-ocular, size very small and can penetrate the smaller capillaries, which allow efficient drug to accumulate at the target sites. Protection from chemical and physical degradation. hydrophilic as well as lipophilic, both types of drugs can be incorporated. Nano-carriers increase the stability of drugs against enzymatic degradation [26]. The particle diameter of the nano-scale system, or submicrometer, is 0.1 nm. This makes this nano-technology more advanced and extensively researched by scientists. These benefits relate to a variety of variables, such as the route of administration and greater therapeutic effects. Nano-scale systems have been used in several research to supplement herbal medication because they can boost activity, cut doses, and lessen negative effects. Nano-technology-based herbal medicines offer a lot of promise and special qualities, such as the ability to turn less soluble, poorly absorbed, and unstable ingredients into promising pharmaceuticals. As a result, nano-technology-based delivery methods offer a great opportunity to improve herbal activity and resolve the problems with herbal therapy [27]. Drug delivery system an effective method for herb delivery as demonstrate in **Table 2** according to some reasons as follow: 1) Effective chloroform, acetone, petrol, there are methanolic, extracts available, but they may not be suitable for delivery. 2) Because these are bulk drugs, dose reduction is intended. 3) For various chronic diseases, currently marketed formulations lack target specificity. 4) Some other side effects, are associated with currently marketed formulations. 5) Patient non-compliance due to less effectiveness and large doses with the available formulations [4].

Table 1 Clinical application of anticancer herbal medicines

Herbal constituent	Suppressive effect on cancer	Ref
Coumarins	Inhibition of cancer cell growth	[29,30]
Inchin-Ko-to(TJ-135)	The ability to prevent liver fibrosis	[31]
Isoflavone	Reduce the risk of breast cancer	[32]
Vitamin A	200 mg/day reduces the recurrence of local breast cancer in premenopausal women	[33]
Abelmoschus moschatus	The anti-proliferative activities of ethanolic and aqueous extracts of Abelmoschus moschatus (Malvaceae) seed against two human cell lines-Colorectal adenocarcinoma (COLO-205) and retinoblastoma (Y79)	[34]
Arnebia nobilis	Beta-dimethyl acryl shikonin, a compound found in the roots of the Arnebia nobilis plant, has anti-cancer properties. It works by blocking cell cycle progression in the G1 phase, which is the first phase of the cell cycle. This leads to a decrease in the expression of Cyclin D, CDK 4, and PCNA, which are proteins that are involved in cell division. Beta-dimethyl acryl shikonin also inhibits the expression of bcl2, a protein that protects cells from death. This leads to an increase in the activity of caspase-3, an enzyme that is involved in cell death.	[35]
Cassia tora	Antiproliferative activity of with cisplatin using human cervical cancer cells (HeLa).	[36]

Table 2 The herbal drug limitation and methods of nanoparticles formulation for herbal drug delivery system

Herbs	Purpose	Limitation	Drug delivery effect	Methods of nano-formulation	Ref
Artemissia annua	Anti-malarial	-Poor pharmacokinetic properties -Short halflife	Improve hydrophilicity	encapsulation	[37,38]

Berberine	Anti-tumor	it is difficult for berberine to penetrate cytomembrane and to be assimilate into the gastrointestinal tract due to its poor lipid solubility	improve cancer treatment	-Single emulsion -Multiple emulsion -Ionic gelation	
Centella asiatica	Anxiolytic Anti-anxiety Anti-oxidant	Physical instability	Improve physical stability	encapsulation	
Curcumin	Anticancer Anti-inflammatory Anti-oxidant Anti-viral Anti-bacterial Anti-fungal	-Short half-life -Water solubility is low -Rapid metabolic rate -Rapid elimination, which leads to poor bioavailability	Rendering hydrophobic properties	wet milling technique	
Cuscuta	Anti-cancer Anti-aging	Poor aqueous solubility	Lower concentrations have higher heptoprotective and antioxidant activities	Nano-precipitation	
Genistein	Antioxidant	-Low aqueous solubility -Poor bioavailability	Improve its solubility and bioavailability	Nano-precipitation	

11. Factors influencing herbal nano-medicines in vivo delivery

11.1. Biological medium

When nano-medicines, particularly those with charged surfaces, enter the systemic circulation, or any other biological medium (such as interstitial fluid, lymph, etc.) via any route, they combine with bio-molecules (such as lipids, and proteins) to change how they are expressed, which can affect, or inhibit, their ability to attack their target site [28].

11.2. Immune and metabolic dysfunction

Macrophages linked to tumors, are far more prevalent than cancer-related inflammatory cells. Thus, focusing on them can indirectly influence the formation of tumors. For instance, adding alendronate to doxorubicin-loaded liposomes improved their ability to target tumor-associated macrophages [28].

11.3. Pathological conditions and structure

Tumor area abnormally differs from the particular body region in several aspects, such as high tumor vascular permeability, high interstitial fluid pressure, and more stiff and dense stromal cells, when seen in the context of their microenvironment [28]. The in vivo transport of nano-medicines to the intended region is significantly influenced by these variables. Desmoplastic tumors have heavily impregnated stromal cells made up of tumor-associated fibroblast, which create a lot of extracellular matrix and obstruct the delivery of nano-medicines.

12. Future of herbal drug delivery

Pharmaceutical experts have recently redirected their attention to developing a scientifically sound medication delivery mechanism for natural remedies. Traditional Chinese medicine frequently uses cuscuta chinensis to support the liver and kidney. Its oral administration may have a limited effect on absorption since its main ingredients, flavonoids and lignans, are poorly soluble in water. Therefore, the corresponding nanoparticles were created. A precipitation technique has recently been established for experimental research on polylactic acid nanoparticles of lipophilic anti-cancer herb medicine (Cucurbitacins and, Curcuminoids). For targeted distribution, better bio-availability, and higher effectiveness, work has also been done on developing and characterizing SLNs (Solid lipid nanoparticles) for traditional Chinese medicine. Polymeric nanoparticles, liposomes, SLNs, polymeric micelles, nano-emulsions, and other nano-structured carrier systems have all been studied recently for their potential to deliver anti-cancer medications orally. Additionally, the oral route has a lot of promise for delivering cytotoxic drugs; hence, the development of oral chemotherapy in cancer has received a lot of attention [4].

Conclusion

Treatment of any disease is based on either the development of better drugs or the improvement of the

efficacy of existing drugs. The majority of scientists are currently interested in the pharmacological effects of herbs, their use, and their development into future medicines and derivative medicinal phytochemicals as anti-tumor and chemoprevention agents. Herbal drug delivery systems based on nanocarriers have shown tremendous promise for a variety of diseases and disorders, particularly cancer theranostics. Also improved are uptake, bio-availability, and precise delivery. Loaded medicinal herbs promise a bright future in the field of medicine.

List of abbreviations

NDDS	Novel drug delivery systems
WHO	World health organization
DNA	Deoxyribonucleic acid
SLNs	Solid lipid nanoparticles
COVID-19	Coronavirus disease 2019
SRs	Systematic reviews

Ethics in publishing

Not applicable

Conflict of interest

There is no conflict of interest

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