

Nnotechnology based drug delivery systems of herbl medicine

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Abstract

Herbal medicine has been utilized extensively throughout ancient times. Advancements in the fields of phytochemistry and phytopharmacology has made it feasible to better understand the chemical composition and biological functions of certain medicinal plant products. The presence of active compounds is necessary for the efficacy of many species of medicinal plants. Most of the physiologically active components present in extracts, like tannins, terpenoids, and flavonoids, are highly soluble in aqueous solutions but show poor absorption because of their high molecular size, low absorption, or inability to pass through lipid membranes in cells. As a result, their bioavailability and efficacy are decreased. Certain extracts are not suitable in healthcare settings because of such problems. There has been a lot of research into combining nanotechnology with herbal medicine because of the potential for nanostructured systems to enhance the benefits of plant extracts by reducing dosage requirements, minimizing side effects, and enhancing activity. Nanosystems may deliver a sufficient quantity of the active component to the targeted site of action during the course of the treatment. Conventional therapy fails to meet these requirements. The aim of this study is to review nanotechnology-based medicine delivery systems and herbal remedies.

Keywords:- biological activity; drug delivery systems; natural products; herbal remedies; nanotechnology.

Introduction

Throughout human evolution, numerous groups have been aware of and used plants as herbal medicines. This has been done from the earliest days of human history, when people learned to choose plants for food and medicine. Throughout the second half of the 20th century, however, allopathic medicines gradually replaced herbal therapies, especially in the West. These days, allopathic medicine is more prevalent than traditional medicine, especially in wealthier countries. However, most developing countries continue to use these herbal medicines, probably since buying synthetic medications is so costly [1]. As per the World Health Organization [2], 80 percent of individuals in developing countries depend on

traditional medicine to either supplement or fulfill their basic medical requirements. Despite the pharmaceutical industry's encouragement and support during the creation of allopathic pharmaceuticals, a considerable portion of the population in many countries still seeks medical attention through alternative methods. Many of these rituals have their roots in medicinal herbs. The majority of those who use these natural resources do so because they cannot afford alternative therapies, but due to global economic, political, and social changes, their therapeutic application has decreased significantly [3–4].

Research on the molecular structure of medicinal plants and their widely used applications is currently a top priority for all scientific associations. The research's findings may lead to more creative drugs that have fewer negative effects than those that are presently on the market [5]. Natural products' enormous diversity of physicochemical and biological properties, in addition to their architecture, have also impressed researchers. Still, except for those used for local medicinal requirements, very few plants have been investigated for their potential as medicines. Consequently, there is inadequate data to describe the true potential [6–8]. The biological properties of therapeutic plants found all over the world have been studied by numerous research teams. These studies explore the potential benefits of various plant species for the pharmaceutical industry, based on scientific research and public knowledge about the therapeutic benefits of medicinal plants. Approximately 50% of approved medications between 1981 and 2006 were derived, directly or indirectly, from natural ingredients [1].

The chemical intricacy of extracts is crucial to the effectiveness of the formulation because it needs to release the active ingredient. Therefore, medicines must control both biological response and active absorption while simultaneously boosting drug solubility, delaying drug breakdown, reducing toxicity, and flavor masking [9–11]. Through phytochemical and phytopharmacological investigations, the biological characteristics and composition of some medicinal plant products have already been obtained. For the most part, the biologically active components of extracts, like tannins, terpenoids, and flavonoids, are highly water-soluble but have low absorption because they are large, cannot cross lipid membranes, and have poor absorption, which reduces bioavailability and efficacy. Some research indicates that in vitro evaluations of herbal treatments show great efficacy, which is not consistent with in vivo experiments. Additionally, some critical ingredients are hardly

ever employed because they have undesirable qualities or are incompatible with other formulation ingredients [12-13].

Numerous nanotechnological techniques, such as liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, precursor systems for liquid crystals (PSLCs), and microemulsions, have been tried to break through this obstacle. These tactics have the ability to change an element's actions within a biological environment and allow the use of many chemicals in the same formulation. These technological developments have changed the way drugs are distributed. The capacity to increase the efficacy of active compounds and restore inert substances that were removed from the formulation is one of the innovative drug delivery technologies.

The potential to enhance novel compounds prior to their therapeutic or commercial application—for example, by increasing their efficacy and selectivity, averting thermal or photodegradation, reducing adverse effects, and controlling the release of active ingredients—further enhances the appeal of this strategy. [14–16]. Combined with the recent advances in pharmacological research, there is an urgent need for progress in nanoscience and nanotechnology relevant to the application of nanoscale materials, which had hitherto only been the purview of the cosmetics sector. Solutions to challenging areas of formulation preparation can be enhanced and revolutionized by scientific breakthroughs [17]. Nanostructures can effectively extend the duration of a formulation's action and mix active substances with differing degrees of lipophilicity and hydrophilicity. Additionally, they can increase the stability and solubility of active ingredients. Additionally, this technology can be used to target the administration of a drug to certain organs or tissues at specific ages [18–21]. Because of its advantages, such as improved release methods and the ability to design novel formulations that were previously unfeasible (because of numerous variables surrounding the active ingredients), nanotechnology has attracted increasing interest from the pharmaceutical sector [22].

It's important to draw attention to some of the drawbacks of nanotechnology, even though it has benefits for many medical fields. Clinical researchers have identified certain drawbacks, including high expense, challenges in scaling up operations, and the easily inhaled nature of nanoparticles, which can cause hazardous lung conditions and frequently result in other illnesses that might cause abnormalities in homeostasis or even death [23-24]. The application of nanotechnology to plant extracts has received an extensive amount of

attention in the literature because nanostructured systems have the potential to improve the therapeutic properties of plant extracts, and support the continuous release of active ingredients, smaller dosage required, minimize side effects, and enhance activity [25–26]. In a review published by [10], many studies that employed nanostructured devices to improve the properties of botanical extracts were highlighted. In order to increase the absorption of the active components, Bhattacharya and Ghosh [27] used lipid-based systems in combination with infusions of green tea and ginseng (*Panax ginseng* CA Meyer) (Araliaceae) in a variety of formulations. *Radix salvia miltiorrhiza* Bunhe (Lamiaceae) was used by Su et al., [28] to create nanoparticles, and they observed a notable increase in the extract's bioavailability. After working with *Artemisia arborescens* L. (Asteraceae) to create liposomes, Sinico et al. found that these systems aided the biologically active ingredients in breaking through the cytoplasmic viral barrier [2].

Rajendran et al. synthesized nanoparticles through a methanolic extract of *Ocimum sanctum* L. (Lamiaceae) and reported that the encapsulated extract demonstrated stronger antimicrobial properties than in free-form preparation against *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* [26]. The effectiveness of herbal products, or medicinal plants, depends on the presence of active compounds. Since conventional therapies fall short of these conditions, novel carriers should route the active constituent toward the chosen target and deliver it at a suitable concentration throughout the duration of the therapy. It may be discovered that a certain action is lost entirely or partially when extracted substances are separated or purified. Furthermore, a few constituents are extremely vulnerable to the stomach's acidic pH, which encourages their breakdown and loss of intended impact after consumption. These barriers prevent the use of some extracts in clinical settings [12]. Numerous nanotechnology-based drug delivery systems, including liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, precursor systems for liquid crystals (PSLCs), and microemulsions, can be used to improve a formulation's most desired properties [10]. Furthermore, tiny particles could offer a future where function is assured, and the difficulties associated with the use of therapeutic plants are overcome [12].

Phytomedicine and Nano-Structured Drug Delivery System

The field of medication delivery systems with nanostructures is becoming more and more well-known. According to published research, these carriers have great promise for changing the way that phytoactive-based medication delivery methods are used today [29]. Instead, a variety of studies have been conducted and reported on, detailing the alteration of the medications' physicochemical and biological properties. Fig. 1 shows the broad application of the nanostructured systems developed for the delivery of phytomedicine. Enhancing the water solubility of weakly soluble phytoactives, such as andrographolide and curcumin, has enabled recent advancements in the delivery of phytomedicine. [30], as well as the release of herbal substances after oral administration; increase targetability by limiting non-specific medication availability to the undesirable site; increase safety; and enhance biological absorption through the gastrointestinal system [31], simplify the dosage schedule for frequently prescribed drugs; increase the phytoactives' stability during the extraction, formulation, and storage processes; and improve therapeutic efficacy to increase patient adherence and decrease dose-dependent adverse effects. [32–33].

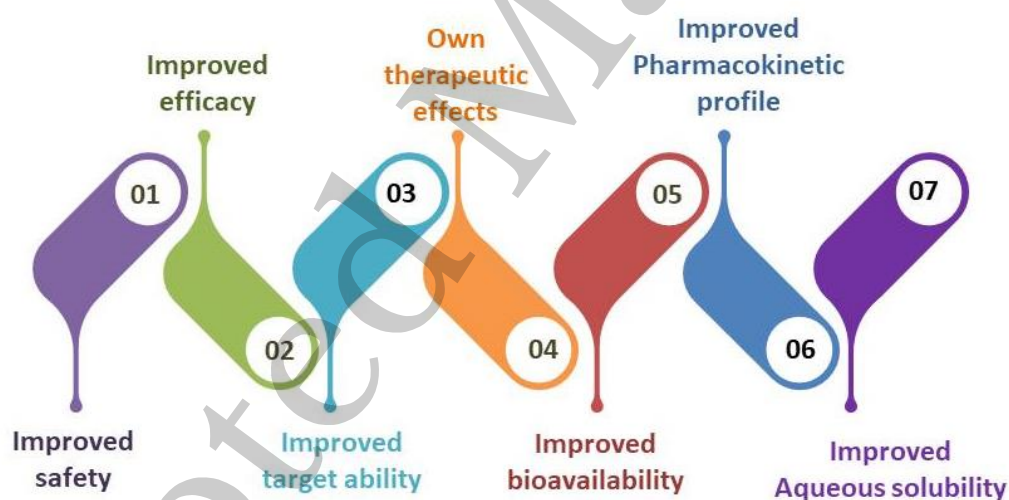


Fig. 1 Advanced phytomedicine delivery via a nanostructured system

Nanocarriers that facilitate the transfer of phytomolecules to the site of action demonstrate a range of advantages, including phytosomes, nanoparticles, nanocapsules, lipid carriers, and solid lipid nanoparticles [34]. Systems such as this are being developed to treat untreated medical disorders for which traditional dosage forms are not appropriate. By enhancing dissolution, pharmacokinetic properties profile (ADME), accessibility, targetability, effectiveness, and safety, nano-phytomedicines present significant potential for

improving the delivery of isolated and validated herbal compounds. That is because they have proven to be superior to traditional dose forms.

Drug Delivery System with Nanostructure for Improving the Aqueous Solubility of Phytomolecules.

The solubility of phytocompound is an important concern that restricts their broad utilization. The method of fractionation and isolation guided by bioactivity yields the majority of phytomolecules. It is not permitted to utilize molecules or extracts other than water-based extracts parenterally or orally. By exercising extra caution while maintaining blood therapeutic levels requires these compounds to be readily accessible in the systemic circulation, the solubility of these molecules inside biological systems has been improved. Reducing the size of the particles, forming solid dispersions and dispersion, adding co-solvents, adding surfactants/solubilizers, etc. are some of the most popular techniques for making the molecules more soluble[35–36].

It has been reported that nanopharmaceuticals improve phytomolecules' solubility. Because of their capacity to create persistent nanoparticles and droplet that are easily loaded with medications or emulsified to alter their physiochemical properties, nanocarriers are unique techniques for enhancing solubility [37–38]. They have the potential to significantly increase the solubility of phytomolecules; curcumin, for example, has become substantially more soluble when present in nanoparticle form [39]. By transforming BCS class 2 medications into easier to dissolve nano-phytomedicines, oral absorption is improved. Different approaches have been attempted to make these drugs more soluble because this is the rate-limiting phase that keeps a large amount of the medicine out of the systemic circulation (Table 1).

The most common methods for achieving solubility augmentation include surface modification with lipids or polymers, nanoparticle formation, and surface area enhancement [39–40]. According to a study by Piazzini et al. [41], Nanoemulsion can improve the permeability of biological membranes and the solubility of Vitex agnus-castus (VAC) extract. Improving oral delivery of VAC extract was the aim of this approach. The size of the drug-encapsulated nanoparticles was reduced to 11.82 ~ 0.125 nm by using triacetin, labrasol,

cremophor EL, and water as the oil, surfactant, co-surfactant, and aqueous phase, respectively. This resulted in a tenfold increase in VAC solubility. This method made the VAC extract completely soluble in water.

Since nanoemulsion has demonstrated high potential in solubilizing the extract, it was expected that improvements in both solubility and permeability would lead to increased oral bioavailability of VAC extract [41]. Systems of nanoparticles have the ability to modify the hydrophobic surface of phytoconstituents. Considerable research has been done on the use of nanoparticles to improve the solubility of hydrophobic medications in water. Nanoparticles are expected to greatly increase the drug's solubility by dispersing it more broadly. Combining surface modification and particle size reduction has been found to be quite efficient in several cases [42–43]. One approach involved using nanoparticles to encapsulate two well-known polyphenols, epicatechin and morin, in protein nanomaterials.

The combination of morin and epicatechin enhanced the release of drugs in biological systems by incorporating serum albumin nanomaterials having tiny particles molecules (170 ~ 6 nm to 200 ~ 12 nm) over the surface [40]. It's not just solubility that matters. It is nearly invariably linked to the dissolution, dispersion, localised availability, and bioavailability of medications. Thus, studies are conducted on it as well as other variables including penetration, absorption, and bioavailability.

Nanoparticles and Improved Pharmacokinetic Profile of Phytomolecules

Pharmacokinetics describes how the body responds to the absorption, distribution, metabolism, and excretion of an active constituent after administration. The drug goes through the different phases denoted by the term LADME once it enters the biological milieu of the GIT. These days, the term "liberation" is also being employed. It signifies the active ingredient's release from the delivery mechanism. It matters just as much for absorption. Most pharmacologists believe that the drug's absorption and release occur during the same procedure. They take into account that the medication is frequently given in an active state, which means that there is no release phase prior to absorption.

However, absorption is a pointless phenomenon until the medication is liberated or released from novel carrier systems. Prior to developing the dosage forms' pharmacokinetic

profile, the liberation process needs to be supported by nano-phytomedicine. The term "toxicological aspect" of medicine is frequently shortened to "ADME-Tox" or "ADMET." Most applications of nano-phytomedicine entail a controlled or gradual release of medicine. When drug release is regulated, the drug remains in the body for a longer amount of time. Increased tissue dispersion and redistribution follow from this, especially when using cytotoxic drugs. As a result, healthy body cells could perish. It is therefore another important issue that is being looked at.

How effectively the medicine crosses the biological barrier depends on a number of factors, such as log P, the mucosal membrane's thickness, and the availability of the active ingredient in a solubilized state. The drug's distribution throughout the body and its organs is influenced by a number of parameters, including its biological half-life, pH or temperature stability, and plasma protein binding. Enzymes involved in drug metabolism, such as glucuronosyltransferases and cytochrome P450, can support or impede the chemical breakdown of drugs. The amount of medication that is dispersed throughout the circulatory system and the amount that has been digested determine how much of it is expelled. Different dosages and methods of medicine administration have an impact on pharmacokinetic properties.

It is the goal of nano-phytomedicines to alter the pharmacokinetic behaviour of the chosen active ingredients. Encapsulation alters the drug's surface directly, affecting the rate at which the less absorbed active ingredients are absorbed. Nanoemulsion may be useful in improving solubility, which could raise the permeability of VAC extract when tested using the parallel artificial membrane permeation assay (PAMPA) (Piazzini et al., 41). When converted into a nanoemulsion, VAC has a higher penetration rate, which may enhance oral bioavailability [41]. The passage of active ingredients through the biological membrane is intimately linked to digestion. Variations in permeability can also occasionally be used to alter the rate of absorption through the skin. This enables transdermal penetration of the formulation into the skin [44]. According to a study by Lin et al. [45], ultra-deformable lipid (UDL) vesicles are useful for expanding the use of Chinese herbal medicine, especially for the transdermal administration of imperatorin (IMP). When compared to its suspension equivalent, cationic UDLs with smaller particle sizes (>100 nm) and high entrapment efficacy (60.32% ~ 2.82%) increased the amount of IMP that penetrated the skin by 3.45 times. In this instance, modifying the surface of IMP by cationic UDLs proved to be rather

advantageous, increasing availability in the various skin layers through enhanced transdermal flux and longer IMP release [45].

The production of a nanoemulsion improved the digestive system's absorption of phytoestrogenic diarylheptanoids. Gynecological illnesses can be effectively treated with phytoestrogenic diarylheptanoids, which are primarily sourced from *C. comosa*. Through the development of *C. comosa*'s nanoemulsion, barriers pertaining to the plant's absorption were revealed and overcome, allowing for a wider range of applications. Once *C. comosa* was emulsified, the hexane extract was tested in terms of intestinal absorptions. (4E,6E)-1,7-diphenylhepta-4,6-dien-3-ol (DA1) and (6E)-1,7-diphenylhept-6-en-3-ol (DA2) make up the majority of this extract. A homogenous size distribution, a negative surface charge, and nanosized droplets of the generated nanoemulsion were some of the chemically and physically changed components that led to improved drug absorption. Compared to pure oil, these nanodroplets demonstrated enhanced gastrointestinal absorption efficiencies that were five to 10 times faster [46].

Other pharmacokinetic requirements, such as distribution, must be satisfied in order to maintain therapeutic blood levels. The drug's stability at a specific pH or temperature, biological half-life, and reduced plasma protein binding for better dispersion are all improved. Preclinical results by Chang et al. indicate that encapsulating silymarin in liposome and ethosome has much improved its oral bioavailability and tissue distribution. Changes to the liposome and ethosome surface were shown to alter the drug's pharmacokinetic profile. The same rationale has led to extensive prior research on lipidic and ethanolic encapsulation.

Due to the silymarin's increased solubility in water, it has expanded its distribution within the systemic circulation. Silymarin's low water solubility was the main factor contributing to its low oral bioavailability; this could be fixed by vesicular techniques, which also improved the drug's overall therapeutic efficacy [47]. The pharmacokinetics and organ distribution of icariin should be improved by the previously investigated production of PG-liposomes for intraperitoneal administration in small animals.

ICAPG-liposomes improved the distribution of icariin into the spleen, liver, lung, kidney, heart, and brain when compared to its solution equivalent. Enhanced AUC(0-t) in the majority of tissues (except from the mouse lung), decreased clearance, extended MRT(0-t),

and biological half-life in all tissues (apart from the brain) were the outcomes of the enhanced volume of distribution of icariin in tissues [48].

Li et al.'s most recent study established the potential of liposomal drug delivery technology to improve baicalin's pharmacokinetics profile and bio-distribution. Chinese hospitals have long used baicalin (BA), which is thought to be the main ingredient in the dry root extract of *Scutellaria baicalensis*, to treat cerebral ischemia since it is neuroprotective. Its poor lipid solubility severely restricts its oral absorption. To improve its therapeutic relevance, it was developed as a special liposomal carrier (BA-LP). The drug's lipophilicity was enhanced, leading to an improvement in its level in the brain due to its increased lipophilicity.

The particle size range of BA-LP was 160–190 nm, its entrapment efficacy was 42%, and its zeta potential was +5.7 mV. Because of its controlled release features, the drug's in vitro release kinetic model—which employed the biphasic dynamic model equation—was shown to offer the best fit to BA-LP. There were greater C_{max} and AUC_{0–t}, or 1.5–2 times, compared to normal rat brain tissue. This shows a larger distribution of BA in the brain compared to normal rats. Changes in tissue distribution following liposome production led to decreased amounts of BA in the kidney and higher concentrations in the liver, heart, brain, and lungs. It was believed that BA-LP may serve as a carrier to improve the therapeutic efficacy of molecules similar to BA, as liposomal drug delivery methods were more effective in delivering BA [49].

When it comes to enhancing absorption and pharmacokinetic properties, nanostructured liposomal drug delivery methods have shown a lot of promise. Plant-based compounds have been extensively researched for their potential to help separate medications from the water phase to the lipid phase, encapsulate aqueous and lipid-based medications, alter the surface, and be compatible with the biological environment. Distribution is essential to drug delivery since it ensures the drugs' higher bioavailability. Tables 1 and 2 present an assortment of nanocarriers that are intended to enhance the pharmacokinetic characteristics of pharmaceuticals.

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Tables 1. Nano-phytomedicines with therapeutic benefits, lipid-based nanomedicines are developed for the enhancement of solubility, pharmacokinetic profile (ADME), bioavailability, target ability, efficacy, and safety. Rai et al., (65)

Phyto- constituent	Value addition	Indication	Route of administration	Reference
Liposomes				
Silymarin	Improve bioavailability	Hepatoprotective	Buccal	[50]
Artemisia arborescens essential oil	Targeting delivery to cells, enhanced permeation	Antiviral	In vitro	[51]
Garlicin	Increased efficacy	–	–	[12]
Usnea acid	Increased solubility, Improved localization and prolonged release	Anti- mycobacterial	In vitro	[51]
Wogonin	Sustained release effect	Anticancer	In vivo	[53]
Colchicine	Enhance skin deposition, prolonged drug release and improved site specificity	Antigout	Topical	[54]
Catechins	Increased permeation through skin	Antioxidant and chemo-preventive	Transdermal	[55]
Breviscapin	Sustained drug delivery	Cardiovascular diseases	Intramuscular	[56]
Nano-structured lipid/polymeric carriers				
Triptolide	Enhanced permeation through stratum corneum by virtue of increased hydration	Anti-inflammatory	Topical	[57]
Flavonoids and lignans	Improved aqueous solubility	Hepatoprotective and antioxidant effects	Oral	[58]

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Triptolide	Improved safety	Anti-inflammatory	Oral	[59]
Artemisinin	Sustained drug release	Anticancer	In vitro	[60]
Breviscapine	Prolong the half-life and decreased RES uptake	Cardiovascular and cerebrovascular	Intravenous	[61]
Camptothecin	Prolonged blood circulation and high deposition in tumors	Anticancer	In vitro	[62]
Phytosomes				
Silybin Flavonoids	Increased oral absorption of silybin	Hepatoprotective, antioxidant	Oral	[63]
Naringenin	Prolonged duration of action	Antioxidant activity	Oral	[64]

Source:- “Sabuj MZ, Islam N. Nanophytomedicine: An Effective Way for Improving Drug Delivery and Bioavailability of Herbal Medicines. Nanophytomedicine: Concept to Clinic. 2020:55-70”.

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Tables 2. Nanoemulsions of phytomedicines for the improved solubility, pharmacokinetic profile (ADME), bioavailability, target ability, efficacy, and safety **Rai et al., (65)**

Phyto- constituent	Value addition	Indication	Route of administration	Reference
Nanoemulsions				
Zedoary turmeric oil	Improved aqueous dispersibility, stability and oral bioavailability	Hepatoprotection anticancer and antibacterial	Oral	[66]
Triptolide	Enhanced penetration of drugs through the stratum corneum by increased hydration	Anti-inflammatory	Topical	[67]
Chlorogenic acid from green coffee	Improved aqueous dispersibility, stability and oral bioavailability	Antioxidant activity	Oral	[68]
Salicylic acid	Controlled release and improved dermal retention	Anti-inflammatory activity	Topical	[32]
Mentha essential oil	Control the release, avoid the contact with the skin and reduce the evaporation	Anti-fungal activity against vaginal candidiasis	Topical	[33]
Vesicular systems				

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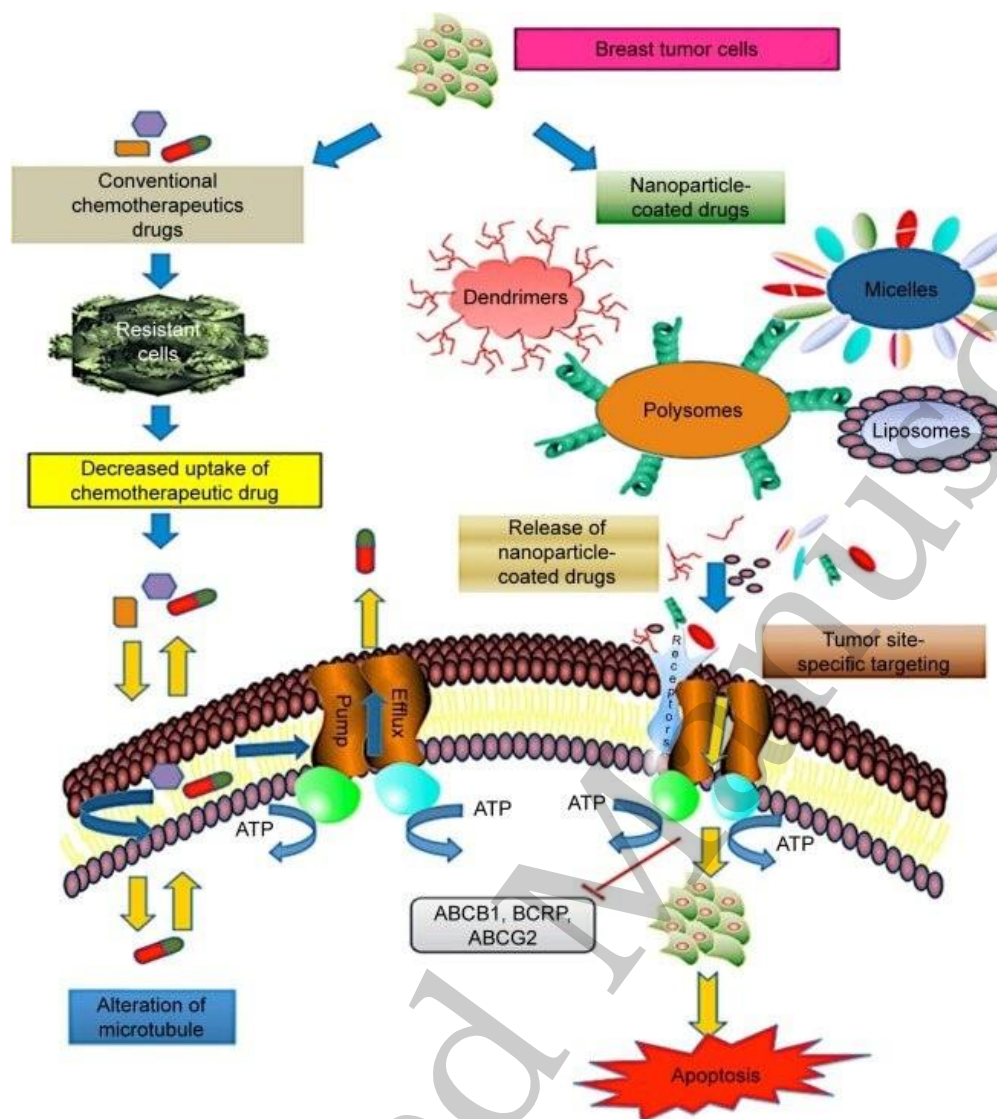
Colchicine	Increase skin penetration	Antigout	In vitro	[69]
Matrine	Improved the percutaneous permeation	Anti-inflammatory	Topical	[69]
Microspheres				
Zedoary oil	Sustained release and Higher bioavailability	Hepatoprotective	Oral	[70]
Quercetin	Significantly decreases the dose size	Anticancer	In vitro	[71]
<i>Mentha spicata</i> L. var. viridis oil (MVO)	Alleviate skin irritation and volatility and to avoid direct contact with the skin	Anti-fungal activity	Topical	[30]

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A Drug Delivery System with Nanostructure for Increased Bioavailability

Reports describe the various efforts made by researchers to create nanocarrier systems that improve the solubility and stability of herbal medications. Drug dissolution at blood pH, drug absorption, drug distribution into systemic circulation, first-pass metabolism, GI stability, and drug molecular weight are other factors that affect bioavailability. Part of the phytomedicine efforts to improve bioavailability include increasing medication absorption [72]. Through the development of nanoformulations, silymarin solubility was increased in one study. This improved the drug's bioavailability and, as a result, its therapeutic efficacy as an antiviral, anticancer, antioxidant, and hepatoprotectant. Water-insoluble active plant components can now be encased in a variety of nanocarriers thanks to technological advancements in solubility enhancement. The most cutting-edge technology accessible is the creation of nanovesicles and nanocarriers. For example, silymarin may greatly promote passive diffusion in aqueous nanovesicles [73]. Additionally, as cyclovirobuxine D's solubility improved, SNEDDSs were created to boost the drug's bioavailability. Propylene glycol, oleic acid, Solutol SH15, and cyclovirobuxine D were combined in the following ratios to create the final SNEDDS formulation: 3:24:38:38. Scattering of the ultimate SNEDDS structure developed impulsively and was changed into a 64.80 ± 3.58 nm globule-sized nanoemulsion. Greater drug solubility, a quick rate of absorption, an enhanced area under the curve, better penetration, and a decreased efflux were all linked to the investigated medication's increased dispersion. All of these qualities led to a 200.22% improvement in SNEDDS's relative bioavailability over commercial tablets. Proposing SNEDDS carriers as a viable option for an oral administration of cyclovirobuxine D-like medications with enhanced bioavailability, the authors highlighted the possible application of SNEDDS in phytomedicine [74]. One of the most researched carriers for increasing the bioavailability of medications is nanoemulsion. Nanoemulsions, which are colloidal particle systems consisting of an organic phase and a water phase, are created by using an appropriate stabilising surfactant, which is an isotropic in nature thermodynamically metastable system. The surfactant-based interface, which can reversibly change the biological membrane's structure, facilitates drug absorption into the membrane.

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Source:- Singh et al., (2017)

Its ability to load drugs that are both hydrophilic and hydrophobic is by far its biggest advantage. The various types of nanoemulsions that have been created for various uses are listed in Table 2. Despite being highly soluble in water, breviscapine has a very limited oral bioavailability. This is because to the GIT's low stability and penetration. By employing nanoemulsion, a nanocarrier that facilitates oral absorption, breviscapine's bioavailability through the oral route has been increased. It also helped to boost the internal stability of medication. Higher drug encapsulation and constant droplet size contributed to the identification of these features. It was discovered that the increase in bioavailability might reach 249.7% when compared to relative bioavailability. The reason behind this was the

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capacity of breviscapine to be encapsulated in a nanoemulsion, so preventing direct exposure to the gastrointestinal environment [75].

Improved Target Ability with Nano-Phytomedicine

When a minority cell or group of minority cells is determined to need therapy, it is referred to as a target. For the greatest potential treatment result, enhanced target specificity is meant to aid in pharmacological target identification and maximal drug concentration. In order to prevent pharmaceutically active chemicals, active ingredients, or treatments from spreading to nearby tissues and organs, specific kinds of drug carrier systems are used to deliver them only to the intended site of action. These are delivery or transport vectors that sequester the medication while delivering it to the intended cells. Specifically, targeted areas of action may include the capillary bed, an intracellular region, or a certain cell type.

Target ability requires the creation of a carrier with an agent that can selectively recognize a certain target. The carrier needs to be able to distinguish between normal and tumour cells, for instance. When a drug is transported by a carrier to its intended location, the ligands aid in its identification and render the carrier site specific. Endogenous hormones, polypeptides, and particular antibodies are examples of ligand systems. Treating or preventing diseases is the main way that pharmaceuticals' target capacities are improved. Biological instability, pharmacokinetic/pharmacodynamic, short biological lifespan, large volume of dispersion, low specificity, low therapeutic index, low drug dissolution, reduced absorption through the gastrointestinal tract, high-plasma adhering of proteins, and instabilities of the drugs in the gastric environment are all taken into account when developing targeted drug delivery systems. Reducing side effects related to the diffusion of drugs into other tissues is the main goal of this strategy. Among other qualities, a system for the delivery of targeted drugs should be immunogenicity-free, chemically and physiologically stable, able to limit drug distribution to specific tissues, cells, or organs, and have a consistent capillary distribution.

It has to be under control in addition to manufacturing the drug at the optimal therapeutic dose. A carrier's design ensures that the least quantity of medication leaks during transit. When designing carriers, additional important considerations include the biodegradability and ease of removal of polymers from the body. These setups should be easy to make, inexpensive, and replicable. When constructing these carriers, other factors are

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taken into account, such as target cell features, marker traits, or transport carriers—vehicles that deliver medications to specific receptors by using ligands and physically changed components.

Cyclovirobotuxine D (CVB-D) is a steroidal alkaloid that is extracted from the Chinese herb *Buxus microphylla*. It is commonly used to treat cerebrovascular issues and various cardiovascular disorders. Its clinical application needs to be enhanced because there aren't many formulations of CVB-D under investigation. Another drug that may be a bioactive phytoconstituent in triple-negative breast cancer is thymoquinone, which is extracted from the volatile oil of *Nigella* black cumin seeds. Several molecular targets in cancer, such as ROS, PPAR- γ , p53, p73, STT3, nuclear factor- κ B, and others, are said to exhibit its antineoplastic action [76].

Angiopep-2-conjugated liposomes have demonstrated potential as a targeted carrier for brain distribution because they naturally bind to the low-density lipoprotein receptor-related protein-1 (LRP1) and are able to cross the blood-brain barrier. There is currently interest in the nasal route of administration due to its ability to target particular brain regions [77]. Furthermore, targeting the liver has shown a lot of promise for nano-phytomedicine [78]. Despite tremendous efforts, millions of individuals worldwide suffer from liver illnesses. Treating illnesses linked to the liver effectively is vital. A number of substances, including alcohol, drugs, plants, waterborne and industrial pollutants, and industrial pollutants, can harm the liver and aggravate liver illnesses. Nevertheless, a variety of herbal medicines are used to cure illnesses like cirrhosis, hepatitis, and cancer. Using herbal remedies to treat liver issues is now well established.

Nonetheless, the idea of customized drug delivery systems was investigated, ensuring the greatest potential usage of these medications. In liver targeting, receptor ligand binding is the basic concept. There are multiple types of liver-resident receptors on the surface of hepatocytes, including Kupffer cells, hepatic stellate cells, sinusoidal endothelial cells, etc. They are utilized in an effort to increase the drug's liver-available form. These receptor targets determine the choice of several ligand types, such as galactosylated, lactobionic acid, and asialofetuin. These ligands are attached to the surface of numerous microparticles, liposomes, nanoparticles, and many more. There have been several particle techniques employed for liver targeting, including liposomes, niosomes, nanoparticles, micelles, and

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nanosuspensions [79]. Apart from improving the drug's liver-targeting properties, vinegar-baked Radix Bupleuri (VBRB), a traditional Chinese medication, offers other medical effects as well. When combined with 10-hydroxycamptothecin (HCPT), VBRB's ability to improve target ability was investigated after loading in polymeric micelles.

VBRB dramatically improved the liver-targeting effectiveness of HCPT encapsulated in polymeric micelles when administered in conjunction with oral medicine. Using meridian directed medications in concert with modern drug delivery methods to better target active pharmaceuticals was a simple yet effective strategy that was demonstrated by this approach [80]. According to a review by Bartneck et al. (2014), nanomedicine may be used to treat liver fibrosis and inflammation. [81] It's possible that some nanomaterials will trigger macrophage activation, such as AuNRs (gold nanorods treated with peptides). Targeting mannose receptors can be utilized to guide macrophages in liver diseases. Targeting HSC, which generate collagen, is possible with nanoconstructs that can identify insulin-like growth factor II, platelet-derived growth factor (PDGF) receptor β , peroxisome proliferator-activated receptor 1, and integrins during fibrosis [81]. A polymeric nanoparticle-based intraperitoneal injection of curcumin called NanoCurcTM has been developed. This technique successfully reduced liver damage and fibrosis [82].

Quercetin is a subcutaneously injected nanomedicine that binds to the galactosyl receptor preferentially and efficiently to hepatocytes [83]. Consequently, the utilization of macromolecular carriers emerged as a feasible approach for efficient bone targeting [84]. To prevent steroid-related osteonecrosis in small animals, icaritin has been administered via a new bone-targeted drug delivery technique. This approach has been shown to be effective in avoiding steroid-induced osteonecrosis. By encouraging bone formation and decreasing fat deposition and bone resorption, it works at osteonecrotic responsive skeletal locations. Once the impact of a novel phytomolecule, icaritin, on osteogenesis was discovered, the authors developed a bone-targeted delivery method with anti-bone resorption and anti-adipogenesis effects. Both Asp8-liposome and liposome-icaritin have not shown any discernible effectiveness against high SAON, while in rats administered steroids, Asp8-liposome-icaritin significantly decreased the death of osteocytes, downregulated osteoclastogenesis, and upregulated osteogenesis.

Administering Asp8-liposome-icaritin resulted in the prevention of bone resorption, suppression of adiposeness, and enhancement of bone formation [85]. Nanomedicine has been applied to hair follicles in addition to the liver, kidneys, and cancers. Bendable

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liposomes that are resistant to MRSA enhanced hair follicle targeting and made it possible to administer chloramphenicol for more efficient therapy of difficult-to-treat bacterial invasions of hair follicles. Deformable liposomes were discovered to have good biocompatibility against keratinocytes and neutrophils and to be safe for topical application on skin [86].

These findings highlight the great potential of nanomedicine in reaching any level of the body, i.e., cells, tissues, or organs, with phytoconstituent delivery. These characteristics of nanomedicine are caused by the nanocarriers' versatile shape and structure, ultra-deformable integrity, surface charge, nano size range, and variety of polymer properties. The potential for targeting phytoconstituents to the brain, liver, kidney, bone, tumor site, and specific cells is considerable; nevertheless, additional study is required to optimize their therapeutic pertinence and incorporate these carriers into a highly scalable production method.

Nano-Phytomedicine and Improved Safety

Physicochemical aspects of the drugs also demonstrate an increase in safety. A potential avenue for enhancing safety is the study of nanophytomedicine and safe medication distribution. That's supported by a ton of new research. Improved safety is a further application for nanomedicine, and these carriers are quite helpful in handling such situations. The purpose of the thymoquinone-rich fraction nanoemulsion (TQRFNE) was to increase the acute toxicity of thymoquinone. TQRFNE lessened the drug's associated toxicity in experiments conducted on Sprague Dawley rats.

Comparing the TQRFNE group to the group that received distilled water, it was discovered that characteristics such common behavior, body weight, food and water consumption, relative organ weight, hematological, histology, and clinical biochemistry remained unaltered. Furthermore, throughout the experimental period, no reports of fatalities or toxicological symbols were recorded [87]. Using MSOT imaging, the potency of a conjugated polymer-based ratiometric nanoprobe against in vivo herb-induced liver injury has been evaluated. This ratiometric nanoprobe was designed for in vivo imaging of hepatic injury employing MSOT imaging, which enables precise identification of the site of liver injury.

In order to create an internal standard, the liposomal nanoprobe was made up of a responsive dye (IX-2NH₂) that could only react with NO and a conjugated polymer based on diketopyrrolopyrrole (DPP-TT). Using 3D data from the mouse model, ratiometric

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optoacoustic diagnosis of liver damage caused by herbal medicines offers a method to reduce liver toxicity without invasive procedures [88]. These processes have been developed into multiple varieties thus far. Nanomedicine-based molecular imaging has been acknowledged as a significant field in safety pharmacology. Optoacoustic and photoacoustic imaging, CT scanning, MRIs, ultrasounds, and scanning are among the techniques now being employed to improve patient safety.

Nano-Phytomedicine: Applications in Therapeutics

Proteins, bioactive lipids, and miRNA are examples of extracellular messengers that function as cell-to-cell messengers in a manner similar to the exosomes secreted by mammalian cells [89]. When it comes to getting low dose drugs (such proteins, peptides, and siRNAs) to where they are supposed to go, chemically manufactured nanoparticles have two main disadvantages. Before the created nanoparticles are deemed therapeutically useful, their components need to be assessed for low fabrication scalability and probable in vivo safety. However, plant-based nanoparticles are thought to be able to get beyond these restrictions.

It is noteworthy that ingesting these nanoparticles has no risks. In interspecies communication, they may serve as natural cures against certain ailments. Moreover, nanoparticles based on plant-derived lipids can help precisely transport drugs to their targeted site. Vegetable nanoparticles derived from plants could be easily manufactured on a big scale, unlike synthetically created nanoparticles. The grape juice nanocarriers, ginger, carrot juice, and tomato juice are extracted using eco-friendly methods. In the field of nanomedicine, these nano-phytocomposites offer a fresh approach to producing therapeutic nanoparticles [90].

Nanoparticles made of botanical ingredients are vital for interspecies communication and beneficial against inflammatory diseases and cancer. Recent findings indicate that oral administration of grape exosome-based nanocarriers to mice promotes the growth of intestinal stem cells throughout the intestine and intestinal epithelial cell proliferation. Moreover, it seemed that saliva, digestive fluids, and intestinal proteolytic enzymes could not degrade grape exosome-like oral nanoparticles. Based on the currently available information, ingestible plant-based nanoparticles can enter the colon through the oral route, where they can be absorbed by intestinal cells and utilized for various purposes like intestinal regeneration.

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Edible nanoparticles with anti-inflammatory and colonic tissue-targeting properties could be a novel, nontoxic delivery method for the management of gastrointestinal tract pain, including inflammatory bowel disease, and could be readily developed on a large scale [91]. Metallic nanoparticles can have additional or beneficial effects when used in combination with other medicinal treatments. They are used as a medicinal ingredient. Among the metallic nanoparticles that have been produced are Ag, Au, Fe, and others. When ingested, the chemical process utilized to produce metallic nanoparticles is hazardous and deadly. As a result, "green" synthesis methods in chemistry are gaining traction. These regulations are desperately needed in light of the environmental problems.

It has been demonstrated to have strong bactericidal and inhibitory properties in addition to anti-fungal, anti-inflammatory, and anti-angiogenesis effects. These attributes make it valuable in the disciplines of catalysis, biosensors, high sensitivity biomolecular recognition, and medicine. Many methods, such as ion sputtering, chemical reduction, and sol gel, can be used to create silver nanoparticles [92]. The manufacture of silver nanoparticles using a unique reducing agent was summarized by Khan et al. This "green reductant" was made from plant extracts and used as a reducing agent to create silver nanoparticles. This investigation was carried out in response to the increased demand for silver nanoparticles (Ag-NPs) in the pharmaceutical industry.

These nanoparticles are used in the biomedical sector because to their antibacterial, antifungal, or anticancer properties. The usage of hazardous chemicals in the chemical synthesis process makes alternative methods necessary, even if it is an effective way to produce nanoparticles with the necessary size, shape, and crystallinity. Nevertheless, the resulting Ag-NPs' size, shape, and crystallinity are not under the control of these biological processes. Novel bio-inspired synthetic procedures have been investigated and have demonstrated some promise in reducing adverse environmental effects [93–94]. An overview of Ag-NP manufacturing via chemical and environmentally friendly methods is given in their compilation. "Green synthesis" was developed as a response to the limitations of chemical and biological synthesis. In order to create Ag-NPs with the right size, morphology, shape, crystallinity, and biological effect while using the fewest amount of hazardous materials possible, various plant extracts and phytomolecules were used, along with their chemical and biological characteristics. Their action on particle synthesis was demonstrated. Olive, beet root, mangosteen, *Ziziphora tenuior*, *Abutilon indica*, *Solanum tricornatum*, *Erythrina indica*,

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leaf extracts of *Acalypha indica*, and *Sesuvium portulacastrum* have all been used in the green synthesis of Ag-NPs.

It has been documented that silver nanoparticles (silver-NPs) range in size from 5 to 20 nm. The potential biological applications of silver nanoparticles surface functionalized by phytomolecules are now under investigation [95]. Ag-NPs' antibacterial properties have led to their extensive use in the medical field, textile coatings, food preservation, wound healing, color reduction, and other environmental applications [96–97]. Compounds containing elemental silver have shown promise in treating a range of bacterial and fungal illnesses. Using *A. indica* extract-mediated silver nanoparticles, potential antibacterial agents have been investigated. Silver nanoparticles produced by green synthesis have been shown to have higher antibacterial action against *S. aureus* and *E. coli*. Consequently, these hold great promise for the management of diverse infectious diseases and conditions.

Conclusion and future prospective

When a drug-loaded innovative carrier system is created using nanotechnology-based methods, it's commonly referred to as nanomedicine. This is because the systems can be effectively used for disease prevention, diagnostics, or therapy. The careful integration of nanotechnology concepts and methods with phytomedicines has become a significant priority in recent times. Researchers are becoming increasingly interested in using these formulations to treat and control chronic diseases like cancer, arthritis, such as, Parkinson's, Alzheimer's, and epilepsy and other conditions because of their success and potential at the clinical level. These formulations' improved absorption and bioavailability, rapid dissolution, quicker onset of action, higher plasma concentration, prolonged actions, site-specific targeting, decreased toxicity, and improved pharmacological performances have already increased interest in these formulations. In summary, the pharmaceutical industries are drawn to the integration of new technology in the production of herbal medicine-based preparations because it offers superior alternatives to conventional dosage forms, hence improving people's health through the use of these "herbal remedies." Even though nanotechnology offers immense potential and benefits, only a small number of these products—nanophytomedicinal meagre—have found their way into clinical settings. This is because these products require sophisticated machinery, complicated scaling procedures, high preparation costs, potential health and environmental

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risks from produced nanoparticles, and short shelf lives for developed formulations. These issues remain significant obstacles that must be addressed in a very systematic manner.

References

- [1] Souza-Moreira TM, Salgado H, Pietro RC. O Brasil no contexto de controle de qualidade de plantas medicinais. *Revista Brasileira de Farmacognosia*. 2010;20:435-40.
- [2] Pires AM, Araújo PS. Percepção de risco e conceitos sobre plantas medicinais, fitoterápicos e medicamentos alopáticos entre gestantes. *Revista baiana de saúde pública*. 2011;35(2):320-.
- [3] Ferreira VF, Pinto AC. A fitoterapia no mundo atual. *Química nova*. 2010;33:1829-.
- [4] Badke MR, Budó MD, Silva FM, Ressel LB. Plantas medicinais: o saber sustentado na prática do cotidiano popular. *Esc Anna Nery*. 2011 Jan;15(1):132-9.
- [5] Costa EM, Barbosa AS, Arruda TA, Oliveira PT, Dametto FR, Carvalho RA, Melo MD. In vitro antimicrobial activity of plant extracts against *Enterococcus faecalis*. *Jornal Brasileiro de Patologia e Medicina Laboratorial*. 2010;46:175-80.
- [6] Verma S, Singh SP. Current and future status of herbal medicines. *Veterinary world*. 2008 Nov 1;1(11):347.
- [7] Bresolin TMB, Filho VC. Fármacos e medicamentos: uma abordagem multidisciplinar [Drugs and medicines: a multidisciplinary approach]. São Paulo: Santos; 2010. Portuguese
- [8] Mazzolin LP, Nasser AL, Moraes TM, Santos RC, Nishijima CM, Santos FV, Varanda EA, Bauab TM, da Rocha LR, Di Stasi LC, Vilegas W. *Qualea parviflora* Mart.: an integrative study to validate the gastroprotective, antidiarrheal, antihemorrhagic and mutagenic action. *Journal of ethnopharmacology*. 2010 Feb 3;127(2):508-14.
- [9] Kluczynik CE, Souza JH, Palmeira JD, Ferreira SB, Antunes RM, Arruda TA, Morais MR, Catão RM. Perfil de sensibilidade de *Salmonella* sp. de ambiente aquático a antimicrobianos comerciais e a extratos hidroalcoólicos de plantas medicinais. *Rev. bras. anal. clin.* 2010:141-4.
- [10] Kesarwani K, Gupta R. Bioavailability enhancers of herbal origin: An overview. *Asian Pacific journal of tropical biomedicine*. 2013 Apr 1;3(4):253-66.
- [11] Holmberg K. Handbook of applied surface and colloid chemistry. (No Title). 2002 Feb 1.
- [12] Ajazuddin SS. Applications of novel drug delivery system for herbal formulations. *Fitoterapia*. 2010;81(7):680–689.

Disclaimer: This is not the final version of the article. Changes may occur when the manuscript is published in its final format.

- [13] Mainardes RM, Urban MC, Cinto PO, Chaud MV, Evangelista RC, Gremiao MD. Liposomes and micro/nanoparticles as colloidal carriers for nasal drug delivery. *Current drug delivery*. 2006 Aug;3(3):275.
- [14] Grill AE, Johnston NW, Sadhukha T, Panyam J. A review of select recent patents on novel nanocarriers. *Recent Patents on Drug Delivery & Formulation*. 2009 Jun 1;3(2):137-42.
- [15] Venugopal J, Prabhakaran MP, Low S, Choon AT, Deepika G, Giri Dev VR, Ramakrishna S. Continuous nanostructures for the controlled release of drugs. *Current Pharmaceutical Design*. 2009 May 1;15(15):1799-808.
- [16] Chorilli M, Brizante AC, Rodrigues CA, Salgado HR, Pombo-Nascimento E, Ventura DM. Aspectos gerais em sistemas transdérmicos de liberação de fármacos. *Rev bras farm*. 2007;88(1):7-13.
- [17] Baley MM, Berkland CJ. Nanoparticle formulations in pulmonar drug delivery. *Med Res Rev*. 2009;29(1):196-212.
- [18] Chen Y, Lin X, Park H, Greever R. Study of artemisinin nanocapsules as anticancer drug delivery systems. *Nanomedicine: nanotechnology, biology and medicine*. 2009 Sep 1;5(3):316-22.
- [19] Pestana KC, Formariz TP, Franzini CM, Sarmiento VH, Chiavacci LA, Scarpa MV, Egito ES, Oliveira AG. Oil-in-water lecithin-based microemulsions as a potential delivery system for amphotericin B. *Colloids and surfaces B: Biointerfaces*. 2008 Oct 15;66(2):253-9.
- [20] Cunha Júnior AD, Fialho SL, Carneiro LB, Oréfice F. Microemulsões como veículo de drogas para administração ocular tópica. *Arquivos Brasileiros de Oftalmologia*. 2003;66:385-91.
- [21] Sintov AC, Shapiro L. New microemulsion vehicle facilitates percutaneous penetration in vitro and cutaneous drug bioavailability in vivo. *Journal of Controlled Release*. 2004 Mar 5;95(2):173-83.
- [22] Lee RW, Shenoy DB, Sheel R. Micellar nanoparticles: applications for topical and passive transdermal drug delivery. In *Handbook of non-invasive drug delivery systems* 2010 Jan 1 (pp. 37-58). William Andrew Publishing.
- [23] Yadav A, Ghune M, Jain DK. Nano-medicine based drug delivery system. *J Adv Pharm Educ Res*. 2011;1(4):201-13.
- [24] Singh R, Tiwari S, Tawaniya J. Review on nanotechnology with several aspects. *Int J Res Comput Eng Electron*. 2013;2(3):1-8.

Disclaimer: This is not the final version of the article. Changes may occur when the manuscript is published in its final format.

- [25] Ghosh V, Saranya S, Mukherjee A, Chandrasekaran N. Antibacterial microemulsion prevents sepsis and triggers healing of wound in wistar rats. *Colloids and Surfaces B: Biointerfaces*. 2013 May 1;105:152-7.
- [26] Rajendran R, Radhai R, Kotresh TM, Csiszar E. Development of antimicrobial cotton fabrics using herb loaded nanoparticles. *Carbohydr Polym*. 2013;91(2):613–617.
- [27] Bhattacharya S, Ghosh, AK. Phytosomes: the emerging technology for enhancement of bioavailability of botanicals and nutraceuticals. *Int J Aesthetic Antiaging Med*. 2009;2(1):87–91
- [28] Su YL, Fu ZY, Zhang JY, Wang WM, Wang H, Wang YC. Preparation of Radix salvia nanoparticles. *Powder Technol*. 2008;184(1):114–121.
- [29] Rai VK, Mishra N, Yadav KS, Yadav NP. Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: Formulation development, stability issues, basic considerations and applications. *Journal of controlled release*. 2018 Jan 28;270:203-25. <https://doi.org/10.1016/j.jconrel.2017.11.049>
- [30] Mishra N, Yadav KS, Rai VK, Yadav NP. Polysaccharide encrusted multilayered nano-colloidal system of andrographolide for improved hepatoprotection. *Aaps Pharmscitech*. 2017 Feb;18:381-92. <https://doi.org/10.1208/s12249-016-0512-4>
- [31] Mishra N, Rai VK, Yadav KS, Sinha P, Kanaujia A, Chanda D, Jakhmola A, Saikia D, Yadav NP. Encapsulation of mentha oil in chitosan polymer matrix alleviates skin irritation. *AAPs PharmSciTech*. 2016 Apr;17:482-92. <https://doi.org/10.1208/s12249-015-0378-x>
- [32] Sinha P, Srivastava N, Rai VK, Mishra R, Ajayakumar PV, Yadav NP. A novel approach for dermal controlled release of salicylic acid for improved anti-inflammatory action: Combination of hydrophilic-lipophilic balance and response surface methodology. *Journal of Drug Delivery Science and Technology*. 2019 Aug 1;52:870-84. <https://doi.org/10.1016/j.jddst.2019.06.007>
- [33] Srivastava N, Patel DK, Rai VK, Pal A, Yadav NP. Development of emulgel formulation for vaginal candidiasis: Pharmaceutical characterization, in vitro and in vivo evaluation. *Journal of drug delivery science and technology*. 2018 Dec 1;48:490-8. <https://doi.org/10.1016/j.jddst.2018.10.013>
- [34] Sharma A, Upadhyay DK, Sarma GS, Kaur N, Gupta GD, Narang RK, Rai VK. Squalene integrated NLC based gel of tamoxifen citrate for efficient treatment of psoriasis: A preclinical investigation. *Journal of Drug Delivery Science and Technology*. 2020 Apr 1;56:101568.

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- [35] Kumar B, Pandey M, Pottoo FH, Fayaz F, Sharma A, Sahoo PK. Liposomes: novel drug delivery approach for targeting Parkinson's disease. *Current Pharmaceutical Design*. 2020 Oct 1;26(37):4721-37. <https://doi.org/10.2174/1381612826666200128145124>
- [36] Sharma S, Rabbani SA, Narang JK, Pottoo FH, Ali J, Kumar S, Baboota S. Role of rutin nanoemulsion in ameliorating oxidative stress: pharmacokinetic and pharmacodynamics studies. *Chemistry and physics of lipids*. 2020 May 1;228:104890. <https://doi.org/10.1016/j.chemphyslip.2020.104890>
- [37] Alam MS, Javed MN, Pottoo FH, Waziri A, Almalki FA, Hasnain MS, Garg A, Saifullah MK. QbD approached comparison of reaction mechanism in microwave synthesized gold nanoparticles and their superior catalytic role against hazardous nirto-dye. *Applied Organometallic Chemistry*. 2019 Sep;33(9):e5071. <https://doi.org/10.1002/aoc.5071>
- [38] Javed MN, Alam MS, Waziri A, Pottoo FH, Yadav AK, Hasnain MS, Almalki FA. QbD applications for the development of nanopharmaceutical products. In *Pharmaceutical quality by design* 2019 Jan 1 (pp. 229-253). Academic Press.
- [39] Bhawana, Basniwal RK, Buttar HS, Jain VK, Jain N. Curcumin nanoparticles: preparation, characterization, and antimicrobial study. *Journal of agricultural and food chemistry*. 2011 Mar 9;59(5):2056-61. <https://doi.org/10.1021/jf104402t>
- [40] Ghosh P, Bag S, Roy AS, Subramani E, Chaudhury K, Dasgupta S. Solubility enhancement of morin and epicatechin through encapsulation in an albumin based nanoparticulate system and their anticancer activity against the MDA-MB-468 breast cancer cell line. *RSC advances*. 2016;6(103):101415-29. <https://doi.org/10.1039/C6RA20441D>
- [41] Piazzini V, Monteforte E, Luceri C, Bigagli E, Bilia AR, Bergonzi MC. Nanoemulsion for improving solubility and permeability of Vitex agnus-castus extract: formulation and in vitro evaluation using PAMPA and Caco-2 approaches. *Drug delivery*. 2017 Jan 1;24(1):380-90. <https://doi.org/10.1080/10717544.2016.1256002>
- [42] Ansari MA, Chung IM, Rajakumar G, Alzohairy MA, Alomary MN, Thiruvengadam M, Pottoo FH, Ahmad N. Current nanoparticle approaches in nose to brain drug delivery and anticancer therapy-a review. *Current pharmaceutical design*. 2020 Mar 1;26(11):1128-37. <https://doi.org/10.2174/1381612826666200116153912>
- [43] Ansari MA, Badrealam KF, Alam A, Tufail S, Khalique G, Equbal MJ, Alzohairy MA, Almatroudi A, Alomary MN, Pottoo FH. Recent nano-based therapeutic intervention of bioactive sesquiterpenes: prospects in cancer therapeutics. *Current Pharmaceutical Design*. 2020 Mar 1;26(11):1138-44. <https://doi.org/10.2174/1381612826666200116151522>

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- [44] Ahmad N, Ahmad R, Al-Qudaihi A, Alaseel SE, Fita IZ, Khalid MS, Pottoo FH. Preparation of a novel curcumin nanoemulsion by ultrasonication and its comparative effects in wound healing and the treatment of inflammation. *RSC advances*. 2019;9(35):20192-206. <https://doi.org/10.1039/C9RA03102B>
- [45] Lin H, Xie Q, Huang X, Ban J, Wang B, Wei X, Chen Y, Lu Z. Increased skin permeation efficiency of imperatorin via charged ultradeformable lipid vesicles for transdermal delivery. *International journal of nanomedicine*. 2018 Feb 8;8:31-42. <https://doi.org/10.2147/ijn.s150086>
- [46] Su J, Sripanidkulchai K, Hu Y, Chaiittianan R, Sripanidkulchai B. Increased in situ intestinal absorption of phytoestrogenic diarylheptanoids from *Curcuma comosa* in nanoemulsions. *AAPS PharmSciTech*. 2013 Sep;14:1055-62. <https://doi.org/10.1208/s12249-013-9996-3>
- [47] Chang LW, Hou ML, Tsai TH. Silymarin in liposomes and ethosomes: Pharmacokinetics and tissue distribution in free-moving rats by high-performance liquid chromatography–tandem mass spectrometry. *Journal of agricultural and food chemistry*. 2014 Dec 3;62(48):11657-65. <https://doi.org/10.1021/jf504139g>
- [48] Yang W, Yu XC, Chen XY, Zhang L, Lu CT, Zhao YZ. Pharmacokinetics and tissue distribution profile of icariin propylene glycol-liposome intraperitoneal injection in mice. *Journal of Pharmacy and Pharmacology*. 2012 Feb;64(2):190-8. <https://doi.org/10.1111/j.2042-7158.2011.01388.x>
- [49] Li N, Feng L, Tan Y, Xiang Y, Zhang R, Yang M. Preparation, characterization, pharmacokinetics and biodistribution of baicalin-loaded liposome on cerebral ischemia-reperfusion after iv administration in rats. *Molecules*. 2018 Jul 17;23(7):1747. <https://doi.org/10.3390/molecules23071747>
- [50] El-Samaligy MS, Afifi NN, Mahmoud EA. Increasing bioavailability of silymarin using a buccal liposomal delivery system: preparation and experimental design investigation. *International journal of pharmaceutics*. 2006 Feb 3;308(1-2):140-8. <https://doi.org/10.1016/j.ijpharm.2005.11.006>
- [51] Kesarwani K, Gupta R. Bioavailability enhancers of herbal origin: An overview. *Asian Pacific journal of tropical biomedicine*. 2013 Apr 1;3(4):253-66. [https://doi.org/10.1016/S2221-1691\(13\)60060-X](https://doi.org/10.1016/S2221-1691(13)60060-X)
- [52] Mendonça EA, Lira MC, Rabello MM, Cavalcanti IM, Galdino SL, Pitta IR, do Carmo A, Lima M, Pitta MG, Hernandez MZ, Santos-Magalhães NS. Enhanced antiproliferative

Disclaimer: This is not the final version of the article. Changes may occur when the manuscript is published in its final format.

activity of the new anticancer candidate LPSF/AC04 in cyclodextrin inclusion complexes encapsulated into liposomes. AAPS PharmSciTech. 2012 Dec;13:1355-66.

<https://doi.org/10.1208/s12249-012-9853-9>

[53] Mosaddik A, Ravinayagam V, Elanthikkal S, Fessi H, Badri W, Elaissari A. Development and use of polymeric nanoparticles for the encapsulation and administration of plant extracts. Natural Products as Source of Molecules with Therapeutic Potential: Research & Development, Challenges and Perspectives. 2018:391-463.

[54] Barupal AK, Gupta V, Ramteke S. Preparation and characterization of ethosomes for topical delivery of aceclofenac. Indian journal of pharmaceutical sciences. 2010 Sep;72(5):582. <https://doi.org/10.4103/0250-474X.78524>

[55] Morsi NM, Aboelwafa AA, Dawoud MH. Improved bioavailability of timolol maleate via transdermal transfersomal gel: Statistical optimization, characterization, and pharmacokinetic assessment. Journal of advanced research. 2016 Sep 1;7(5):691-701. <https://doi.org/10.1016/j.jare.2016.07.003>

[56] Zhong H, Deng Y, Wang X, Yang B. Multivesicular liposome formulation for the sustained delivery of breviscapine. International journal of pharmaceutics. 2005 Sep 14;301(1-2):15-24. <https://doi.org/10.1016/j>.

[57] Mei Z, Chen H, Weng T, Yang Y, Yang X. Solid lipid nanoparticle and microemulsion for topical delivery of triptolide. European journal of pharmaceutics and biopharmaceutics. 2003 Sep 1;56(2):189-96.

[58] Yen FL, Wu TH, Lin LT, Cham TM, Lin CC. Nanoparticles formulation of Cuscuta chinensis prevents acetaminophen-induced hepatotoxicity in rats. Food and chemical toxicology. 2008 May 1;46(5):1771-7. <https://doi.org/10.1016/j.fct.2008.01.021>

[59] Jain S, Jain S, Khare P, Gulbake A, Bansal D, Jain SK. Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. Drug delivery. 2010 Aug 1;17(6):443-51. <https://doi.org/10.3109/10717544.2010.483252>

[60] Kothamasu P, Kanumur H, Ravur N, Maddu C, Parasuramrajam R, Thangavel S. Nanocapsules: the weapons for novel drug delivery systems. BioImpacts: BI. 2012;2(2):71. <https://doi.org/10.5681/bi.2012.011>

[61] Liu M, Li H, Luo G, Liu Q, Wang Y. Pharmacokinetics and biodistribution of surface modification polymeric nanoparticles. Archives of pharmacal research. 2008 Apr;31:547-54. <https://doi.org/10.1007/s12272-001-1191-8>

Disclaimer: This is not the final version of the article. Changes may occur when the manuscript is published in its final format.

- [62] Min KH, Park K, Kim YS, Bae SM, Lee S, Jo HG, Park RW, Kim IS, Jeong SY, Kim K, Kwon IC. Hydrophobically modified glycol chitosan nanoparticles-encapsulated camptothecin enhance the drug stability and tumor targeting in cancer therapy. *Journal of Controlled Release*. 2008 May 8;127(3):208-18. <https://doi.org/10.1016/j.jconrel.2008.01.013>
- [63] Yanyu X, Yunmei S, Zhipeng C, Qineng P. The preparation of silybin-phospholipid complex and the study on its pharmacokinetics in rats. *International journal of pharmaceutics*. 2006 Jan 3;307(1):77-82. <https://doi.org/10.1016/j.ijpharm.2005.10.001>
- [64] Maiti K, Mukherjee K, Murugan V, Saha BP, Mukherjee PK. Exploring the effect of hesperetin-HSPC complex—a novel drug delivery system on the in vitro release, therapeutic efficacy and pharmacokinetics. *AAPS PharmSciTech*. 2009 Sep;10:943-50. <https://doi.org/10.1208/s12249-009-9282-6>
- [65]. Rai, V.K., Gupta, G.D., Potttoo, F.H., Barkat, M.A. (2020). Potential of Nano-Structured Drug Delivery System for Phytomedicine Delivery. In: Beg, S., Barkat, M., Ahmad, F. (eds) *Nanophytomedicine*. Springer, Singapore. https://doi.org/10.1007/978-981-15-4909-0_6
- [66] Zhao Y, Wang C, Chow AH, Ren K, Gong T, Zhang Z, Zheng Y. Self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil: formulation and bioavailability studies. *International journal of pharmaceutics*. 2010 Jan 4;383(1-2):170-7. <https://doi.org/10.1016/j.ijpharm.2009.08.035>
- [67] Mei Z, Chen H, Weng T, Yang Y, Yang X. Solid lipid nanoparticle and microemulsion for topical delivery of triptolide. *European journal of pharmaceutics and biopharmaceutics*. 2003 Sep 1;56(2):189-96.
- [68] Desai NM, Gilbert Stanley J, Murthy PS. Green coffee nanoparticles: Optimisation, in vitro bioactivity and bio-release property. *Journal of Microencapsulation*. 2020 Jan 2;37(1):52-64. doi: 10.1080/02652048.2019.1692946. Epub 2019 Nov 20. PMID: 31714160
- [69] Zheng Y, Hou SX, Chen T, Lu Y. Preparation and characterization of transfersomes of three drugs in vitro. *Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica*. 2006 May 1;31(9):728-31.
- [70] You J, Han X, Wang YS, Yang L, Yu YW, Li QP. Study of the preparation of sustained-release microspheres containing zedoary turmeric oil by the emulsion-solvent-diffusion method and evaluation of the self-emulsification and bioavailability of the oil. *Colloids and Surfaces B: Biointerfaces*. 2006 Mar 1;48(1):35-41. <https://doi.org/10.1016/j.colsurfb.2005.12.011>

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[71] Chao P, Deshmukh M, Kutscher HL, Gao D, Rajan SS, Hu P, Laskin DL, Stein S, Sinko PJ. Pulmonary targeting microparticulate camptothecin delivery system: anticancer evaluation in a rat orthotopic lung cancer model. *Anti-cancer drugs*. 2010 Jan 1;21(1):65-76. <https://doi.org/10.1097/CAD.0b013e328332a322>

[72] Di Costanzo A, Angelico R. Formulation strategies for enhancing the bioavailability of silymarin: the state of the art. *Molecules*. 2019 Jun 7;24(11):2155. <https://doi.org/10.3390/molecules24112155>

[73] Sabuj MZ, Islam N. Nanophytomedicine: An Effective Way for Improving Drug Delivery and Bioavailability of Herbal Medicines. *Nanophytomedicine: Concept to Clinic*. 2020:55-70

[74] Ke Z, Hou X, Jia XB. Design and optimization of self-nanoemulsifying drug delivery systems for improved bioavailability of cyclovirobuxine D. *Drug design, development and therapy*. 2016 Jun 28;2049-60. <https://doi.org/10.2147/dddt.s106356>

[75] Ma Y, Li H, Guan S. Enhancement of the oral bioavailability of breviscapine by nanoemulsions drug delivery system. *Drug development and industrial pharmacy*. 2015 Feb 1;41(2):177-82. <https://doi.org/10.3109/03639045.2014.947510>

[76] Barkat MA, Ahmad J, Khan MA, Beg S, Ahmad FJ. Insights into the targeting potential of thymoquinone for therapeutic intervention against triple-negative breast cancer. *Current Drug Targets*. 2018 Jan 1;19(1):70-80. <https://doi.org/10.2174/1389450118666170612095959>

[77] Wei H, Liu T, Jiang N, Zhou K, Yang K, Ning W, Yu Y. A novel delivery system of cyclovirobuxine D for brain targeting: Angiopep-conjugated polysorbate 80-coated liposomes via intranasal administration. *Journal of biomedical nanotechnology*. 2018 Jul 1;14(7):1252-62. <https://doi.org/10.1166/jbn.2018.2581>

[78] Harshita, Barkat MA, Rizwanullah M, Beg S, Potttoo FH, Siddiqui S, Ahmad FJ. Paclitaxel-loaded nanolipidic carriers with improved oral bioavailability and anticancer activity against human liver carcinoma. *AAPS PharmSciTech*. 2019 Jan 23;20(2):87. <https://doi.org/10.1208/s12249-019-1304-4>

[79] Rohilla R, Garg T, Goyal AK, Rath G. Herbal and polymeric approaches for liver-targeting drug delivery: novel strategies and their significance. *Drug delivery*. 2016 Jun 12;23(5):1645-61. <https://doi.org/10.3109/10717544.2014.945018>

[80] Wu H, Yu T, Tian Y, Wang Y, Zhao R, Mao S. Enhanced liver-targeting via coadministration of 10-Hydroxycamptothecin polymeric micelles with vinegar baked Radix

Bupleuri. Phytomedicine. 2018 May 15;44:1-8.

<https://doi.org/10.1016/j.phymed.2018.04.022>

[81] Bartneck M, Warzecha KT, Tacke F. Therapeutic targeting of liver inflammation and fibrosis by nanomedicine. *Hepatobiliary surgery and nutrition*. 2014 Dec;3(6):364.

<https://doi.org/10.3978/j.issn.2304-3881.2014.11.02>

[82] Bisht S, Khan MA, Bekhit M, Bai H, Cornish T, Mizuma M, Rudek MA, Zhao M, Maitra A, Ray B, Lahiri D. A polymeric nanoparticle formulation of curcumin (NanoCurc™) ameliorates CCl₄-induced hepatic injury and fibrosis through reduction of pro-inflammatory cytokines and stellate cell activation. *Laboratory Investigation*. 2011 Sep 1;91(9):1383-95.

<https://doi.org/10.1038/labinvest.2011.86>

[83] Mandal AK, Das S, Basu MK, Chakrabarti RN, Das N. Hepatoprotective activity of liposomal flavonoid against arsenite-induced liver fibrosis. *Journal of Pharmacology and Experimental Therapeutics*. 2007 Mar 1;320(3):994-1001.

<https://doi.org/10.1124/jpet.106.114215>

[84] Yamashita S, Katsumi H, Sakane T, Yamamoto A. Bone-targeting dendrimer for the delivery of methotrexate and treatment of bone metastasis. *Journal of drug targeting*. 2018 Oct 21;26(9):818-28. <https://doi.org/10.1080/1061186X.2018.1434659>

[85] Chen S, Zheng L, Zhang J, Wu H, Wang N, Tong W, Xu J, Huang L, Zhang Y, Yang Z, Lin G. A novel bone targeting delivery system carrying phytomolecule icaritin for prevention of steroid-associated osteonecrosis in rats. *Bone*. 2018 Jan 1;106:52-60.

<https://doi.org/10.1016/j.bone.2017.09.011>

[86] Hsu CY, Yang SC, Sung CT, Weng YH, Fang JY (2017) Anti-MRSA malleable liposomes carrying chloramphenicol for ameliorating hair follicle targeting. *Int J Nanomedicine* 12:8227–8238. <https://doi.org/10.2147/ijn.s147226>

[87] Tubesha Z, Imam MU, Mahmud R, Ismail M. Study on the potential toxicity of a thymoquinone-rich fraction nanoemulsion in Sprague Dawley rats. *Molecules*. 2013 Jun 26;18(7):7460-72. <https://doi.org/10.3390/molecules18077460>

[88] Wu Y, Sun L, Zeng F, Wu S. A conjugated-polymer-based ratiometric nanoprobe for evaluating in-vivo hepatotoxicity induced by herbal medicine via MSOT imaging. *Photoacoustics*. 2019 Mar 1;13:6-17. <https://doi.org/10.1016/j.pacs.2018.11.002>

[89] Potttoo FH, Barkat MA, Ansari MA, Javed MN, Jamal QM, Kamal MA. Nanotechnological based miRNA intervention in the therapeutic management of

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neuroblastoma. In *Seminars in cancer biology* 2021 Feb 1 (Vol. 69, pp. 100-108). Academic Press.

<https://doi.org/10.1016/j.semcancer.2019.09.017>

[90] Zhang M, Viennois E, Xu C, Merlin D. Plant derived edible nanoparticles as a new therapeutic approach against diseases. *Tissue barriers*. 2016 Apr 2;4(2):e1134415. <https://doi.org/10.1080/21688370.2015.1134415>

[91] Ju S, Mu J, Dokland T, Zhuang X, Wang Q, Jiang H, Xiang X, Deng ZB, Wang B, Zhang L, Roth M. Grape exosome-like nanoparticles induce intestinal stem cells and protect mice from DSS-induced colitis. *Molecular Therapy*. 2013 Jul 1;21(7):1345-57. <https://doi.org/10.1038/mt.2013.64>

[92] Ahmed S, Ahmad M, Swami BL, Ikram S. Green synthesis of silver nanoparticles using *Azadirachta indica* aqueous leaf extract. *Journal of radiation research and applied sciences*. 2016 Jan 1;9(1):1-7. <https://doi.org/10.1016/j.jrras.2015.06.006>

[93] Mishra S, Sharma S, Javed MN, Pottoo FH, Barkat MA, Alam MS, Amir M, Sarafroz M. Bioinspired nanocomposites: applications in disease diagnosis and treatment. *Pharmaceutical nanotechnology*. 2019 Jun 1;7(3):206-19. <https://doi.org/10.2174/221173850766619042512150951>.

[94] Sharma S, Javed MN, Pottoo FH, Rabbani SA, Barkat MA, Sarafroz M, Amir M. Bioresponse inspired nanomaterials for targeted drug and gene delivery. *Pharmaceutical nanotechnology*. 2019 Jun 1;7(3):220-33. doi: 10.2174/2211738507666190429103814.

[95] Khan M, Shaik MR, Adil SF, Khan ST, Al-Warthan A, Siddiqui MR, Tahir MN, Tremel W. Plant extracts as green reductants for the synthesis of silver nanoparticles: Lessons from chemical synthesis. *Dalton Transactions*. 2018;47(35):11988-2010. <https://doi.org/10.1039/c8dt01152d>

[96] Qing YA, Cheng L, Li R, Liu G, Zhang Y, Tang X, Wang J, Liu H, Qin Y. Potential antibacterial mechanism of silver nanoparticles and the optimization of orthopedic implants by advanced modification technologies. *International journal of nanomedicine*. 2018 Jun 5;3311-27. <https://doi.org/10.2147/IJN.S165125>

[97] Barkat MA, Beg S, Naim M, Pottoo FH, Singh SP, Ahmad FJ. Current progress in synthesis, characterization and applications of silver nanoparticles: precepts and prospects. *Recent Patents on Anti-Infective Drug Discovery*. 2018 Apr 1;13(1):53-69. <https://doi.org/10.2174/1574891X12666171006102833>