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Nanoencapsulation of Herbal Extracts for Enhanced Bioavailability

Dr. Rohit Srivastava[1*]

[1]St. Andrew's College. Gorakhpur. 273001. U. P

***Corresponding Author E-mail: srivastav.rohit24@gmail.com**

ABSTRACT

Nanoencapsulation is a revolutionary approach to enhancing the therapeutic performance of herbal extracts by addressing some of their major weaknesses, such as poor solubility, low stability, and low bioavailability. This review underscores the promise of different nanocarrier systems in enhancing the pharmacokinetic and pharmacodynamic properties of phytochemicals, e.g. curcumin, quercetin and resveratrol, i.e. polymeric nanoparticles, liposomes, solid-lipid nanoparticles (SLNs), and nanostructured-lipid carriers (NLCs). In preclinical experiments, there has been a remarkable advancement in selective delivery and organ-selective performance, as well as decreased toxicity, particularly in neurodegenerative, hepatic, metabolic, and inflammatory diseases. Despite improvements in studies, long-term safety, immunogenicity, and clinical translation issues persist. The review also indicates the necessity to develop universal nano formulation guidelines, toxicity testing, and clinical trials meant to help obtain regulatory approval and commercialisation. A combination of nanotechnology and herbal medicine creates potential applications for safer, effective, and user-friendly medicines.

Key Words:

Nanoencapsulation, Herbal Extracts, Bioavailability, Nanocarriers, Phytochemicals, Preclinical Studies, Targeted Delivery, Pharmacokinetics.

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1. INTRODUCTION

The practice of using herbal medicine has cut across cultures globally over a course of centuries with the provision of therapeutic sustainability in the form of bioactive plant-derived compounds. However, being potentially promising, many herbal extracts are highly challenged in terms of poor solubility, poor permeability, a lack of stability in the physiological environment, and low bioavailability when these substances are used in case of a conventional delivery route[1]. Such pharmacokinetic restrictions inhibit uniform therapeutic effectiveness of the herbal medicines where greater amounts of medications are usually necessary or more applications are required to realize the wanted impacts. The lack of these functionalities is being overcome increasingly by

modern drug delivery technologies, more specifically the use of nanotechnology in drug delivery methodologies, which aim at enhancing efficacy of herbal formulations.

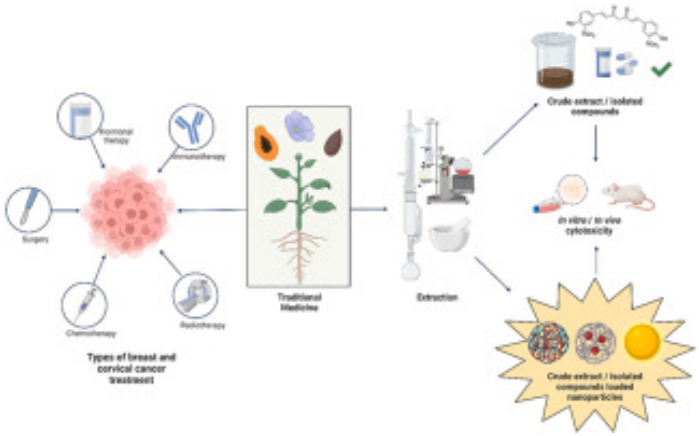

Figure 1: Traditional Medicine and Nanotechnology in Cancer Therapy[2]

Nano encapsulation has come out as a potential method to improve delivery and bioavailability of herbal extracts. Trapping the bioactive compounds in nanocarriers: Inclusion of bioactive compounds in nanocarriers, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, and nanoemulsions has allowed researchers to shield the active substances against degradation, achieve a sustained release, and allow targeted activation of particular tissues or cells. Besides enhancing pharmacological profile of herbal compounds, this technology will create new opportunities in developing safer, more effective and patient-friendly natural therapies. With the advancements in the research in this area, researchers are very much likely to change the face of herbal medicine by combining the conventional wisdom about herbs with contemporary development in the field of pharmaceuticals through nano encapsulation.

1.1.Background Information and Context

The therapeutic potential of herbal medicines has been acknowledged long enough due to the existence of a multitude of bioactive phytochemicals. Nevertheless, limited clinical usefulness of various herbal extracts is most often defined by lack of water solubility, high metabolic rate, low permeability and unstable nature in the gastrointestinal tract. These increase the rates of low bioavailability and variable therapy effect. Nanotechnology has made this possible and innovative drug delivery systems are coming up to address these shortcomings and enhance the pharmacokinetics of herbal bioactives. One possible solution to this problem is nanoencapsulation i.e. herbal compounds embedded in nanocarriers which helps protect the active ingredient, augment the absorption and also to certify its bioavailability.

1.2.Objectives of the Review

This review explores how nanoencapsulation improves the delivery and effectiveness of herbal extracts.

1. To identify limitations of conventional herbal formulations.

2. To highlight preclinical findings on nanoencapsulated herbal compounds.
3. To summarize key nanocarrier types and their applications.
4. To explain mechanisms enhancing bioavailability through nanoencapsulation.
5. To assess safety and biocompatibility in animal models.

1.3.Importance of the Topic

The use of nanotechnology and herbal medicine is a transition to the further promotion of the effectiveness and safety of plant-based treatment. The aim to optimize the provision of herbal compounds has become a priority area, given that the world has shifted toward natural and holistic healthcare. Besides increasing herbal extracts pharmacological capacity, nanoencapsulation also leads to patient compliance with the benefit of controlled release and selective effect. This issue, therefore, is tremendously vital to the researchers, clinicians, and the pharmaceutical sector because it offers secure, efficient, and soundly justified herbal medicines[3].

2. PRECLINICAL EVALUATION OF NANOENCAPSULATED HERBAL COMPOUNDS: KEY FINDINGS AND METHODOLOGICAL INSIGHTS

Herbal encapsulation has been one of the strategies identified as a means to increase solubility, stability, bioavailability, and targeted delivery of the phytochemicals and preclinical studies shown improved pharmacokinetics, therapeutic efficacy, and the ability to use lower doses with reduced dosing frequency in animals. Major techniques are sophisticated formulation procedures (e.g. solvent evaporation, high- pressure homogenization), elaborate characterization (DLS, TEM, zeta potential) and in-vivo experiments measuring pharmacokinetics, tissue distribution, efficacy and safety. Nonetheless, there still exist some disadvantages to these strengths such as species specificity, limited formulation stability/consistency, poor long-term toxicity data and significant regulatory and manufacturing barriers to clinical translation and commercialization[4].

2.1.Key Research Studies and Methodologies

Nanoencapsulation of herbal compounds has been attracting much interest as a revolutionary way to overcome significant pharmacological concerns concerning the traditional herbal medicine, i.e., low solubility, low stability, low bioavailability, and lack of predictability in the therapeutic effects. Many experiment studies nearly on rodent models had given good evidence on the use of nanocarrier systems to improve the pharmacokinetics and pharmacodynamics of herbal phytochemicals. Such experiments do not only support the capability of nanoencapsulation to improve drug delivery but also confirm its potential to increase the efficacy of a therapy in various disease models.

- **Curcumin (Curcuma longa)**

A Curcumin is a polyphenolic agent composed of turmeric which has shown strong anti-inflammatory and antioxidant effects but has had very poor orally bioavailability because it is hydrophobic, quickly metabolized and eliminated systemically. Researchers have also used solid lipid nanoparticle (SLN) to deliver curcumin in order to surmount these obstacles. In the single

case study of Wistar rats with collagen-induced arthritis, curcumin-SLN-based formulations put an enormous reduction in the levels of the inflammatory cytokines (TNF-alpha, IL-1beta), and paw edema than that of free curcumin. The nanoformulation facilitated a long circulation lifetime, enhanced tissue adjuvants and controlled drug release, which enhanced the complete ant-arthritic effect and lowered systemic toxicity.

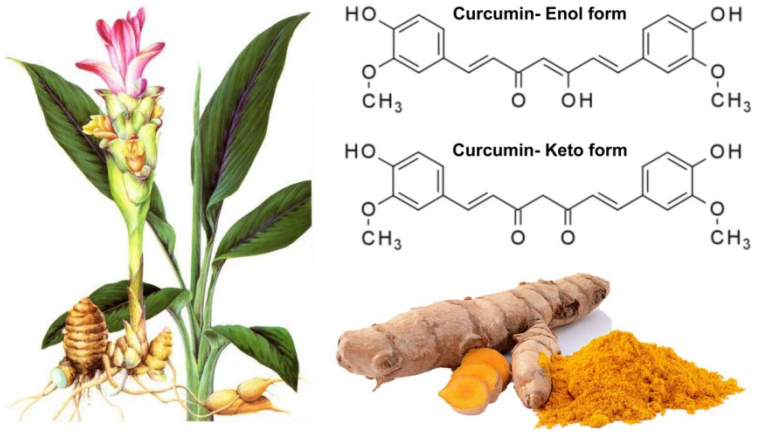

Figure 2: Curcumin Forms and Source from Turmeric Plant[5]

Quercetin

A common neuroprotective and anti-inflammatory flavonoid, quercetin, has poor permeability through the blood-brain barrier (BBB) when expected. To overcome this, reports have explored the use of polymeric nanoparticle using biocompatible and biodegradable materials such as PLGA and chitosan. Quercetin encapsulated nanoparticles were found to exhibit much greater penetration to the brain in the mouse models of AD and reduced oxidative stress parameters (like MDA and ROS) as well as cell apoptosis. Cognition was also measured by means of behavioral tests (Morris water maze and Y-maze) and improvement was noted, suggesting that delivery by nanoparticles improves both pharmacological and behavioral efficacies.

Resveratrol

Resveratrol works as a powerful antioxidant with anti-aging properties and cardioprotective properties and is debilitated by the fact it has a low-plasma half-life and furthermore a low resistance to metabolism. Its therapeutic profile has been demonstrated to become improved through encapsulation in nanostructured lipid carriers (NLCs). NLC-formulated resveratrol caused a higher systemic retention and superoxide dismutase (SOD), Catalase (CAT) and glutathione (GSH) concentration, and a significant reduction of lipid peroxidation concentration in experiments with Sprague-Dawley rats. NLC system gave a prolonged release curve and was useful in keeping the therapeutic concentration in plasma and decreased the number of administrations needed[6].

Berberine and Other Phytoconstituents

Berberine, an isoquinoline alkaloid with hypoglycemic and hypolipidemic effect, derived by plant, has been nanoformulated as polymeric micelles carriers and nanoemulsions. In diabetic rat model,

nanocarriers loaded with berberine attenuated fasting blood glucose and enhanced insulin sensitivity and lipid profiles better than non-encapsulated berberine. EGCG (epigallocatechin gallate) and andrographolide were also shown to have an increased anticancer, hepatoprotective and anti-inflammatory effect when administrated through nanoencapsulation. These additions are mainly due to increased solubility, cell uptake, and topical loading of the active contents.

2.2.Methodologies

Herbal delivery in nanoparticles Nanoparticle based herbal delivery shows custom formulation, characterization (size, charge, morphology) and in vivo protocols to evaluate drug kinetics, biodistribution, therapeutic activities and safety. The measures guarantee an increased bioavailability, specific delivery, and low toxicity in preclinical models.

1. Formulation of Nanoparticles

The process of nanoparticles design to deliver herbal extracts consists of the choice of fabrication methods in regards to the intended nanocarriers type and the physicochemical characteristics of the bioactive component. Nanoparticles Solvent evaporation Polymer-based nanoparticle drug materials are typically dissolved in an organic volatile solvent, emulsified and then remove under low-pressure conditions. When it comes to the lipid-based nanoparticles e.g., Solid Lipid Nanoparticles (SLNs) with Nanostructured Lipid Carriers (NLCs), high-pressure homogenization or ultrasonication-dependent processes allow the production of uniform particle sizes and the increase of encapsulation efficiency. Hybrid nanocarriers involve the use of emulsification-solvent diffusion where lipid and polymer matrices have been used to enhance the stability and regulating drug release. Prevention of aggregation and promoting colloidal stability of the nanoparticle is often achieved by the addition of stabilizers such as Tween 80 or polyvinyl alcohol (PVA) or lecithin.

2. Characterization of Nanoparticles

Nanoparticles suffer thorough characterization following their formulation so as to assess the physicochemical characteristics. The average particles size (usually in 50-300 nm), polydispersity index (PDI) and uniformity of the particles are measured by dynamic Light Scattering (DLS). Surface charge is determined by Zeta potential analysis and colloids with a surface charge of over 30 + mV or -30 mV are said to be well stated. The most important parameters to be measured on the basis of their therapeutic potential are the encapsulation efficiency (EE%) and drug loading capacity that are usually measured via UV-Vis spectroscopy or high-performance liquid chromatography (HPLC). Morphological properties e.g. size and surface texture can be viewed through a Transmission Electron Microscope (TEM) or a Scanning Electron Microscope (SEM) as may indicate evidence of agglomeration[7].

3. In Vivo Administration Protocols

In order to assess pharmacological efficacy of nano formulated herbal extracts in vivo administration procedures are adopted with suitable animal models. The popularly used species are the Wistar rat, BALB/c mouse and sprague-Dawley rats because of their predictable biological responses. Oral is the most desired delivery method because it is highly conducive to the intake of

drugs in a human way, however intravenous and intraperitoneal administrations are also applied whenever the systematical fast reaction or the local introduction of drug is needed. Comparative analysis is developed through the construction of the control groups, usually consisting of control (untreated) and the one treated with a free (non-encapsulated) compound in order to evaluate the extra value that nanoencapsulation adds to the mixture.

4. Pharmacokinetic and Biodistribution Studies

The pharmacokinetic characterization of nanoparticles formulations and biodistribution studies are critical in determining the in vivo behavior of nanoparticle formulations. Techniques such as liquid chromatography-tandem mass spectrometry (LC-MS/MS) are used to quantify the levels of drugs in the plasma to give the pharmacokinetic parameters that include the maximum concentration (Cmax), the time taken to reach maximum concentration (Tmax), the area under the plasma concentration-time curve (AUC) as well as the half-life (T12). In order to study the tissue distribution, the most important of the organs that is administered has to be harvested following administration such as liver, kidney, brain and spleen so that researchers can determine the extent and pattern of nanoparticle across the various biological compartments with respect to the degree of accumulation and clearance of the same[8].

5. Therapeutic Efficacy and Toxicity Evaluation

The nanoencapsulated herbal extracts are evaluated regarding their effectiveness and the safety of therapy; both histologically and biochemically. Histopathology which can be performed by Hematoxylin and Eosin (H&E) stain or immunohistochemistry is used to assist in the detection of tissue damage, inflammation and changes. Oxidative stress, inflammation, and organ functionality are detected as markers in a biochemical analysis of ALT, AST, malondialdehyde (MDA), interleukin-6 (IL-6), and superoxide dismutase (SOD). Behavioral tests through the Morris Water Maze, Open Field Test and the Rotorod Test are a measure in the determination of cognitive functionality and motor coordination, which will bring understanding as to the functional gains that the nano formulations may be offering in neuroprotective studies.

2.3. Strengths and Weaknesses

- **Strengths**

Some of the advantages of nanoencapsulation in the delivery of herbal compounds are reported. Among the main advantages is an improvement in pharmacokinetics: nanoformulations remarkably augment the solubility, stability, and bioavailability of poorly water-soluble phytochemicals hence increasing their therapeutic capabilities. Targeted delivery and temporal control of nanoparticles offer the possibilities to localize nanoparticles in the targeted organs and reduce systemic side-effects: this is valuable in the management of localized or chronic within physical conditions. These are long-acting characteristics that enhance patient compliance as it minimizes the number of doses it would take a patient to complete a treatment regimen and hence it can be used to treat diseases on a long-term basis. Also, they have been shown to have good efficacy and safety based on preclinical validation in an extended animal model anticipating that good outcomes will occur in human clinical trials[9].

- **Weaknesses**

Nanoencapsulated herbal formulations have a number of limitations in spite of their potential. Species-specific responses are one of the most important issues, as due to the differences in physiology and metabolism of animal models and humans, preclinical findings are often far more difficult to translate into humans directly. Moreover, there is formulation variability, whereby modifications in particle size, use of surfactants and encapsulation will result in different outcomes, making it harder to replicate and compare the studies. The second significant issue is that there is a lack of chronic information, especially concerning chronic toxicity, organ accumulation of nanoparticles, and immunogenic response, which are underresearched and dose not allow continuation of clinical studies. Finally, there are manufacturing and inspection obstacles that impede large implementation. The scale, up of laboratory nanoformulations into Good Manufacturing Practice (GMP) compliant production is technically challenging and expensive. In addition, the fact that herbal nanomedicines are considered both pharmaceutical and botanical product requires more vigilance and adherence further skewing the regulatory approval process.

3. MECHANISTIC INSIGHTS AND ORGAN-SPECIFIC APPLICATIONS OF HERBAL NANOCARRIERS

3.1.Nanocarrier Types and Applications

Nanoencapsulation approaches in herbal medicine exploit broad spectrum of nanocarriers systems optimally suited to enhance pharmacological activity of bioactive plant components. These nanocarriers have different physicochemical properties as well as their structural configurations, and affect the key aspects like improvement of the solubility, enzymatic protection, regulated release, and tissue-specific targeting. The engineering of a suitable nanocarrier plays a sole role in enhancing the therapeutic index of herbal compounds which are generally characterized by low water solubility, short half-life, and low absorption rates.[10].

- Polymeric nanoparticles**:** Polymers are mostly used as nanoparticle especially those involving biocompatible and biodegradable such as poly(lactic-co-glycolic acid) (PLGA), chitosan, polylactic acid (PLA), and polyethylene glycol (PEG). These polymers have been known to have controlled and sustained drug release properties alike. These particles can be made invisible to the immune system or to target particular tissues by surface engineering, e.g. PEGylation. As an example, quercetin-loaded PLGA nanoparticles demonstrated the capacity to penetrate blood-brain barrier (BBB) and increase neuroprotection in models of Alzheimer disease by restoring cognitive behavior and decreasing the build-up of amyloid-beta plaques. On the same note, the use of chitosan nanoparticles has been able to increase mucosal uptake owing to its mucoadhesive and cationic properties hence should be used to restore intranasal delivery of herbal antivirals and anti-inflammatory agents.

- Solid lipid nanoparticles (SLNs): Solid lipid nanoparticles (SLNs) are also composed of solid lipids: glyceryl behenate or stearic acid that are stabilized within a surfactant. They

have a number of strengths such as good biocompatibility, physical stability of the drug delivery system as well as the capacity to entrap both hydrophilic and lipophilic drugs. All of liposomal nanoparticles (SLNs) offer a protective encapsulation to labile herbal components and fit well in oral and topical products. As a case in point, curcumin encapsulated SLNs have been of great benefit in ameliorating anti-inflammatory effects in arthritis models whereas Berberine containing SLNs have been of significant benefit in improving glycemic control and insulin sensitivity in diabetic rat models[11].

- Liposomes: Liposomes which are vesicles that are composed of phospholipid bilayers have developed prominence because they can encapsulate a large range of herbal compounds. They are biomimetic in nature and have high biocompatibility, thus, can be used to passively and actively target. It has been reported that administration of ginseng-loaded liposomes significantly improves immune response as lymphocyte proliferation and cytokine secretion increased whereas EGCG (epigallocatechin gallate)-loaded liposomes showed greater anticancer effect with increased cellular internalization and cytotoxic effect on cancer cells.

- Nanostructured lipid carriers (NLCs): A second generation of lipid nanoparticle nanostructured lipid carriers (NLCs) comprises a mixture of solid and liquid lipids. Such a hybrid structure enables the loading process to be high as well as stable with less drug expulsion and offering extended release. NLCs loaded with resveratrol have demonstrated to lessen the oxidative stress condition through increasing the antioxidant enzyme levels in the lactate-induced liver injury model, and andrographolide-loaded NLC suspensions have improved oral availability as well as demonstrated to confer significant hepatoprotective properties on rat against increasing hepatic enzymes in the chemically-induced hepatotoxicity models.

3.2.Bioavailability Enhancement Mechanisms

The low therapeutic characteristics of herbal compounds have been attributed to low bioactivity of most herbal drugs, which is attributed to various physiological and physicochemical obstacles that include, low aqueous solubility, biological degradation mediated by biological enzymes within the gastrointestinal tract, low permeability through biological membranes and high first-pass metabolism to the liver. Nanoencapsulation provides a complex answer to this dilemma through modifications of the pharmacokinetic behavior of the herbs constituents by a number of synergistic actions that improve the stability, absorption, and systemic availability of the constituents[12].

1. **Protection from Gastrointestinal and Hepatic Degradation:** Numerous bioactive phytochemicals such as; curcumin, resveratrol, and epigallocatechin-gallate (EGCG), have low chemical stability under acidic gastric conditions and they have high vulnerability to enzyme reactions and their hepatic conversion. Nanocarriers fulfil this protective activity through incorporation of these labile compounds into polymeric or lipidic matrices to effectively protect them in rigorous pH environments, digestative

enzymes, and oxidative stress. This protective complexation helps avoid premature biodegradation in the stomach and intestines, hence the increase in the proportion of the active compound entering the system, as well as the extension of its biological half-life.

2. **Enhanced Solubility and Dissolution Rate:** Nanoencapsulation has a great effect of enhancing hydrophobic herbal molecules solubility and dissolution behavior. When the size of the particle is decreased to nanometer scale, its surface area to volume ratio is significantly increased which improves its interaction with the gastrointestinal fluids with the encapsulated compound. This is particularly advantageous to lipophilic herbal actives including silymarin, boswellic acid, and resveratrol which generally exhibit poor dissolution rates as it is processed. These compounds are fast-dissolved and evenly dispersed when made as nanosuspensions or within lipid-based vehicles; they are more absorbed through the intestinal epithelium than those that do not use nanosuspensions or within lipid-based vehicles.

3. **Improved Gastrointestinal Absorption:** Nanosized carriers may promote intestinal absorption in a number of ways. Mucoadhesive nanoparticles, especially of the chitosan and other cationic polymers, attach into the intestinal mucosa and stay at the sites of absorption longer. This prolongs sojourn of time here and improves transportation of the drug over the epithelium. others of the nanocarriers can also transiently disrupt tight junctions among epithelial cells, facilitating paracellular passage of otherwise poorly permeable phytochemicals flavonoids, alkaloids, glycosides. Also, nanoparticles find favorable environment in the tiny size enabling them to be more easily taken into the body through endocytosis or transcytosis across enterocytes.

4. **Lymphatic Uptake:** Solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and self-emulsifying drug delivery systems (SEDDS) are lipid-based nanocarriers, which could improve the absorbability of lipophilic herbal compounds to the lymph system through the lymphatic transport. They are absorbed preferentially by intestinal M cells in Peyer patches of lymphoid tissue in the gut, thus avoiding circulation to the portal and hepatic elimination of the nanocarrier by the liver. The alternative route increases systemic bioavailability of compounds such as andrographolide, boswellic acid and other terpenoids and steroids with poor water solubility; hence, lymphatic absorption is of special benefit when it comes to sustained release with chronic diseases[13].

5. **PEGylation for Extended Circulation:** PEGylation, a process by which nanoparticles are rendered non-immunogenic and have a non-opsonizable surface (having been modified by polyethylene glycol (PEG)), is another general result of surface functionalization. PEGylated nanocarriers avoid fast excretion in the blood resulting in a long systemic half-life and kinetics. This has particular advantage when used in treatments involving long duration of drug exposure in circulating systems like

cancer or central nervous system (CNS) targeting. The process also improves the entry and transport of drugs in the biological barriers such as blood-brain barrier (BBB), promoting the effective pharmacological effect of neuroactive herbal components through increased penetrating capacity.

3.3.Target Organ Delivery and Efficacy

Advanced nanocarrier-based technologies have transformed herbal therapeutics delivery to provide site-specific targeting, and, thus, it improves therapeutic efficacy and minimizes systemic toxicity and off-target effects[14]. This specificity can be realized by building nanoparticles that only react under certain physiological (e.g. pH gradients) or pathological (e.g. overexpressed enzymes) signals in the diseased tissue. Nanoformulations will deliver therapeutic agents in diseased tissue either through passive targeting (e.g. enhanced permeability and retention effect) or active (e.g. ligand-receptor interaction) thereby accomplishing better clinical outcome and reducing the dosage needed.

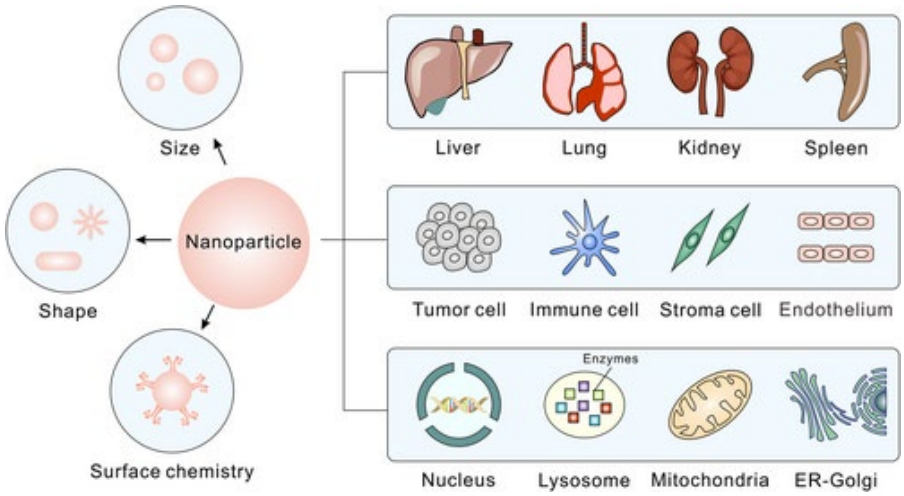

Figure 3: Influence of Nanoparticle Properties on Biological Targeting and Cellular Uptake[15]

- **Brain**

The brain poses a great challenge to drug delivery because of the existence of blood-brain barrier (BBB), a highly controlled endothelial layer which undergoes controlled paracellular Rather than binding to most therapeutic molecules. Nanocarriers have come out as very strong means to break this barrier. As an example, quercetin-loaded nanoparticles based on PLGA are allowed to penetrate the BBB through receptor-mediated transcytosis increasing their bioavailability in the brain. This selective delivery showed a decrease in the oxidative stress and build up of amyloid plaques in disease models of Alzheimer and neuroprotective effects were achieved. On the same note, solid lipid nanoparticle (SLN) formulations with curcumin inhibited neuroinflammation, stimulated antioxidant defense, and augmented memory retention in models of Parkinson and Alzheimer disease, and, therefore, demonstrated the ability of nanoencapsulation to elicit CNS delivery and effect in models of Parkinson and Alzheimer disease[16].

- **Liver**

They are useful in the targeted hepatic delivery of chronic diseases, including hepatitis, liver fibrosis, and non-alcohol fatty liver disease (NAFLD). Nanocarriers may be built to harness the particular vasculature and the reticuloendothelial route of uptake within the liver. Another example is the black seeds, which have been demonstrated to affect the liver tissue preferentially by accumulation of silymarin nanoparticles that are known to mitigate the CCl 4 induced hepatotoxicity in a manner that decreases lipid peroxidation, inflammatory cytokines, and fibrosis profilers. Similarly, berberine-loaded nanostructured lipid carriers (NLCs) showed good reversal of hepatic steatosis, recovery of lipids and normalization of liver blood and serum values (ALT, AST) in a NAFLD model pointing to the increased therapeutic efficacy of nanoencapsulated herbal-based extracts as protective and regenerative agents of the liver.

- **Skin**

The skin is an easily accessible organ and an apt target to which the application of nanoencapsulated herbian actives can be delivered topically, in the treatment of wound healing, inflammation and antimicrobial protection. The Aloe vera nanoemulsions have been shown to have a faster effect with regard to wound healing, augmented re-epithelialisation as well as more collagen production and angiogenesis on preclinical models. They are explained by enhanced penetration of the skin and length of action at the wound site of the bioactives. Such efficacy can also be found in topically delivered curcumin-loaded liposomal, which alters the wound microenvironment by decreasing pro-inflammatory cytokines (IL-6, TNF-a), reactive oxygen scavengers, and inducing tissue repair and remodelling[17].

- **Other Organs**

The inhalable nanocarriindices containing herbal bronchodilator compounds and anti-inflammatory compounds such as glycyrrhizin, eugenol or thymol had promising outcomes in pulmonary applications to treat respiratory diseases like asthma, bronchitis and chronic obstructive pulmonary disease (COPD). These nanoformulations have a better alveolar deposition, increase mucociliary clearance, and minimized airway inflammation that requires little systemic exposure.

Nanoparticles that can deliver antioxidant phytoconstituents (e.g. apigenin or naringenin) in kidney have been found to have beneficial effects to nephrotoxicity models, particularly cisplatin-induced kidney toxicity. Such nanoparticles accumulate in the kidney tissues, which reverses oxidative shortages, redistribute antioxidant enzymes, and maintain indicators of kidney health, including creatinine and blood urea nitrogen (BUN)[18].

4. TOXICOLOGICAL ASSESSMENT AND BIOCOMPATIBILITY IN ANIMAL MODELS

The important piece in preclinical evaluation of nanoencapsulated herbal products is toxicological evaluation. Herbal bioactives are natural compounds, thus they can also be toxic when presented at high doses or in different forms in nanocarrier. Thus long term in vivo studies to determine

safety, tolerability, and dose related effects of nanoformulated herbal compounds are highly necessary. In animal models, especially the rodents, parameters like acute and sub-chronic toxicity, the organ-specific toxicity, hematological alteration, and biochemical markers of the liver and kidney functions, are largely utilized[19].

The biocompatibility of the carrier system, namely the nanocarrier itself, is not only one of the major issues when developing nanoformulations. Material employed in making the nanoparticle, including PLGA, chitosan, lipid matrices, and PEG, needs to be non-toxic, not immunogenic, which can be metabolized or cleared without any unfavorable implications20. Studies on the behaviour of these materials in biological systems (their degradation profile, their interactions with immune cells) are made by the use of animal studies. Some vital organs (e.g., liver, kidneys, spleen, lungs, and brain) are analyzed histopathologically after the administration to ascertain that there is no structural or inflammatory changes that occur because of the nanocarrier.

Repeated dose toxicity studies provide a basis on dose optimization and safety margin through animal models. The studies assist in determination of the No Observed Adverse Effect Level and Lowest Observed Adverse Effect Level of each nanoformulated herbal compounds21. Clinical biochemistry along with behavioral alterations, food and water consumption, body weight and survival are observed on the way to certainty of systemic safety. As one could provide an example of curcumin-loaded SLNs, which were proven to exhibit a good safety record in rats and mice, with minimal changes in liver enzymes, hematological values, or histologic organizations even at a high dose, or as in the case of curcumin-loaded SLNs and quercetin-loaded polymeric nanoparticles, which were reported to exhibit good safety profiles in rats and mice, with no significant changes in liver enzymes, hematologic parameter or histologic structures even at high doses[22].

Immunotoxicity and oxidative stress assessments are very essential to the interpretation of long term effects. Oxidative damage can be the result of some nanocarriers activating immune cells, or forming reactive oxygen species (ROS). Thus, cytokine concentration, antioxidant enzyme activity (such as SOD, CAT and GPx), and inflammatory factors (such as TNF-a and Il-6) are applied in the in vivo assays used in toxicological studies. Altogether, there is invaluable information on the safety, systemic distribution, and tolerability of nanoencapsulated herbal products that animal model studies can offer and take towards clinical translation along with reduction in the risk that nanomedicine treatment may cause.

Table 1: Key Studies on Nanoencapsulation for Bioavailability[23]

Author(s)	Study	Focus Area	Methodologies	Key Findings
Pateiro et al. (2021)[24]	Nanoencapsulation of bioactive compounds in food products	Food systems, nanoencapsulation, bioavailability	Literature review on food-based nanotechnology applications	Nanoencapsulation enhanced stability, absorption, and improved sensory and visual qualities of food products.

Rashwan et al. (2023)[25]	Micro-/nano-encapsulation of anthocyanins	Anthocyanins, stability, bioavailability	Comparative analysis of encapsulation systems: lipid-, protein-, and polysaccharide-based systems	Encapsulation protected anthocyanins from degradation and improved stability and bioavailability in food and pharma applications.
Rosales & Fabi (2023)[26]	Pectin-based nanoencapsulation for bioactive compounds	Polysaccharide-based nanocarriers, biocompatibility	Review of nanoformulation strategies using pectin as a delivery vehicle	Pectin effectively encapsulated hydrophilic and hydrophobic compounds; suitable for targeted delivery due to its natural and biodegradable properties.
Roshanpour et al. (2021)[27]	Antioxidant enhancement of Mentha piperita phenolics via nanoencapsulation	Herbal antioxidants, phenolic compounds	Experimental encapsulation and antioxidant activity analysis	Encapsulation improved antioxidant efficiency and protected phenolics from environmental damage, validating its therapeutic enhancement potential.
Sabuj & Islam (2020)[28]	Application of nanophytomedicine for herbal drug delivery	Herbal medicines, nanocarriers, drug delivery	Review of nanocarrier types including liposomes, SLNs, and nanoemulsions	Nanotechnology improved delivery and pharmacokinetics of herbal drugs, offering promise for clinical application of traditional remedies.

5. DISCUSSION

Nanoencapsulation enhances bioavailability and targeting promising herbal extracts in preclinical studies to improve the delivery and effectiveness of the given extract. It promotes safer, more expedient therapies that are not clinically proven and fail to provide safety data in the long term. The possible future studies ought to be based on standardization, toxicological studies, and clinical trials in humans.

5.1.Interpretation and Analysis of Findings

The preclinical evidence given shows that nanoencapsulation process greatly enhances the solubility, stability, absorption and therapeutic effectiveness of herbal extracts. The classes of formulations including polymeric nanoparticles, SLNs, NLCs and liposomes have been used effectively to improve the pharmacokinetic characteristics of some poorly bioavailable phytochemicals including curcumin, quercetin, and resveratrol29. These have borne fruits towards improved outcomes of the diseases in animals where inflammations, oxidative stress, and organ toxicity have further declined. Moreover, the capacity to overcome biological barriers (e.g. BBB)

and provide delivery in a controlled (or targeted) manner is an important step in the development of herbal drugs.

5.2.Implications and Significance

Nanotechnology being injected in herbal medicine has the transformative capacity in preventing and curative medicine. Nanoencapsulation acts by enhancing the stability and strength of natural ingredients thus mitigating the difference existing between natural and pharmacological norms. Such progression facilitates the further innovation of more efficient, safer, and patient-concordant natural formulations with a view of them being accepted by regulations and implemented in clinical practice. Moreover, the lowered administration rates and the possibilities of the non-invasive route of administration could increase patient compliance and the applicability of herbal based interventions in chronic and lifestyle related diseases.

5.3.Gaps and Future Research Directions

Although this shows great preclinical results, there are various obstacles. Long-term data on toxicity and immunogenicity are missing, particularly the data on chronic effects and bioaccumulations of nanocarriers. Also, there are inconsistencies of the formulation procedure and species reaction which reduce reproducibility and clinical translation. Future studies need to concentrate on: (1) standardization of nanoformulation protocols; (2) carrying out long term toxicity and pharmacovigilance studies; (3) scaling up production to GMP conditions; and (4) initiating well-designed human clinical trials. A better understanding of how nanoherbal formulations interact with the human microbiome and immune system can also provide additional understanding on their effects on health as a whole[30].

6. CONCLUSION

Nanoencapsulation is a bright and new strategy to overcome the limitations in the pharmacokinetics aspects of conventional herbal medicine by substantially increasing the solubility, stability, bioavailability, as well as site-specificity of bioactive phytochemicals. It has been found that most nanoformulated herbal compounds, e.g. curcumin, quercetin and resveratrol, have a positive therapeutic effect, reduced toxicity, as well as organ-specific delivery in preclinical studies. Although nanotechnology integration has the potential of transforming herbal therapeutics by fostering their entry into the mainstream of medicine, there are key gaps such as the absence of long-term safety data, standardized research protocols and clinical validation of nanotechnology-based solutions, which must be resolved. Future research and like-minded regulations will form major considerations to the achievement of true clinical and commercial potential to nanoencapsulated herbal formulation in preventive and therapeutic healthcare.

REFERENCES

1. Abdul Rahim, R., Jayusman, P. A., Muhammad, N., Ahmad, F., Mokhtar, N., Naina Mohamed, I., ... & Shuid, A. N. (2019). Recent advances in nanoencapsulation systems using PLGA of bioactive phenolics for protection against chronic diseases. International journal of environmental research and public health, 16(24), 4962.

2. Anusha Siddiqui, S., Redha, A. A., Esmaeili, Y., & Mehdizadeh, M. (2023). Novel insights on extraction and encapsulation techniques of elderberry bioactive compounds. Critical Reviews in Food Science and Nutrition, 63(22), 5937-5952.
3. Azizkhani, M., & Sodanlo, A. (2021). Antioxidant activity of Eryngium campestre L., Froriepia subpinnata, and Mentha spicata L. polyphenolic extracts nanocapsulated in chitosan and maltodextrin. Journal of food processing and preservation, 45(2), e15120.
4. Bilia, A. R., Piazzini, V., Asprea, M., Risaliti, L., Vanti, G., & Bergonzi, M. C. (2018). Plants extracts loaded in nanocarriers: An emergent formulating approach. Natural product communications, 13(9), 1934578X1801300914.
5. Bilia, A. R., Piazzini, V., Risaliti, L., Vanti, G., Casamonti, M., Wang, M., & Bergonzi, M. C. (2019). Nanocarriers: A successful tool to increase solubility, stability and optimise bioefficacy of natural constituents. Current medicinal chemistry, 26(24), 4631-4656.
6. Chowdhury, S., Kar, K., & Mazumder, R. (2024). Exploration of different strategies of nanoencapsulation of bioactive compounds and their ensuing approaches. Future Journal of Pharmaceutical Sciences, 10(1), 72.
7. Dib, T., Pan, H., & Chen, S. (2023). Recent advances in pectin-based nanoencapsulation for enhancing the bioavailability of bioactive compounds: Curcumin oral bioavailability. Food Reviews International, 39(6), 3515-3533.
8. Harwansh, R. K., Deshmukh, R., & Rahman, M. A. (2019). Nanoemulsion: Promising nanocarrier system for delivery of herbal bioactives. Journal of Drug Delivery Science and Technology, 51, 224-233.
9. Hazarika, H., Krishnatreyya, H., Chattopadhyay, P., Saha, A., Pathak, Y. V., & Zaman, M. K. (2020). Nanoemulsion delivery of herbal products: prospects and challenges. Nano Medicine and Nano Safety: Recent Trends and Clinical Evidences, 267-288.
10. Khatoon, S., Kalam, N., Shaikh, M. F., Hasnain, M. S., Hafiz, A. K., & Ansari, M. T. (2022). Nanoencapsulation of polyphenols as drugs and supplements for enhancing therapeutic profile-a review. Current Molecular Pharmacology, 15(1), 77-107.
11. Kumar, M., Kumar, D., Kumar, S., Kumar, A., & Mandal, U. K. (2022). A recent review on bio-availability enhancement of poorly water-soluble drugs by using bioenhancer and nanoparticulate drug delivery system. Current Pharmaceutical Design, 28(39), 3212-3224.
12. Kumar, R., & Sharma, M. (2018). Herbal nanomedicine interactions to enhance pharmacokinetics, pharmacodynamics, and therapeutic index for better bioavailability and biocompatibility of herbal formulations. Materials NanoScience, 5(1), 35-60.
13. Ling, J. K. U., Hii, Y. S., Jeevanandam, J., Chan, Y. S., & Danquah, M. K. (2019). Nanoencapsulation of Phytochemicals and in-vitro Applications. In Phytochemistry: An in-silico and in-vitro Update: Advances in Phytochemical Research (pp. 315-330). Singapore: Springer Singapore.
14. Linh, N. T., Qui, N. H., & Triatmojo, A. (2022). The effect of nano-encapsulated herbal essential oils on poultry's health. Archives of Razi Institute, 77(6), 2013.
15. Luu, N. D. H., Dang, L. H., Bui, H. M., Nguyen, T. T. T., Nguyen, B. T., Hoang, L. S., & Tran, N. Q. (2021). Nanoencapsulation of Chromolaena odorata extract using pluronic F127 as an effectively herbal delivery system for wound healing. Journal of Nanomaterials, 2021(1), 6663986.

16. Mandlik, D., Mandlik, S., & Rajput, A. (2022). Herbal bioenhancers and improvement of the bioavailability of drugs. Drug Delivery Technology: Herbal Bioenhancers in Pharmaceuticals, 211.

17. Mishra, S., Sahani, S., Arvind, & Pal, V. (2021). Encapsulation of herbal extracts. In Sustainable Agriculture Reviews 55: Micro and Nano Engineering in Food Science Vol 1 (pp. 115-133). Cham: Springer International Publishing.

18. Moradi, S. Z., Momtaz, S., Bayrami, Z., Farzaei, M. H., & Abdollahi, M. (2020). Nanoformulations of herbal extracts in treatment of neurodegenerative disorders. Frontiers in bioengineering and biotechnology, 8, 238.

19. Mosaddik, A., Ravinayagam, V., Elaanthikkal, S., Fessi, H., Badri, W., & Elaissari, A. (2018). Development and use of polymeric nanoparticles for the encapsulation and administration of plant extracts. In Natural Products as Source of Molecules with Therapeutic Potential: Research & Development, Challenges and Perspectives (pp. 391-463). Cham: Springer International Publishing.

20. Muhamad, I. I., Zaidel, D. N. A., Hashim, Z., Mohammad, N. A., & Bakar, N. F. A. (2020). Improving the delivery system and bioavailability of beverages through nanoencapsulation. In Nanoengineering in the beverage industry (pp. 301-332). Academic Press.

21. Murthy, K. C., Monika, P., Jayaprakasha, G. K., & Patil, B. S. (2018). Nanoencapsulation: An advanced nanotechnological approach to enhance the biological efficacy of curcumin. In Advances in plant Phenolics: From chemistry to human health (pp. 383-405). American Chemical Society.

22. Parham, S., Parham, S. S., & Nur, H. (2023). Plant extracts: Antioxidant and antimicrobial properties and their effect of nanoencapsulation. In Nanotechnology in Herbal Medicine (pp. 195-219). Woodhead Publishing.

23. Parvez, S., Wani, I. A., & Masoodi, F. A. (2022). Nanoencapsulation of green tea extract using maltodextrin and its characterisation. Food Chemistry, 384, 132579.

24. Pateiro, M., Gómez, B., Munekata, P. E., Barba, F. J., Putnik, P., Kovačević, D. B., & Lorenzo, J. M. (2021). Nanoencapsulation of promising bioactive compounds to improve their absorption, stability, functionality and the appearance of the final food products. Molecules, 26(6), 1547.

25. Rashwan, A. K., Karim, N., Xu, Y., Xie, J., Cui, H., Mozafari, M. R., & Chen, W. (2023). Potential micro-/nano-encapsulation systems for improving stability and bioavailability of anthocyanins: An updated review. Critical Reviews in Food Science and Nutrition, 63(19), 3362-3385.

26. Rosales, T. K. O., & Fabi, J. P. (2023). Pectin-based nanoencapsulation strategy to improve the bioavailability of bioactive compounds. International journal of biological macromolecules, 229, 11-21.

27. Roshanpour, S., Tavakoli, J., Beigmohammadi, F., & Alaei, S. (2021). Improving antioxidant effect of phenolic extract of Mentha piperita using nanoencapsulation process. Journal of Food Measurement and Characterization, 15(1), 23-32.

28. Sabuj, M. Z. R., & Islam, N. (2020). Nanophytomedicine: An Effective Way for Improving Drug Delivery and Bioavailability of Herbal Medicines. In Nanophytomedicine: Concept to Clinic (pp. 55-70). Singapore: Springer Singapore.

29. Sanati, P., Chua, L. S., Nasiri, R., & Hashemi, S. S. (2020). Nanoencapsulation of andrographolide rich extract for the inhibition of cervical and neuroblastoma cancer cells. Journal of biomedical nanotechnology, 16(9), 1370-1380.

30. Siraj, A., Naqash, F., Shah, M. A., Fayaz, S., Majid, D., & Dar, B. N. (2021). Nanoemulsions: Formation, stability and an account of dietary polyphenol encapsulation. International Journal of Food Science and Technology, 56(9), 4193-4205.