Revolutionizing Herbal Extracts by Nanotechnology Approaches for Enhanced Delivery and Efficacy

L.H.H. Erangika and A.I. Kuruppu

[1]*The Institute for Combinatorial Advanced Research and Education, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka.*
Corresponding author- Dr. Anchala I. Kuruppu- Kuruppua@kdu.ac.lk

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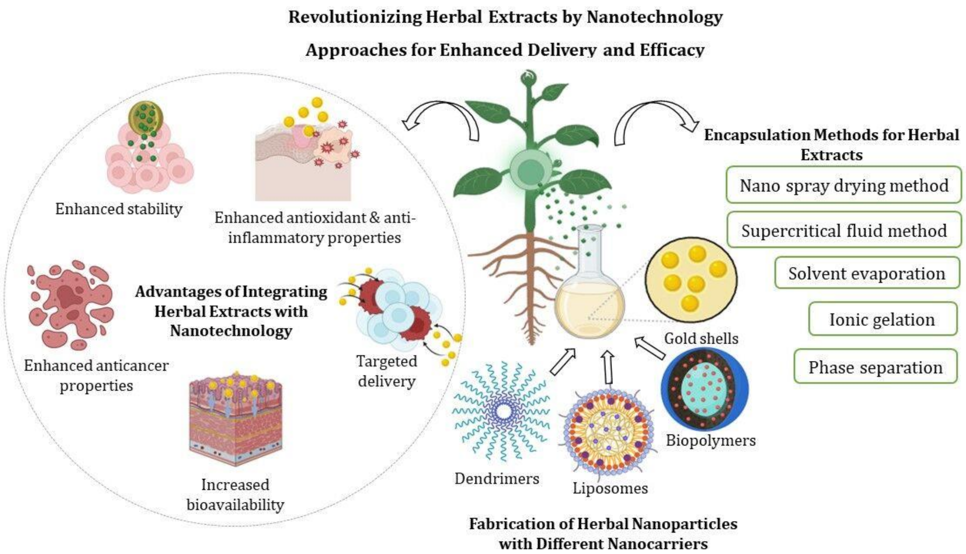

Abstract

Recent advances in nanotechnology have revolutionized medicine by enabling innovative drug delivery systems and treatment strategies. For centuries, medicinal plants have been considered the cornerstone of traditional medicine due to their diverse biological functions, attributed to the natural compounds they contain. Approximately 75% of the global population currently relies on medicinal plant extracts or formulations to address health issues, benefiting from their antioxidant, antibacterial, anti-inflammatory, and anticancer properties. Integrating herbal medicine with modern nanotechnology offers exciting opportunities to enhance therapeutic efficacy, enabling more targeted and efficient treatments. Nanoformulation techniques, which embed active compounds within nanostructures such as nanoparticles, nanocapsules, and nanogels, enhance herbal extracts' delivery, stability, and bioavailability. These methods address limitations in traditional drug delivery by reducing particle size to the nanoscale, thereby improving absorption, distribution, and efficacy. Furthermore, innovative encapsulation techniques, significantly enhance the therapeutic potential of herbal extracts. By merging traditional herbal medicine with modern nanotechnology, researchers aim to unlock new disease prevention and management strategies, promoting safer and more effective medical treatments. This mini-review focuses on various aspects of encapsulating herbal extracts in nanocarriers and their effectiveness in enhancing the activity of these extracts.

Keywords: *Nanoformulations, Nanoencapsulation, Herbal extracts, Therapeutic effects*

**Correspondence: Kuruppua@kdu.ac.lk*

1. Introduction to Nanoformulations in Medical Applications

The term "nano" has become increasingly prevalent in scientific writing, expanding over the past decade to encompass a broader range of disciplines. It is now a popular prefix in contemporary research across diverse fields (Findik, 2021; Pal et al., 2011). Nanomaterials are distinguished by having at least one dimension within the nanoscale range of 1 to 100 nm. Any material with one, two, or all three dimensions in this range qualifies as a nanomaterial (De et al., 2008; Lorusso et al., 2008).

Nanomaterials are categorized into five groups, based on their dimensions, pore sizes, origin, structural makeup, and toxicity (Figure 1) (Findik, 2021; Mekuye and Abera, 2023; Santos et al., 2015). Due to their unique qualities, nanoparticle matter exhibits distinct chemical, physical, and biological features at the nano range compared to its bigger scale particles. A different state of matter from the solid, liquid, gaseous, and plasma states is called nanoparticulate matter. These nanomaterials have unique optical, magnetic, and electrical characteristics in the nano range (Santos et al., 2015). Despite the existence of other methods to fabricate nanomaterials, top-down and bottom-up are the main techniques. Top-down techniques will start with bulk material and break it down to the nanoscale, while bottom-up techniques assemble materials from individual molecules to form nanostructures. Examples of top-down processes include lithography, ball milling, sputtering, laser ablation, electron explosion, arc discharge, and thermal decomposition (Santos et al., 2015). Chemical vapor deposition, sol-gel, spinning, pyrolysis, and biological synthesis are bottom-up methods (Ealia and Saravanakumar, 2017; Joudeh and Linke, 2022). The study of nanoscale phenomena in materials emphasizing the unique, size-dependent properties of solid-state materials, is the subject of the scientific discipline known as nanoscience (Buzea et al., 2007; Ealia and Saravanakumar, 2017; Joudeh and Linke, 2022).

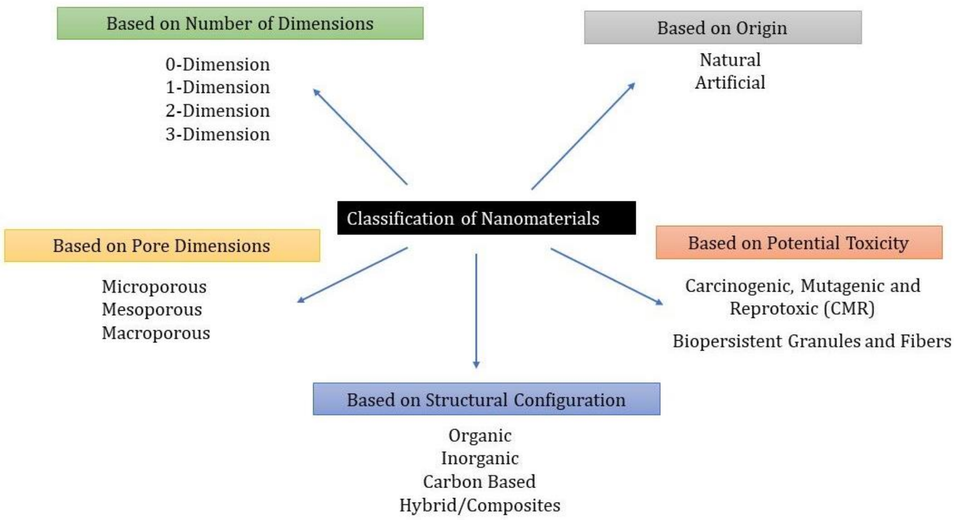

Figure 1: Classification of Nano Materials

Recent advances in nanotechnology have revolutionized medicine by introducing innovative approaches to drug delivery and treatment (Jeevanandam et al., 2016a; Mekuye and Abera, 2023; Siddiqui et al., 2020). The potential of nanoformulations, which encapsulate or integrate active substances into nanostructures, to significantly improve the stability, bioavailability, and targeted administration of medicines has gained substantial interest (Jeevanandam et al., 2016a; Siddiqui et al., 2020). This review highlights the strategies employed in the development of nanoformulations and various encapsulation methodologies. It delves into the advantages and limitations of these approaches, providing a balanced perspective on their potential. Additionally, the review explores the

*Correspondence: Kuruppua@kdu.ac.lk

transformative applications of nanoparticles derived from herbal ingredients, offering insights into their future utility.

2. Nanoformulations and Herbal Extracts

Plants are rich in bioactive compounds, and research has identified their advanced potential, especially in therapeutic functions since ancient times. These compounds were used to treat a variety of ailments. Almost 75% of people worldwide use plant extracts or medicinal formulae to treat various health issues (Fabricant and Farnsworth, 2001). These plant extracts, are a concoction of various substances with biological activity, and are primarily made from medicinal plants' leaves, stems, flowers, fruits, or roots. Plant extracts' most notable biological effects include antioxidant, antibiotic, antifungal, (Butler and Buss, 2006), antiparasitic, antiinflmmatory, anticancer (Clark, 1996), hypoglycemic (Surya et al., 2014), and antihypertensive properties (Butler and Buss, 2006; Clark, 1996; Memvanga et al., 2015; Surya et al., 2014).

Nanoformulation is the process of embedding active chemicals within nanostructures such as nanoparticles, nanocapsules, and nanogels, to improve their transport within the body and boost therapeutic effectiveness (Nasimi and Haidari, 2013a; Siddiqui et al., 2020; Weng et al., 2017; Yallapu et al., 2015) (Figure 2). Nanoformulations of herbal extracts incorporate herbal compounds as the active ingredients within a nanostructure, enhancing their delivery, stability, and bioavailability for improved therapeutic effects.

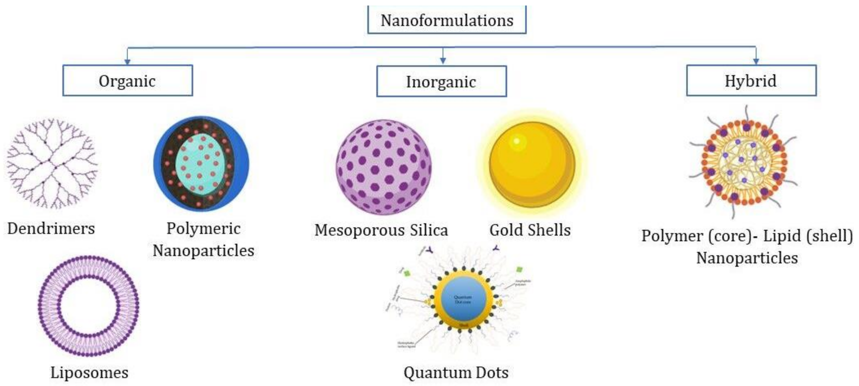

Figure 2: Types of Nanoparticles

Liposomes, nano-emulsions, dendrimers, solid lipid nanoparticles, polymers, and protein/peptide-based nanoparticles are organic nanocarriers composed of proteins, lipids, carbohydrates, or other organic components. These organic nanoparticles facilitate drug transport to specific tissues or cells improving the versatility (Khiev et al., 2021a), and various methods are available for synthesizing each type of nanoformulation.

2.1 Nano-emulsions

Nano-emulsions, a colloidal system typically ranging from 20 to 200 nm in droplet size, are stabilized by surfactants to form minuscule droplets within a heterogeneous mixture of immiscible liquids, usually oil-in-water or water-in-oil. These systems hold significant promise in enhancing the bioavailability of active ingredients, such as herbal extracts, by improving their solubility, stability, and absorption efficiency (Gupta, 2020). The droplets are more stable and appropriate for delivering hydrophilic (water soluble) and hydrophobic (fat soluble) herbal components due to their small size, usually less than 200 nm (Gupta et al., 2016). This cutting-edge technology is a breakthrough in drug delivery systems. Furthermore, it demonstrates the critical role of scientists in understanding and applying this technology to boost bioavailability, making them feel indispensable to the advancement of medicine. Synthesizing methods include high-pressure homogenization, ultrasonication, phase inversion temperature, and spontaneous emulsification (Ismail et al., 2020).

*Correspondence: Kuruppua@kdu.ac.lk

2.2 Polymeric nanoparticles

Polymeric nanoparticles (1–1000 nm) are biodegradable, solid structures containing natural polymers like chitosan or polymers like polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), or both. Active herbal ingredients can be encapsulated in these nanoparticles, enabling a gradual, controlled release (Nasimi and Haidari, 2013b; Wilczewska et al., 2012). Polymeric nanoparticles could be designed to diffuse medications in response to particular stimuli, including temperature or pH changes; thus, they can be handy for drug delivery. These characteristics benefit long-term medication delivery for chronic illnesses where targeted and long-term drug release is crucial. Some examples of these chronic diseases are cancer, diabetes, cardiovascular disease, and autoimmune diseases. Synthesizing methods include emulsion-solvent evaporation, nanoprecipitation, ionic gelation and spray drying (Mishra et al., 2018; Yadav et al., 2019).

2.3 Liposomes

Liposomes are spherical structures that are usually 50-500 nm in diameter, consisting of one or more phospholipid bilayers that enclose an aqueous core. They allow the transport of hydrophilic molecules (within the aqueous core) and hydrophobic molecules (inside the lipid bilayer) (Rehman et al., 2020; Reimondez-Troitiño et al., 2015). The benefits of liposomes include minimal toxicity, biocompatibility, the capacity to preserve and improve the absorption of herbal extracts, and a high drug-loading efficiency. The Food and Drug Administration (FDA) has approved several liposomal-based contemporary medication delivery systems for use in the market to treat various chronic illnesses. Synthesizing methods for liposomes include thin film hydration, ethanol injection, reverse-phase evaporation, and microfluidics (Asasutjarit et al., 2020).

2.4 Dendrimers

Dendrimers (1-10 nm) are extremely branched structures, which will increase the number of attaching sites for active materials such as herbal extracts, proteins, and dyes (Chaplot and Rupenthal, 2014; Kalomiraki et al., 2016). Dendrimers can effectively control drug loading and release, and the surface modification of dendrimers can improve drug delivery to specific targets. Furthermore, dendrimers are versatile as they bind herbal components to their tree-like structure or core. Due to these characteristics, dendrimers are used in antimicrobial and cancer treatments. Some of the synthesizing methods are divergent growth and convergent growth (Jeevanandam et al., 2016b; Rodríguez Villanueva et al., 2016).

2.5 Micelles

Amphiphilic molecules (5-100 nm), which contain hydrophilic and hydrophobic components, self-assemble to create micelles. The hydrophilic heads of these molecules face outward, making the structure water-soluble (Zhang, 2024). At the same time, hydrophobic tails form a core that can capture herbal components that are less soluble in water. Micelles help increase hydrophobic herbal extracts' bioavailability, enabling more effective medication delivery. They are an excellent choice for targeted therapeutics as a result of their potential to release contained substances when triggered by external factors, such as temperature or pH changes. Synthesizing methods include direct dissolution, film rehydration, solvent evaporation, and dialysis (Figueiras et al., 2022).

On the other hand, inorganic nanoparticles, are nanostructures made from non-carbon-based materials (Figure 2). They consist of quantum dots, mesoporous silica nanoparticles, and metallic nanoparticles (Khiev et al., 2021b). Over a hundred years ago, Faraday demonstrated that metallic nanoparticles could exist in solution. Today, interest in the field has significantly increased (Yu et al., 2019). Metal nanoparticles, metal oxide nanoparticles, doped metal–metal/oxide–metal nanoparticles, metal sulfide, and metal-organic frameworks are the four groups into which they are subdivided (Khiev et al., 2021c). Metal nanoparticles such as silver (Ag), gold (Au), copper (Cu), magnesium (Mg), titanium (Ti), platinum (Pt), zinc (Zn), and iron (Fe) have yielded positive results, reliable drug delivery

*Correspondence: Kuruppua@kdu.ac.lk

systems that minimize harmful effects (Khiev et al., 2021b). Furthermore, hybrid nanoparticles (Figure 2) are composite nanostructures blending diverse materials, typically integrating organic and inorganic components. This combination is intended to harness each component to enhance performance for various applications, particularly in drug delivery, imaging, and sensing.

Conventional herbal drug administration approaches, which do not incorporate nanoscale modifications or advanced technologies, often encounter challenges such as low solubility, poor stability, restricted bioavailability, and an unpleasant taste associated with traditional formulations (Chen et al., 2011; Mosaddik et al., 2018a; Talegaonkar et al., 2018). Another drawback of this conventional herbal therapy is drug resistance, such as multidrug resistance, especially in cancers (Negi et al., 2014). Previous studies have shown that liposomes combined with hyaluronan effectively reduce multidrug resistance in cancer cells due to their unique properties, such as biocompatibility and specific affinity for cancer cell receptors. Hyaluronan, a naturally occurring biopolymer, enhances targeted drug delivery and uptake by interacting with overexpressed cell surface receptors in cancer cells. This interaction improves the precision of liposome-mediated delivery systems, ensuring that therapeutic agents are directed to cancerous tissues while minimizing off-target effects. Additionally, hyaluronan's biodegradability and ability to facilitate receptor-mediated endocytosis contribute significantly to overcoming multi-drug resistance, enabling efficient intracellular drug accumulation and improved therapeutic efficacy (Negi et al., 2015).

By utilizing different nanoformulations, the traditional medical field can achieve safer and more effective outcomes in drug delivery, disease treatment, and diagnostics. Nanoformulations, such as nanoparticles, liposomes, micelles, and dendrimers, allow for controlled release, enhanced bioavailability, and targeted delivery of therapeutic agents (Torchilin, 2000). Theranostic application is another advantage, which means the dual function of a single nanocarrier as a therapeutic and diagnosis agent. This phenomenon involves drug-loaded nanocarriers combined with fluorescent materials, nuclear imaging agents, and Magnetic Resonance Imaging (MRI) techniques to enable simultaneous therapy and diagnosis in a single treatment (Kelkar and Reineke, 2011). Further, nanoformulations could address challenges in traditional drug delivery by reducing particle size and enhancing absorption, distribution, and efficiency. By combining traditional herbal medicine with modern nanotechnology, these formulations could enhance disease management, offering safer and more effective treatments.

3. Challenges and Methodologies for Nano-Encapsulation or Loading Herbal Extracts

It is uncommon for a remedy to have no restrictions or undesirable side effects while still delivering exceptional benefits. The application of nanoformulations has positively impacted healthcare, though it also presents challenges. According to the literature, these challenges are primarily categorized into two critical aspects: difficulties in large-scale production, health and safety issues (Maniam et al., 2018a).

Large-scale synthesis of nanoformulations is crucial for their widespread application, but scaling up can be challenging. Despite advances in synthesis technologies, controlling particle size and ensuring uniform encapsulation remain critical. Methods like solvent evaporation or nanoprecipitation face limitations in large-scale production due to high solvent usage and energy consumption. Overcoming these challenges requires innovative methodologies and advanced equipment to ensure efficient, scalable, and cost-effective production (Matthew et al., 2022; Zeljković, 2022). Another important factor is maintaining consistent quality in batch-to-batch synthesis. Recent studies on nanoparticle fabrication for vitamins and oils have highlighted variations in particle size between benchtop and pilot-scale production (Bordón et al., 2023; Katouzian and Jafari, 2016). Expensive chemicals and highly skilled labor are also needed to scale up. Significant increases in operating expenses could impact the risk-benefit ratio of the nanoformulations (Tighe et al., 2013).

The most significant obstacle for scientists in successfully applying nanocarriers to improve disease management is addressing the safety concerns associated with these nanoformulations.

*Correspondence: Kuruppua@kdu.ac.lk

Although nano size has shown great promise for the therapeutic field, its non-specific interactions with bodily cells also present safety issues (Siddiqui et al., 2020). Furthermore, past research has reported concerns about the safety of long-term exposure of nanoparticles to biological systems such as the blood-brain barrier (Brun et al., 2012), and the effect on the metabolism (Chen et al., 2014). On the other hand, challenges related to toxicity and biocompatibility could be mitigated by using biopolymers like chitosan in nanofabrication, as their properties make them promising candidates for biomedical applications (Geszke-Moritz and Moritz, 2024; Yadav et al., 2024). Another challenge for nanoformulations is controlling the targeted residence time, rapid metabolism, and degradation in the body. For instance, resveratrol, a natural product, found in grapes, berries, and peanuts faces these issues. Recent research has focused on developing effective delivery systems for resveratrol to enhance its plasma stability and reduce its metabolism rate (Yee et al., 2022). However, macrophages often recognize circulating nanoformulations as foreign particles, leading to their rapid elimination from circulation. This issue can be partially mitigated by modifying the nanoformulation's surface to make it hydrophilic, thereby helping to evade immune recognition and extend circulation time (Maniam et al., 2018b).

4. Methodologies for Nano-encapsulation of Herbal Extracts

Nano-encapsulation is a cutting-edge technique for entrapping bioactive compounds, such as herbal extracts, within nanostructures (Figure 3). This procedure encapsulates the active components in a nanoscale carrier material, including micelles, liposomes, or polymeric nanoparticles (Mosaddik et al., 2018b). Nano-encapsulation aims to shield these extracts from environmental deterioration while enhancing their stability, bioavailability, targeted delivery, masking unpleasant tastes or odors, and controlling the release of herbal agents.

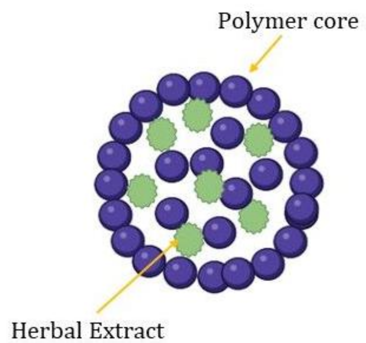

Figure 3: Drug encapsulation schematic representation

Different strategies have been found to fabricate herbal encapsulates. Some of them are discussed below (Armendáriz-Barragán et al., 2016) (Mora-Huertas et al., 2011).

4.1 Solvent Evaporation Method

This method utilizes an appropriate organic solution that contains both the herbal extract and a polymer, followed by an emulsification step in an aqueous phase. The evaporation of the solvent allows the formation of nanoparticles encapsulating herbal compounds. This technique is widely used for producing polymeric nanoparticles; however, it requires precise control over the solvent and surfactant concentrations to achieve uniform particle size and optimal encapsulation efficiency (Figure 4) (Andrade et al., 2017; Yesil-Celiktas and Cetin-Uyanikgil, 2012; Yourdkhani et al., 2017).

Many researchers have used this method to encapsulate various plant extracts and compounds. For example, ursolic acid, a plant compound, was used to fabricate nanoparticles with this method, to improve oral delivery, bioavailability, and water solubility. As a result, the bioavailability increased by 2.68 times compared to the raw form. Additionally, the antioxidant activity was enhanced, with the EC_{50} reduced by 37.5 times compared to raw ursolic acid (Qiu et al., 2019). Another study employed

*Correspondence: Kuruppua@kdu.ac.lk

this method to prepare silymarin nanoparticles, where silymarin, a flavonoid complex, resulted in a 3.66-fold increase in oral bioavailability compared to the raw form. Additionally, the antioxidant activity was significantly enhanced in the nano form (IC_{50} 0.052 mg/mL compared with 0.097 mg/mL of raw silymarin) (Zhao et al., 2016).

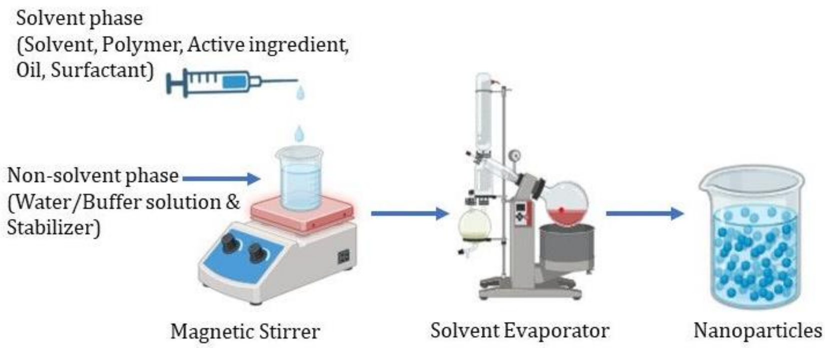

Figure 4: An illustration of the solvent evaporation method

4.2 Coacervation/Phase Separation

The separation of a polymer-rich phase from a polymer-poor phase is used to encapsulate nanocapsules of herbal extracts. There are two coacervation processes: simple and complex coacervation. Simple coacervation involves using a poor solvent to form two phases, resulting in a variation in the particle distribution of colloids and the polymer. In complex coacervation, two polymers with opposing charges undergo complexation, leading to the formation of the nanocapsules (Figure 5). Initially, the cationic polymer solution (gelatin) containing the active substance (oil) is mixed with another anionic polymer solution (Arabic gum) to create a dispersion. Complexation between the two oppositely charged polymers results in the shell's deposition on the active substance. However, the stability of this technique is limited to a specific pH and temperature range (Mosaddik et al., 2018b; Zhang et al., 2014).

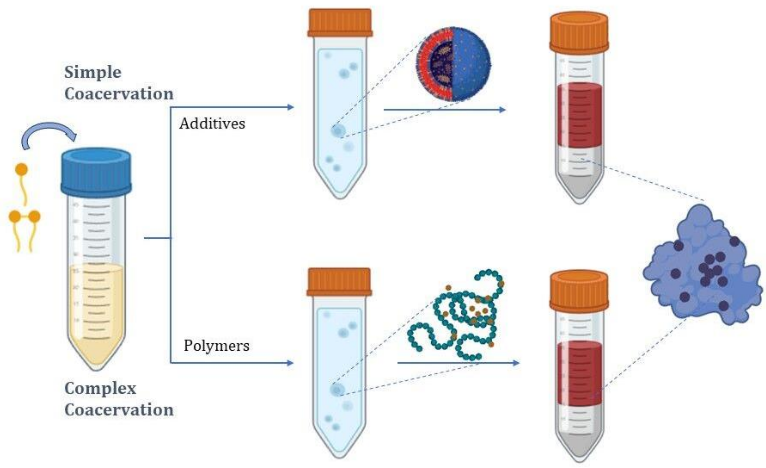

Figure 5: An illustration of simple and complex coacervation

Resveratrol has been encapsulated using gelatin through this method to enhance its bioavailability and anticancer efficacy. When compared to resveratrol alone, the resveratrol-loaded nanoparticles treated group showed a considerable increase in p53 and p21 protein expression (4.6 and 3.8-fold), which is equivalent to 1.7 and 2.1-fold increases, respectively. Furthermore, the findings indicated a larger proportion of the cells in the G0/G1 phase. Notably, the G0/G1 phase was significantly enhanced (54.58%) when cells were incubated with resveratrol-loaded nanoparticles, and the control group and resveratrol alone did not differ significantly (Karthikeyan et al., 2015).

*Correspondence: Kuruppua@kdu.ac.lk

4.3 Nano-spray Drying

Herbal extracts are dissolved or suspended in a solution, atomized into fine droplets, and rapidly dried to form nanoparticles. The solvent evaporates during spraying, causing shell material to deposit on the active component (Chopde et al., 2020) (Figure 6). This process yields tiny, spherical microparticles with a homogenous distribution. However, it is limited to temperature-sensitive herbal extracts, which use air at high temperatures. Spray-dried items have a shorter shelf life since their components are easily oxidized (Mosaddik et al., 2018b). Despite the simplicity and cost-effectiveness of this method, it is required to pay attention to the process parameters as they stem from the degradation of active ingredients.

Previous research has used this method to make nanoparticles from various bioactive ingredients such as vitamins, antioxidants, and oils (Arpagaus, 2019). A study used this method to fabricate curcumin-loaded nanoparticles for antimicrobial treatments, achieving effective antibacterial photoactivity. The curcumin nanoparticles reduced more than 99% of *Staphylococcus saprophyticus* species. It also reduced 95% of *Escherichia coli* DH5 alpha activity (Preis et al., 2019). Another study used this method for the *Kalanchoe daigremontiana* plant extract (aquoethanolic extract) to test its anticancer efficacy in breast cancer cells. The nano form reported better anticancer efficacy (IC_{50} 48.53 µg/mL) than the non-encapsulated extract (IC_{50} 61.29 µg/mL) against the MDA-MB 231 breast cancer cells (Alvarado-Palacios et al., 2015).

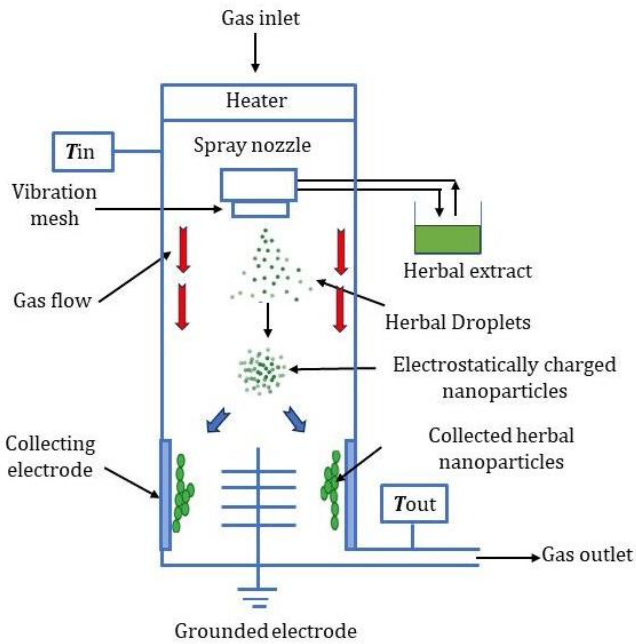

Figure 6: An illustration of nano spray drying method

4.4 Ionic Gelation

This method involves forming nanoparticles containing the herbal extract through ionic interactions between a polymer and a cross-linker. This technique is based on the electrostatic interaction between oppositely charged polymer and polyelectrolyte. Particulate production results from cross-linking an oppositely charged polyelectrolyte and a charged polymer solution applied dropwise while swirling continuously (Fan et al., 2012). Although it offers a gentle, solvent-free method, pH and ionic strength control must be exact (Figure 7).

This technique usually creates biodegradable nanoparticles derived from chitosan, gelatin, and alginate (Avadi et al., 2010; Jafarinejad et al., 2012; Li et al., 2011). Recent studies have utilized this method for herbal extracts. For example, Reed root (*Imperata cylindrica L*) was used to create nanoherbal formulations by varying the surfactant concentration. The optimal concentration resulted

*Correspondence: Kuruppua@kdu.ac.lk

in more uniform, spherical-shaped nanoparticles (Rahaiee et al., 2023). Furthermore, many studies have reported the synthesis, process optimization, and characterization of plant-based extracts using this method. It is noteworthy that researchers encapsulated the leaves of *Elephantopus scaber* into nanoparticles using the ionic gelation method and found that the leaves have the potential to be developed as an efficient drug delivery system with further modifications (Aisyah and Sutoyo, 2023; Cerrón-Mercado et al., 2022).

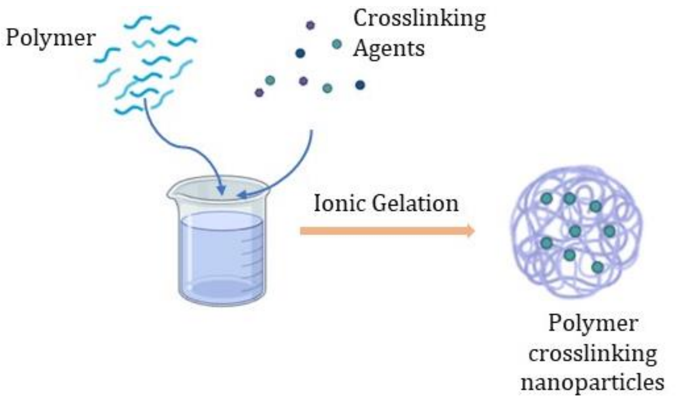

Figure 7: An illustration of ionic gelation method

4.5 Supercritical Fluid Technology

This novel technique dissolves and encapsulates plant compounds into nanoparticles using supercritical fluids, such as carbon dioxide, as solvents. Through a tiny nozzle, highly compressed gases that include the core and shell materials are kept at high pressure and are discharged at atmospheric pressure. The shell material surrounds the active component (core) and dissolves due to the rapid decrease in pressure (Figure 8). This method uses paraffin wax and polyethylene glycol as the coating ingredient. The primary prerequisite for this method is that the coating material and the active component must dissolve in supercritical fluid. Although specific equipment and circumstances are needed, the technique is safe for the environment and appropriate for chemicals sensitive to temperature changes (Mosaddik et al., 2018b). A research group used this technique to encapsulate *Curcuma longa* extracts with supercritical carbon dioxide, resulting in quasi-spherical particles with an average diameter of 47±20 nm (Momenkiaei and Raofie, 2019). They reported that the particle size ranged between 7 and 100 nm using this method (Salehi et al., 2020).

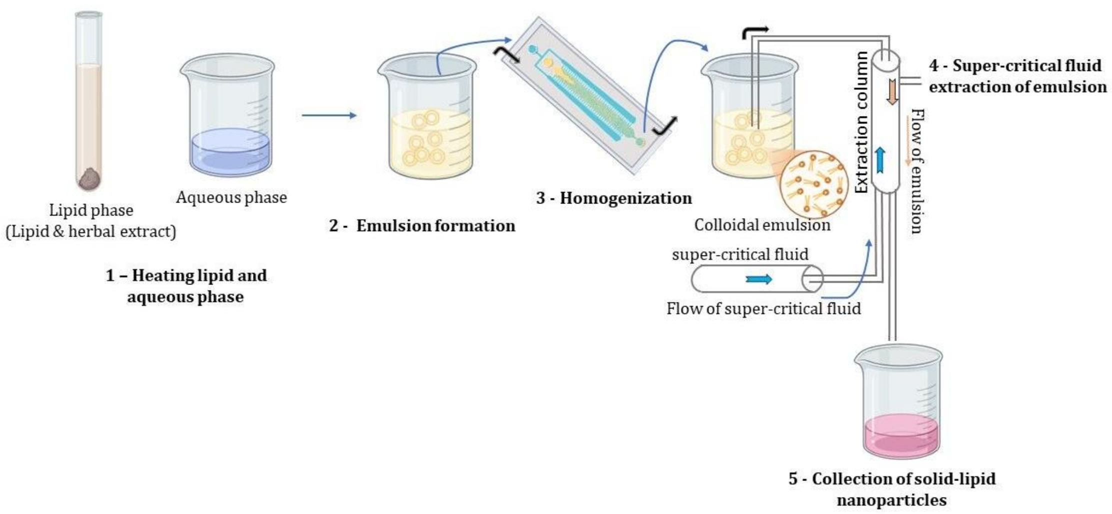

Figure 8: An illustration of supercritical fluid method

*Correspondence: Kuruppua@kdu.ac.lk

Table 1: Summary of the encapsulation methods

Method	Description	Advantages	Challenges	References
Solvent evaporation method	It utilizes an appropriate organic solution containing both herbal extract and a polymer, and the emulsification step occurs. The solvent's evaporation allows the formation of nanoparticles.	Simple and scalable.	It requires precise control over the solvent and surfactant concentration.	Andrade et al., 2017. Yesil-Celiktas and Cetin-Uyanikgil, 2012. Yourdkhani et al., 2017.
Coacervation method	The separation of a polymer-rich phase from a polymer-poor phase encased the nanocapsules of herbal extracts.	Relatively high encapsulation rate and mild processing conditions.	The stability of the technique is limited to a specific pH and temperature range.	Mosaddik et al., 2018b. Zhang et al., 2014
Spray drying method	Herbal extracts are dissolved or suspended in a solution, atomized into fine droplets, and rapidly dried to form nanoparticles. The solvent evaporates during spraying, causing shell material to deposit on the active component.	Simple and cost-effective.	It is limited to temperature-sensitive herbal extracts. Spray-dried items have a shorter shelf life. Components are easily oxidized. Attention to the process parameters, which stem from the degradation of active ingredients, is required.	Mosaddik et al., 2018b. Arpagaus, 2019.
Ionic gelation method	It involves forming nanoparticles containing the herbal extract through ionic interactions between a polymer and a cross-linker based on the electrostatic interaction.	Gentle and solvent-free method.	pH and ionic strength control must be exact.	Fan et al., 2012. Avadi et al., 2010. Jafarinejad et al., 2012. Li et al., 2011.
Supercritical fluid method	Dissolves and encapsulates plant compounds into nanoparticles using supercritical fluids through a tiny nozzle. Highly compressed gases, including the core and shell materials, are kept at high pressure and discharged at atmospheric pressure.	Safe for the environment and appropriate for the chemicals that are sensitive to temperature changes.	Specific equipment and circumstances are needed.	Mosaddik et al., 2018b.

*Correspondence: Kuruppua@kdu.ac.lk

As mentioned above when medicinal plant extracts are processed at the nanoscale, their antioxidant, antibacterial, anti-inflammatory, and anticancer properties can be significantly enhanced. The increased surface area of the nanoparticles ameliorates the interactions with bioactive compounds, whereby it provides an effective transportation system. For instance, studies have shown that combining silver nanoparticles with herbal extracts, such as *Malus domestica* (apple extract), enhanced their antioxidant activity, with results showing a 75.16% radical inhibition. Additionally, extract-loaded silver nanoparticles demonstrated improved antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (Nagaich et al., 2016). These formulations demonstrated a more remarkable ability to scavenge free radicals than their bulk equivalents, bolstering cellular defense against oxidative stress. It has been also discovered that *Echinacea purpurea* nanoformulations have enhanced efficacy concerning antibacterial activity against a range of illnesses (Al-Hakkani et al., 2021; Fierascu et al., 2022; Moghtaderi et al., 2021). Research findings have indicated that the extract, when encapsulated in liposomes, demonstrated improved antibacterial properties, significantly hindering the growth of antibiotic-resistant strains relative to conventional formulations. Medicinal plants also significantly improve their anti-inflammatory properties when formulated at the nanoscale. For example, a combination of curcumin from *Curcuma longa* and *Echinacea purpurea* nanoparticles has shown a more pronounced anti-inflammatory effect in animal models of arthritis. These nanoformulations enhanced curcumin absorption, leading to a more marked reduction in pain and inflammatory markers (Boarescu et al., 2022; Peng et al., 2021).

Biocompatibility is crucial for herbal extracts to effectively distribute their bioactive ingredients and avoid unintended biological reactions from these nanocarriers. A growing number of people are using gold nanoparticles because of their superior biocompatibility and simplicity in functionalization. Gold nanoparticles possess safer conditions for biomedical applications. For example, functionalizing gold nanoparticles with herbal extracts such as those derived from *Zingiber officinale* or *Camellia sinensis* significantly improved the extracts' medicinal efficacy while demonstrating no cytotoxicity. The ability of gold nanoparticles to facilitate customized distribution increases their potential as carriers of herbal ingredients (Bursy et al., 2023; Koliyote and Shaji, 2023; Sysak et al., 2023). Mesoporous silica nanoparticles are an additional potential nanocarrier for herbal treatments due to their remarked biocompatibility, pore size, and large surface area. For instance, a study has shown that plant extracts containing silica nanoparticles provide continuous drug releasement and improved therapeutic potential while minimizing side effects. Furthermore, *Curcuma longa* loaded silica nanoparticle extracts also reported enhanced bioavailability and anti-inflammatory activities with minimum cytotoxicity (Bojanić et al., 2023; Pande et al., 2023).

5. Future Trends

The future of nanoformulations in herbal medicine is expected to focus on several key trends. Targeted drug delivery systems will become more precise, enhancing therapeutic effects while minimizing side effects. Improved bioavailability of plant based extracts will continue to be a major goal, allowing active compounds to be more effectively absorbed. In the context of cancer treatment, nanoformulations will play a critical role in enhancing the delivery and efficacy of anticancer compounds, potentially improving outcomes in chemotherapy and reducing the toxicity typically associated with traditional cancer treatments. The combination of nanoformulations with other therapies, such as antibiotics, immunotherapies, or chemotherapy agents, will lead to synergistic effects, improving treatment efficacy. Additionally, personalized medicine will enable tailored nanoformulations to optimize efficacy and reduce adverse effects based on individual patient profiles. The shift towards sustainable and green nanotechnology will address environmental concerns, using plant-based materials and eco-friendly solvents for nanoparticle synthesis. As clinical development progresses, clearer regulatory guidelines will ensure the safety and efficacy of these innovations, facilitating their transition into clinical practice. With the rise of antimicrobial resistance and cancer drug resistance, nanoformulations will enhance the antimicrobial and anticancer activity of plant

**Correspondence: Kuruppua@kdu.ac.lk*

compounds, offering new solutions for resistant strains and cancers. Finally, the integration of therapy and diagnosis (theranostics) in nanomedicine will allow for better monitoring and personalized treatment strategies, particularly in oncology. Together, these trends will significantly enhance the effectiveness, safety, and sustainability of nanoformulations in herbal medicine in the future.

6. Conclusions

In summary, herbal extract nanoformulations could enhance therapeutic efficacy, stability, and target distribution compared to conventional formulations, marking a significant advance in nanotechnology and traditional medicine. At present, these systems have shown promising results in various medical applications, such as treating inflammation and cancer. The development of various encapsulation methods enables the efficient transport of medicinal properties while safeguarding sensitive herbal ingredients from degradation. Although studies have shown that nanoparticles are biocompatible and nano herb preparations are safe, there are still challenges in large-scale production, regulatory approval, and clinical translation. More research on advanced strategies such as surface functionalization and biocompatible polymers is needed to maximize the safety and therapeutic potential of these delivery methods and open the door to more effective and long-lasting medical treatments.

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*Correspondence: Kuruppua@kdu.ac.lk

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*Correspondence: Kuruppua@kdu.ac.lk

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**Correspondence: Kuruppua@kdu.ac.lk*

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**Correspondence: Kuruppua@kdu.ac.lk*