Open Access

Review

PRNANO

Precis. Nanomed. 2023, 6(3):1109-1132

ANDOVER HOUSE

Green Synthesized Nanoparticle-Based Drug Delivery: Recent Trends and Future Prospects

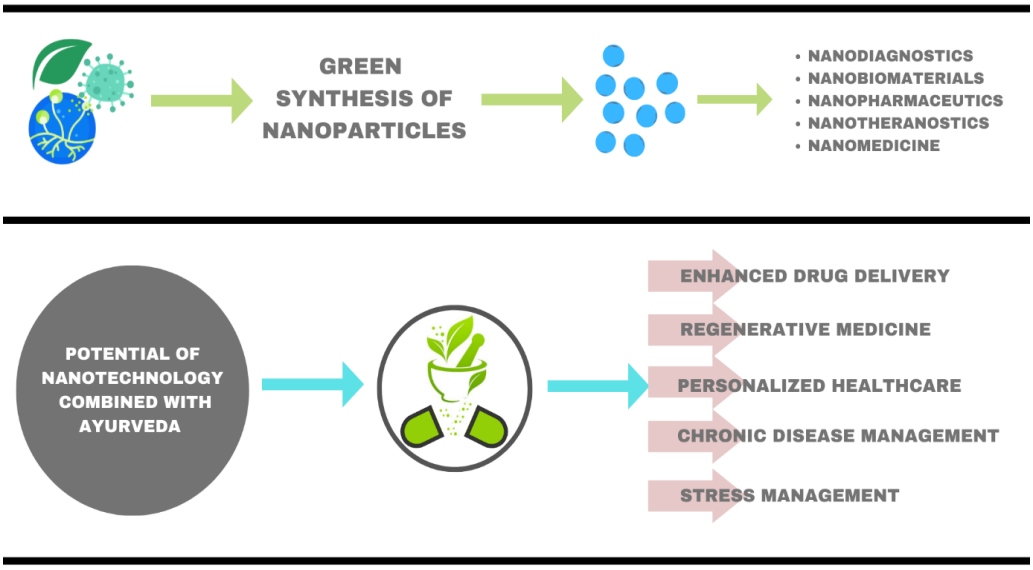
Aparna Kaushik[1], Ravi Kant Singh*[1], Pankaj Kumar Tyagi*[2]

[1]*Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, U.P.-201313*

[2]*Department of Biotechnology, Noida Institute of Engineering & Technology, Greater Noida, U.P.-201306*

Submitted: September 11, 2023 Accepted: October 15, 2023 Published: October 19, 2023

Graphical Abstract



Abstract:

Nanotechnology has revolutionized several scientific disciplines with its ability to engineer and modify materials at the nanoscale. Due to its environmental friendliness and prospective uses across many industries, green nanoparticle synthesis has attracted much attention. Green nanoparticle synthesis produces nanoparticles by using natural resources instead of toxic chemicals and energy-intensive processes, such as plants, microorganisms, and biomolecules. Recent trends include utilizing microbes, biomolecules including enzymes and proteins, and plant extracts as reducing and stabilizing agents. This process gives nanoparticles unique features that increase their potential applications across medicine, catalysis, and agriculture. A notable fusion of ancient wisdom and modern science can be seen in applying nanotechnology to Ayurveda. Ayurveda focuses on a comprehensive approach to health and well-being, using natural medicines and individualized care. Using environmentally friendly nanoparticles, ayurvedic may improve treatment outcomes, drug-delivery systems, and diagnostic procedures. The bioavailability and targeted administration of Ayurvedic medicines may be enhanced using nanoparticles, maximizing their efficacy while reducing potential adverse effects. This review examines current trends in the environmentally friendly production of nanoparticles, emphasizing

* Corresponding Authors: rksingh1@amity.edu (RKS), pktgenetics@gmail.com (PKT)

License: CC BY-NC 4.0

its ethical implications and cutting-edge approaches. To develop a creative synergy between conventional wisdom and contemporary scientific advancements, it also explores merging nanotechnology with Ayurveda, the traditional Indian holistic healthcare system.

Key-words: Biogenic, Nanoparticles, Drug-Delivery System, Ayurvedic Medicines

Purpose, Rationale, and Limitations

Purpose: This review article examines the potential benefits of combining Ayurveda and nanotechnology to address infectious diseases. It explores how the holistic principles of Ayurveda can complement the innovative antimicrobial properties of nanotechnology. The purpose is to propose a promising approach for effective and holistic infectious disease management by leveraging the strengths of both disciplines.

Rationale: The convergence of nanotechnology and Ayurveda holds immense potential for addressing complex and evolving infectious disease challenges. Nanoparticles (NPs), due to their unique properties, offer novel antimicrobial solutions that can circumvent resistance. They disrupt pathogens' membranes or generate free radicals, reducing toxicity, costs, and resistance while enhancing drug delivery as well as aiding in diagnostics development. Ayurveda, rooted in holistic well-being and personalized care, complements nanotechnology's advancements. Its preventive, nature-aligned principles align well with nanotech solutions. This review explores the synergy between Ayurveda and nanotechnology, aiming to harness their combined strength for effective healthcare solutions.

Limitations: Combining nanoparticles with Ayurveda offers potential but faces significant challenges. Safety concerns, historical misalignment, complex formulations, and conflicts with holistic principles are prominent. Regulatory barriers, research gaps, costs, and accessibility add to the complexity. Balancing benefits and maintaining Ayurvedic values demands thorough research, ethics, and a cautious approach.

Introduction:

Whether caused by intracellular, extracellular, biofilm-mediated, or medical device-associated infections, infectious diseases have always been a major public health concern, claiming millions of lives yearly. Since the invention of antibiotics in the twentieth century, the deaths and illnesses caused by these infectious diseases have significantly decreased. Antimicrobial resistance and the advent of novel diseases are influenced by changes in society, the environment, technology, and microorganisms [1]. Creating new medicines and modifying chemically existing medications can overcome bacterial resistance to certain antibiotics. The creation of new antimicrobial medications does not guarantee that they will defeat the microbial infection quickly enough to prevent the emergence of resistance in the years to come. For instance, there are now more hospital and nosocomial illnesses caused by Gram-positive and Gram-negative bacteria, and the ongoing development of antimicrobial resistance with the usage of antibiotics at sub-lethal concentrations is posing significant risks to human health. As a result, there is a pressing need for longer-term, more powerful remedies to this challenge [2].

One of the promising efforts to address this challenging and dynamic pattern of infectious diseases is the use of nanotechnology. Nanotechnological applications in medicine have yielded an entirely new field of technology set to bring momentous advances in the fight against a range of diseases [3]. Nanoparticles (NPs) are defined as "particulate dispersions, or solid particles with a size in the range of 10-1000 nm." This small size range gives them specific properties such as a high surface area and enhanced reactivity [4]. NPs consisting of metals and metal oxide may be promising antimicrobial agents to which pathogens may not develop resistance. These NPs use various antimicrobial mechanisms against pathogens; they may disrupt the cell membrane directly or form free radicals.

License: CC BY-NC 4.0

Compared to conventional antibiotics, nanostructured antimicrobial agents help reduce toxicity, overcome resistance, and lower costs. In addition, nano-sized drug carriers are also available, which can efficiently administer the antibiotics by improving the therapeutics and pharmacokinetics of the drug. Nanotechnology also assists in developing fast, accurate, and cost-effective diagnostics for the detection of pathogenic microbes. Thus, the horizon of the potential applications of nanotechnology needs to be widened. The Indian traditional medical system known as Ayurveda is crucial for overall health. It emphasizes harmony between the mind, body, and spirit while considering each person's individuality. Ayurveda, rooted in natural medicines and individualized care, emphasizes prevention over cure. Its guiding concepts promote harmony with Nature and the self by guiding lifestyle, nutrition, herbal medicines, and therapeutic procedures. The importance of Ayurveda rests in its tried-and-true knowledge, which offers a comprehensive approach to health that is embraced by all cultures and continues to inspire well-being on many levels.

Green Synthesis:

Green synthesis produces nanoparticles (NPs) using microorganisms, including human cell lines, fungi, bacteria, plants, algae, and biocompatible biomolecules.

Many phytochemicals found in plants, including tannins, alkaloids, flavonoids, saponins, and other metabolites, play a significant role in the production of nanomaterials and have important implications for developing future cancer therapies. Herbal extracts offer a potential method to produce nanomaterials through safer pathways. The idea of "Green Chemistry" for "Sustainable Development" has been extensively researched during the past ten years[5]. Sustainable development is defined as growth that satisfies present requirements while simultaneously maintaining a balance with the capacity of future generations to meet their own needs[6]. Sustainable growth is crucial for many chemistry-based industries because it raises issues such as pollution as well as inconsiderate utilization of natural resources[7]. The three most crucial conditions for green production of NPs are the choice of a green or ecologically conscious solvent (the most frequently used being ethanol, water, and their mixes), an acceptable non-hazardous reducing agent, and a safe chemical for stabilization. A wide variety of synthetic processes have been employed to create nanoparticles, the most common being physical, chemical, and biosynthetic. Chemical treatments typically cost too much money and require dangerous and poisonous chemicals, which pose several environmental problems[8]. Green synthesis, in contrast, is a secure, biocompatible, and environmentally sound technique for creating NPs for various functions, including biomedical ones [9]. This "green synthesis" has been accomplished using microorganisms and plants. However, it has been frequently used to synthesize various NPs from parts of plants, such as stems, leaves, roots, fruits, and seeds [10]. Indeed, NPs with specific sizes, shapes, and content can be made using plant extracts. Additionally, the large variety of phytochemicals included in their extract may serve as organic stabilizers or reducing agents for forming NPs. It is widely acknowledged that plant-derived NPs have a lower risk of having negative side effects on people than chemically produced NPs do. They also have a high biological potential and can be used in various fields, including food science and technology, bioengineering, agriculture, cosmetics or nanomedicine, and human health protection. [11]

Plant extracts are used to reduce metal ions under specific conditions, which results in the creation of metal nanoparticles utilizing plants. Three stages make up the synthesis process: (1) the activation phase, in which the phytoconstituents in the plant extracts reduce the metal ions prior to nucleation; (2) the growth phase, in which NPs put together to form larger-sized NPs; and (3) the termination phase, in which the final NPs with a particular shape are produced. This method is straightforward, economical, environmentally beneficial, and uses safe solvents and non-toxic capping/stabilizing agents. This process often yields metal nanoparticles (NPs) with high surface functionalities, increasing the likelihood of agglomeration. Therefore, capping agents—such as natural polymers—are typically employed to prevent agglomeration and regulate the ultimate size of the nanoparticles.

Depending on where the NPs are created, either extracellular or intracellular synthesis is

License: CC BY-NC 4.0

used to produce them utilizing microorganisms. Intracellular or extracellular biomolecules/enzymes aid in the process. Metal ions are transported into microbial cells through intracellular enzymes to create NPs during intracellular microbial production. The process of extracellular microbial production entails the build-up of metal ions beyond the microbial cell membrane, which are subsequently reduced by extracellular enzymes. Metal ions are produced into phosphate, carbonate, sulfide, and phytochelatin (metal ions binding to peptides) derivatives in microbial systems through volatilization via ethylation or methylation and direct redox reactions. [12]

For instance, it has been shown that adding chloroauric acid to the cellular milieu of specific cancer cells can cause the cells to produce plasmonic gold nanoparticles. [13] Additionally, several recent studies have shown that green synthesized AgNPs exhibit anti-cancer potential against various cancer cell lines in vitro. Aside from that, metal nanoparticles (NPs) have been effectively used for many years to treat different viral infections. More recently, they have demonstrated potential utility in several diagnostic, prophylactic, and therapeutic endeavors during the COVID-19/SARS-CoV-2 pandemic. [12].

Ayurveda and Its Importance: from Ancient to Modern Times:

Metal and mineral nanomedicines are a gold mine in the Ayurvedic medical system. Rasashastra, a branch of Ayurveda, focuses on the creation and therapeutic use of nanomedicines, particularly metallic as well as mineral NPs. These minerals and metals are repeatedly heated while being treated with a variety of organic components, and the resultant mineral or metal ashes are said to be organically oriented nanoparticles. The term “Bhasma” in Ayurveda refers to these produced organometallic or organo-mineral nanoparticles [14]. These preparations are said to have a variety of biological effects and to be safe for human consumption.

Ayurvedic principles were not scientifically evaluated sufficiently by the Indian scientific community, resulting in poor interdisciplinary collaboration. As a result, this idea was prematurely put to rest until it was recently revived with more solid supporting data. The new insight is that effective use of Ayurveda requires a deeper comprehension of its basics. Fortunately, this knowledge has led to the possibility of a pro-Ayurvedic generation that is impulsive and argumentative [15]. The scientific presentation of Ayurveda was necessary for its proliferation worldwide, along with the reduction of semantic hurdles that prevented people from understanding it. Fortunately, a few individuals in the new genre have been moved to see this fact and act as translators, communicating in a language that is shared by both parties and recovering the connection between Ayurveda and science while preserving its original flavor.[16], [17]

Only lately have the true value and potential of nanomedicine been understood. Although there are many uses for nanomedicine, its main applications now include the diagnosis of different diseases that are challenging to detect with the currently available conventional techniques, as well as the development of effective and biosafe drug-delivery mechanisms for site-specific targeting with the aim of treating diseases [18]. Furthermore, with the potential to create fabricated cells, enzymes, and genes, nanomedicines can be used to study cellular motions and molecular modifications frequently linked to diseased disorders [19]. Nanomedicines can also be considered nanoscale carrier systems that transport many substances, including medications, antibodies, diagnostic agents, imaging agents, and others. Researchers in the medical field now use nanotechnology, a state-of-the-art technology, to lower the size of medication carriers for an effective line of combat against diseases. The development of highly successful medical treatment procedures is where nanotechnology’s grand commercial and scientific potential in human health care lies[20]. One key benefit of nanotechnology is its adaptability, which allows for the creation nanomedicines in various forms, including dendrimers, liposomes, nanoparticles, and nanocrystals, to satisfy the demands of specific biomedical applications [21].

Numerous cancers, autoimmune disorders, tonsillitis, jaundice, anemia, persistent cysts in the ovaries, and other infectious diseases can be successfully treated with Bhasma[11]. Table 1 lists a few of the Bhasma that are used to cure various diseases:

License: CC BY-NC 4.0

Table 1: Different Bhasma Formulations as Treatments

BHASMA	MAIN INGREDIENT	TARGET TREATMENTS	REFERENCES
Abhraka Bhasma	Mica	Chronic cough, anemia, and tropical sprue	[22]
Lauha Bhasma	Fe	Hematinic, chronic fever, breathlessness, anti-aging	[22], [23]
Naga Bhasma	Pb	Diarrhea, spleen enlargement and diabetes	[24]
Rajata Bhasma	Ag	Irritable bowel syndrome, acidity, pitta disorders	[25], [26]
Ras-Sindoor	Hg	Syphilis, genital disorders, and for rejuvenation	[27]
Shankh Bhasma	Calcium carbonate or oxide (conch shells)	Indigestion, flatulence, abdominal pain, vomiting, belching, diarrhea, belching and gastritis	[28]
Swarna Bhasma	Au	Tuberculosis, diabetes mellitus, rheumatoid arthritis, and nervous diseases	[29], [30]
Swarn makshik Bhasma	Copper pyrite	Anemia, jaundice, convulsions, insomnia, stomatitis, chronic fever, and skin diseases	[26], [31]
Tamra Bhasma	Cu	Ascites, anemia, asthma, hyperacidity	[32]
Trivanga Bhasma	Pb, Zn, and Sn	Diabetes mellitus and urinary disorders	[33]
Vanga Bhasma	SnO_2	Genitourinary disorder, diabetes, anemia, asthma, gastric ulcers, and urinary diseases	[34]
Vaikranta Bhasma	Black Tourmaline	Diabetes	[26], [35]
Yashada Bhasma	Zn	Diabetes, eye disorder, urinary disorder	[36]
Krishna Vajra Abhraka Bhasma	Biotite mica	Respiratory diseases	[37]

Nano-Based Drug-Delivery Systems:

By using nanostructures and nanophases in a variety of scientific domains, particularly in nanomedicine and nano-based drug-delivery systems, in which such particles are of great interest, nanotechnology has been shown to bridge the gap between biological as well as physical sciences [38], [39]. Nanomaterials, which affect the frontiers of nanomedicine from biosensors, drug delivery, microfluidics, and tissue engineering, can be precisely described as materials with diameters ranging from 1 to 100 nm [40]. Nanoparticles have been the driving force behind the development of nanobiotechnology, biosensors, drug delivery, and tissue engineering technologies in the biomedical industry. Nanoparticles are typically small nanospheres because they are made of materials engineered at the molecular or atomic level [41]. As a result, they can travel within the human body with greater freedom than bulkier materials. The structural, mechanical, chemical, electrical, magnetic, and biological features of nanoscale-sized particles are distinctive. Nanostructures can be used as delivery agents to enclose medications or bind therapeutic pharmaceuticals and transport them to target tissues more accurately with a controlled release [42]. This developing subject, nanomedicine, applies nanoscience knowledge and methods to biology, disease prevention, and medical treatment. It refers to using nano-dimensional materials such as nanorobots and nanosensors for delivery, diagnostics, sensory functions, and actuating materials in living cells. For instance, a nanoparticle-based approach that combines cancer detection and treatment modalities has been created [43]. Currently, FDA-approved lipid systems such as liposomes and micelles

License: CC BY-NC 4.0

were a part of the earliest generation of nanoparticle-based therapies [44]. Inorganic nanoparticles, including Ag(gold) or magnetic nanoparticles, may be present in these liposomes and micelles [45]. These characteristics have led to a rise in the usage of inorganic nanoparticles, particularly for therapeutic, imaging, and drug-delivery purposes. According to reports, nanostructures also improve the transport of sparsely water-soluble medications to their intended place and prevent drugs from becoming tainted in the gastrointestinal area. Nano-drugs have better oral bioavailability due to their usual absorptive endocytosis uptake processes.

Nanostructures allow the release of combined medications at the prescribed dose since they persist in the blood circulation system for a long time. They result in fewer plasma variations and adverse effects [46]. Due to their nanoscale, these structures can quickly enter the tissue system, make medication administration more effective, and ensure that the medicine acts where it is intended. Nanostructures are far more readily absorbed by cells than big particles, falling in the range of 1-10 µm in size [47]. As a result, they work together directly to treat the sick cells more effectively and with fewer, if any, adverse effects.

Nanoparticles have been discovered to be helpful in gathering information at all phases of clinical procedures due to their application in several innovative tests for treating and diagnosing diseases. The main advantages associated with these nanoparticles are linked to their surface characteristics because different proteins can attach to the surface. For example, gold nanoparticles are utilized as tumor labels and biomarkers in a variety of biomolecule detection procedures.

While using nanomaterials for drug delivery, the drug's physicochemical characteristics are considered when choosing a nanoparticle. Using bioactive natural chemicals with nanoscience is highly appealing and has grown significantly in recent years. When it boils down to administering natural remedies for treating cancer, along with many other diseases, it offers several benefits. As a result of their numerous distinctive properties, including their ability to induce tumor-suppressing autophagy and function as antimicrobial agents, natural chemicals have been thoroughly researched in treating diseases. Curcumin and caffeine have been linked to autophagy, whereas cinnamaldehyde, carvacrol, curcumin, and eugenol have been linked to antimicrobial properties [48], [49]. Adding nanoparticles enhanced their features, such as bioavailability, targeting, and controlled release. For instance, the bioactive ingredient in Nigella sativa called thymoquinone is examined after being enclosed in a lipid nanocarrier. Its bioavailability increased sixfold after encapsulation compared to free thymoquinone, protecting the gastrointestinal tract [50]. Additionally, it improved the natural product's pharmacokinetic properties, improving therapeutic effects.

When creating target-specific drug-delivery systems, metallic, organic, inorganic, and polymeric nanostructures, such as dendrimers, micelles, and liposomes, are commonly considered. These nanoparticles are added explicitly to medications that have limited solubility and poor absorption [51]. The effectiveness of these nanostructures in drug-delivery systems, however, differs based on their size, shape, and additional inherent biophysical/chemical properties. For instance, polymeric nanoparticles with diameters between 10 and 1000 nm have qualities that make them excellent delivery systems. Numerous synthetic polymers, including poly-L-lactic acid, polyvinyl alcohol, polyethylene glycol, and poly (lactic-co-glycolic acid), as well as natural polymers, like alginate and chitosan, are widely used in the nanofabrication of nanoparticles because of their high biocompatibility and biodegradability properties [52]–[54]. Both types of polymeric nanoparticles—nanospheres and nanocapsules are good drug-delivery methods. Like liposomes and micelles, compact lipid nanostructures and phospholipids are particularly helpful in delivering targeted drugs.

The biophysical and biochemical characteristics of the targeted medications chosen for therapy have a significant role in selecting the best nano-drug delivery technology [55]. Problems like the toxicity that nanoparticles exhibit must be considered when thinking about the use of nanomedicine. Nanoparticles have also been used in conjunction with natural products. Creating drug-loaded nanoparticles is a popular green chemistry strategy since it reduces the potentially harmful components involved in the biosynthetic process. As a result, utilizing green nanoparticles to carry drugs can decrease their

License: CC BY-NC 4.0

adverse effects [42]. The bioactivity of these nanomaterials can also be improved by modifying the nanostructure's size, hydrophobicity, shape, and surface properties.

Thus, the site-specific and target-oriented administration of medications made possible by nanotechnology has many advantages in treating chronic human diseases. However, the lack of knowledge regarding the toxicity of nanostructures is a significant concern and unquestionably calls for more research to increase the efficacy while maintaining better safety, allowing for safer actual application of these medications. Therefore, tackling the issues related to the utilization of these nanoparticles may benefit from careful design. Considering the aforementioned information, the review aims to discuss various nano-based drug-delivery systems. These notable applications utilize natural compound-based nanomedicines alongside the targeting sites, bioavailability, precisely controlled release of these nano-drugs, and other difficulties related to nanomaterials in pharmaceuticals.

Fundamentals of Nano-Based Drug-Delivery Systems:

Nanomedicine uses the science of nanotechnology [54]–[56] using nanoscale material diagnosis, sensorial nanoparticles, and nanorobots for various applications, including diagnosis, sensory, delivery, or actuation purposes inside a living organism. Drugs with extremely low solubility have a variety of biopharmaceutical delivery problems, such as limited bio accessibility following oral intake, reduced ability to diffuse into the outer membrane, needing more for intravenous intake, and unfavorable side effects prior to the conventionally formulated vaccination process. However, all these restrictions could be removed by incorporating nanotechnology methods into the medication delivery system.

Because of its potential benefits, including the ability to alter properties such as solubility, diffusivity, drug release profiles, bioavailability, and immunogenicity, drug designing at the nanoscale is by far among the latest developments in nanoparticle applications. As a result, more effective and convenient delivery routes may be created, along with fewer side effects, decreased toxicity, enhanced biodistribution, and a prolonged drug life cycle [57]. The designed drug-delivery systems are either intended for the regulated release of therapeutic substances at a specific spot or are directed to a particular place. Their development involves self-assembly, in which predetermined forms or patterns emerge from constituent parts [58]. They must also overcome obstacles such as being opsonized or sequestered via the mononuclear phagocyte system [59].

Nanostructures can deliver drugs in two different ways: passively and actively. In the former, the hydrophobic effect primarily incorporates pharmaceuticals into the structure's inner cavity. Due to the drug's low concentration and its hydrophobic environment, the intended amount of the medication is released whenever the nanostructure materials are directed to specific places. In contrast, the medications intended for release are immediately attached to the carrier nanostructure material, the latter permitting simple distribution. In this method, the timing for release is essential because otherwise, the drug is unlikely to reach the target site and will soon dissociate from the carrier; conversely, if the drug is released from the nanocarrier system at the proper time, its bioactivity, as well as efficacy, will increase [58]. Another important component of medication delivery is targeting, which can be active or passive and utilizes nano-formulations or nanomaterials for drug-delivery systems. In active targeting, drug-delivery systems are combined with moieties, such as antibodies and peptides, to bind them with the receptor complexes expressed at the target region. In passive targeting, the produced drug carrier complex is transported to the target site via affinity or binding influenced by factors including pH, temperature, molecular size, and shape as it circulates through the circulation. Receptors upon cell membranes, lipids in the cell membrane, and antigens/proteins on cell surfaces are the primary targets in the body[60]. Most drug-delivery systems made possible by nanotechnology today are geared toward treating cancer and finding a cure.

Drug Design and Mechanism of Drug Delivery:

Several treatment procedures have been suggested to improve the drug specificity and diagnostic accuracy, and conventional clinical diagnostic approaches have been investigated.

License: CC BY-NC 4.0

These developments in nanomedicine, drug discovery/design, and drug-delivery systems have all contributed to these developments. For example, new medication administration methods are being investigated, and emphasis is being placed on ensuring that they function specifically in designated areas, minimizing their toxicity and enhancing their accessibility to cells in the organism [61].

Drug designing has emerged as a promising aspect of identifying novel lead medications based on understanding a biological target in this context. For this industry to expand and flourish, experimental techniques for classifying and purifying proteins and biological targets must evolve, as well as computer science breakthroughs [62], [63]. Additionally, several studies and reviews in this field emphasize the rational planning of various molecules and highlight the significance of researching various drug release mechanisms [64]. Furthermore, natural products can inspire the creation of new drugs with desired physicochemical features and offer workable and intriguing answers to the problems associated with drug design [65]–[67].

Additionally, over the past few years, the importance of medication delivery systems has increased. Such systems are simple to create and have the potential to encourage the body's customized release from active substances. For instance, Chen et al. [66] explored the therapeutic impact of their system that used nanocarriers for visualization and sensory applications. Additionally, Pelaz et al.'s [68] discussion of fresh potential and difficulties for this industry included an up-to-date description of many nanocarrier applications to nanomedicine.

It's interesting to note that every one of these drug-delivery systems has distinct chemical, physical, and morphological properties and may prefer drug polarities through chemical or physical interactions, such as electrostatic as well as van der Waals interactions, or covalent bonds and hydrogen bonds. For instance, Mattos et al. [69] showed that the release profile of biogenic silica nanoparticles grafted with neem bark extract (chemical interactions) was lesser than that of biogenic silica nanoparticles loaded with neem bark extract. Thus, these variables impact how nanocarriers interact with the biological systems [70] and how quickly the active ingredient is released into the body [64]. Additionally, Sethi et al. [71] created a cross-linkable lipid shell (CLS) with wortmannin and docetaxel as model medicines for regulating drug discharge kinetics. After studying the CLS' discharge profile, they discovered that it was impacted by both in vitro and in vivo settings. Other factors that are essential to comprehending the drug-delivery profile of nanocarriers include their composition (e.g., inorganic, organic, and hybrid materials), as well as the way that drugs are attached to them (e.g., core-shell system or matrix system). Numerous investigations into the drug release mechanisms in nanocarriers have been carried out and conducted collectively. Figure 1 shows several mechanisms, including chemical reaction, solvent, diffusion, and stimulus-controlled release, that can describe how pharmaceuticals are released from nanocarriers. The extensive evaluation of controlled-release systems by Kamaly et al. [72] was centered on research on regulating the release of drugs from polymeric nanocarriers. Although there are numerous nanocarriers with various drug release profiles, strategies are currently being developed to increase the specificity of the nanostructures to the organism's target areas [73] and to lessen their immunogenicity by coating or chemically functionalizing them with a variety of substances, like natural polysaccharides [74], [75], polymers [76], antibodies [77], tuneable surfactants [78], cell membranes [79], peptides [80], etc.

The ligand-modified nanocarriers were used to penetrate through the cell membrane and enable a programmed drug delivery in a specific environment in some cases where drugs do not exhibit binding alongside affinity with a particular target or fail to penetrate certain barriers (such as the blood-brain barrier or the blood-cerebrospinal fluid barrier) [81].

License: CC BY-NC 4.0

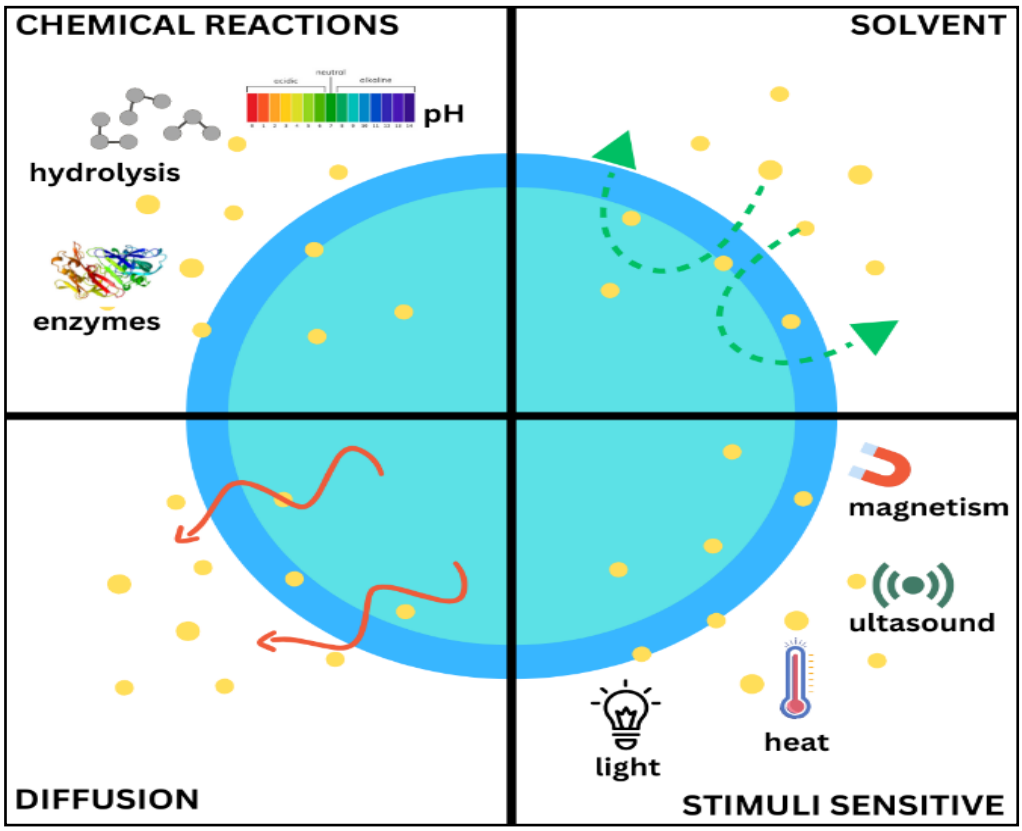


Figure 1. Mechanisms concerning the release of drugs by the use of various types of nanocarriers.

For example, hyaluronic acid (a polysaccharide found in the extracellular matrix) was recently used as a ligand-appended in multiple nanocarriers, demonstrating promising outcomes in enhancing the antitumor effect against breast cancer cells [82], the melanoma stem-like cells [83], pulmonary adenocarcinoma cells [84], and also to help with intravitreal drug delivery for retinal gene therapy [75] as well as to reduce the immunogenicity of the formed protein corona [74]. However, building ligand-appended systems for drug delivery requires a lot of work, and numerous targeting designs must be made in advance, considering physiological factors like blood flow, illness severity, and tissue architecture [85]. More research is needed to determine how ligand-appended nanocarriers interact with the membranes of cells, and it is yet unknown how they are absorbed.

Furthermore, it is well known that phagocytic or non-phagocytic pathways (such as caveolae-mediated endocytosis, clathrin-mediated endocytosis, and others) are used by cells to take up nanoparticles [86], [87]. However, due to the unique physicochemical properties of each delivery system, it has been challenging to standardize the mechanism of action/interaction of these systems in cells. For instance, Salatin and Khosroushahi [88] highlighted the key endocytosis pathways in a review that oversees cell uptake of polysaccharide nanoparticles carrying active ingredients. However, by using external stimuli like heat [89]–[91], ultrasound [92], magnetism [93], [94], pH [95], light [96], and ionic strength [97], stimuli-responsive nanocarriers have demonstrated the capacity to control the release profile of drugs (as a triggered release) that can enhance targeting and enable greater dosage control (Fig. 1). For instance, lipids or polymeric nanocarriers are joined with superparamagnetic iron oxide nanoparticles [98] to first initiate a controlled-release system through the application of an external magnetic field. Ulbrich et al. [99] also discussed the effectiveness of covalently / non-covalently attached medicines for the treatment of cancer while reviewing current developments in drug-delivery systems, particularly those based on polymeric and magnetic nanoparticles. For use in NIR-triggered chemo-photothermal treatment, Au/Fe3O4 polymer nanoparticles were additionally created [100]. Due

License: CC BY-NC 4.0

to their ability to combine the characteristics of various systems into a single system and thereby guarantee materials with improved performance both in therapeutic and diagnostic applications (i.e., theragnostic systems), hybrid nanocarriers are, at present, among the most promising tools for nanomedicine. Despite this, there is a need for more research because little is understood about the true mechanisms of action as well as the toxicity of these drug-delivery systems. Studies that use plant extracts along with microorganisms to create ecologically friendly chemical processes to create nanocarriers have also grown in number [101].

Green Nanoparticles and Drug Delivery:

According to a World Health Organization (WHO) assessment, traditional medicine provides basic healthcare to 80% or more of the population in underdeveloped nations [102]. The scientific community is currently researching bioactive substances, their chemical makeup, and the pharmacological properties of various plant species to develop novel active components with fewer adverse side effects than current molecules [103]. Plants have long been recognized as significant sources of natural chemicals with therapeutic value, and they continue to hold a wealth of information for the development of novel, highly effective medications. However, because they come from living things whose metabolite composition shifts under stress, active chemicals from natural sources are linked to several problems. Pharmaceutical firms have decided to pool their resources to develop synthetic molecules in this way [103], [104]. Despite these obstacles, research on active compounds derived from natural products is now again receiving attention as the total quantity of marketed synthetic molecules continues declining [105]. Most commercially available natural chemicals with therapeutic potential that are of economic significance were found in higher plants [103], [106]. There are multiple naturally derived therapeutic agents which already exist in commercially available drugs.

Numerous natural chemicals' makeup and activities have already been investigated and established. The bioactive molecules present in plants include, among others, alkaloids, tannins, flavonoids, terpenes, steroids, saponins, and phenolic compounds. However, these substances typically have low absorption capacities because they cannot permeate lipid membranes due to their large molecular sizes, which results in decreased bioavailability along with efficacy [107]. These compounds also have high systemic clearance, which necessitates frequent administration and/or high doses and reduces the therapeutic efficacy of the medicine. By delivering instruments capable of resolving the issues raised above that prevent the use of these compounds on a wide scale in nanomedicine, the scientific advancement of nanotechnology has the potential to revolutionize the research and development of natural product-based formulations. In the past few years, there has been a lot of research done on the use of nanotechnology methods throughout the medical profession [108]. Therefore, they can get around these obstacles and enable the use of various substances and mixes in the creation of an identical formulation. They can also alter a compound's characteristics and behavior within a biological system. In addition to improving a product's solubility and stability, release systems also route a compound to a specific region, boost bioavailability, prolong the duration of a compound's activity, and mix molecules with different levels of hydrophilicity and lipophilicity. Additionally, there is proof that the combination of release mechanisms along with natural compounds may delay the emergence of drug resistance and, as a result, play a crucial role in the search for novel therapeutic options for several diseases that do not respond well to conventional modern medical approaches [105].

The materials made from natural products fall into one of two categories: (1) those that are released at specific locations to treat a variety of ailments [60], [109] or (2) those that are mostly used in the process of synthesis [110]. Since cancer is currently the leading cause of death worldwide, most of the research is focused on developing treatments for the disease [111]. Yet several applications of nanomedicine for other illnesses are also being worked on [112], [113]. Since cancer affects various body organs, the need to develop another form of medicine to target cancerous cells is of the utmost importance to modern researchers. These delivery methods are divided into groups based on their particle size, surface charge, size dispersion,

License: CC BY-NC 4.0

form, stability, encapsulation potential, and biological activity, which are then used in accordance with their specific needs [114]. Fig. 2 gives some illustrations of biological chemicals derived from higher plants and their applications in the field of nanomedicine. For the advancement and design of contemporary pharmaceuticals as well as the improvement of current ones, the pharmaceutical industries have consistently sought the development and implementation of new technologies [68], [115]. In this regard, the rapid advancement of nanotechnology has prompted the development of new formulations using a variety of strategies, including delivering the drug to its site of action (nano pharmaceutics), imaging and diagnosing (nano diagnostic), implanting medical devices (nano biomaterials), and combining disease diagnosis and treatment (nano-theragnostic) [68], [116], [117].

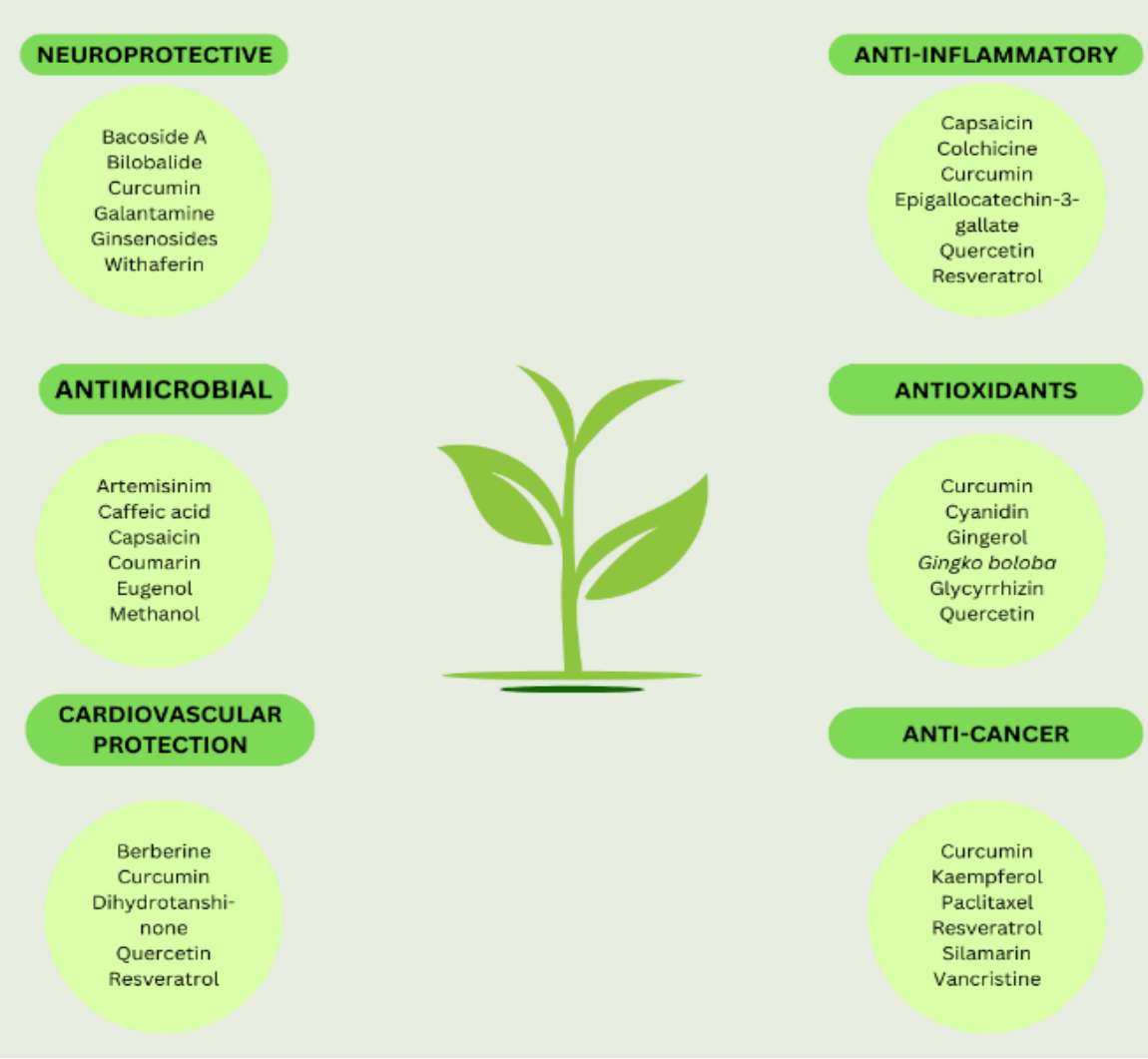


Figure 2. Different plant-derived substances that may be employed for nanoparticle synthesis.

Many of the nanomedicines currently under development involve altered release mechanisms for active ingredients that have been utilized to treat patients [117], [118]. It is assessed for this type of strategy whether the sustained release alters the pharmacokinetic profile and biodistribution of these ingredients. If the active ingredients are directed into the target tissue and exhibit enhanced uptake/absorption by the cells and a decreased toxicity profile for the organism, it can be determined that the nano-formulation offers benefits over the current formulation [119], [120]. Resveratrol, berberine, ellagic acid, curcumin, and quercetin are the main topics of this section [8]. Doxorubicin, paclitaxel, and vancomycin are a few additional

License: CC BY-NC 4.0

substances that were suggested; they are all derived from natural materials.

Natural substances have been used to create nanoparticles. For instance, it has been reported that various microorganisms, such as bacteria, fungi, algae, yeast, and so on [121] or plant extracts, can be used to generate metallic, metal oxide, and sulfide nanoparticles. The first method involves preparing the microbe that helps with the synthesis process in the appropriate growth medium, mixing it with a metal precursor in solution, and then allowing it to incubate to produce nanoparticles intracellularly/extracellularly [122]. In the second method, the plant extract is made, combined with the metal precursor in solution, and then further incubated at either ambient temperature or boiling temperature or exposed to light, which acts as an external stimulus [123].

Because they have intriguing qualities like being biodegradable, biocompatible, readily available, renewable, and exhibiting low toxicity, these natural product-based materials are currently considered crucial ingredients in preparing and processing novel nano-formulations [124]–[126]. Biomaterials typically allow for chemical alteration in addition to the characteristics, which ensures that they have unique and desired qualities for their prospective applications in the growing field of nanomedicine [127], [128]. Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae have all been used to synthesize distinct morphological forms of gold, silver, cadmium sulfide, and titanium dioxide [122]. Due to their greater potential among all metal nanoparticles, these nanoparticles, particularly the silver ones, have been extensively examined in vitro for their antifungal, antibacterial, and cytotoxicity potential [129], [130]. When nanoparticle production is mediated by microorganisms, most of the research is concentrated on how the microorganisms decrease metal precursors and produce the nanoparticles. As an illustration, Rahimi et al. [131] produced silver nanoparticles using Candida albicans and investigated their antibacterial effectiveness against two harmful bacteria, Staphylococcus aureus and E. coli. Similarly, Ali et al. [132] created silver nanoparticles using an aqueous extract of Artemisia absinthium and tested their efficacy against Phytophthora parasitica and Phytophthora capsici.

Additionally, Malapermal et al. [133] created nanoparticles from extracts of Ocimum basilicum and Ocimum sanctum and investigated their antibacterial and antidiabetic properties against *E. coli, Salmonella spp., S. aureus*, and *P. aeruginosa*. Similarly, Sankar et al. [134] investigated the antibacterial and anti-cancer effects of silver nanoparticles on a human lung cancer cell line. Besides the use of microorganisms, silver, gold, and iron oxide nanoparticles were also synthesized using various food waste materials such as extracts of *Zea mays* leaves [135], onion peel extract [136], silky hairs of *Zea mays* [137], outer peel of fruit of *Cucumis melo* and *Prunus persica* [135], outer peel of *Prunus persica* [138] and the rind extract of watermelon [139], etc. and have tested their potential antibacterial effects against various foodborne pathogenic bacteria, anticandidal activity against a number of pathogenic *Candida* spp., for their potential antioxidant activity and proteasome inhibitory effects. However, it needs to be kept in mind that some of the metals (i.e., cadmium, silver) may be toxic in vivo if released prematurely from microbial carriers, as these may be charged ions and, therefore, not inert, potentially rendering them unsuitable for human use.

Liposomes, crystal nanoparticles, micelles, polymeric nanoparticles, superparamagnetic iron oxide nanoparticles, solid lipid nanoparticles, silica-based nanoparticles, and dendrimers are the most frequently researched nanocarriers for drug delivery [140]–[142]. These nanocarriers are all designed for medicine delivery using natural product-based ingredients. Gupta et al. [143] created chitosan-based nanoparticles filled with paclitaxel (Taxol), a substance derived from the Taxus brevifolia plant, for the treatment of various cancers. Compared to pure paclitaxel, the authors found that the drug-loaded with nanoparticles displayed improved activity, high cell uptake, sustained release, and lower hemolytic toxicity [143]. The barberry plant produces the alkaloid known as berberine. A heparin/berberine combination was developed [144] to boost *Helicobacter pylori* growth suppression while also minimizing harmful effects on infected cells.

To encapsulate vancomycin, a glycopeptide antibiotic produced in Amycolatopsis orientalis cultures, ellagic acid-SLNs (Solid Lipid Nanoparticles) were created [145]. Additionally, in

License: CC BY-NC 4.0

vivo testing on rabbits showed that ellagic acid inhibited the production of free oxygen radicals, and their clearance encouraged healing. Citrus vegetables and citrus fruits include the polyphenol quercetin, a member of the flavonoid family with antioxidant effects. Polymeric micelles were utilized to transport quercetin in a study by Dian et al. [146], and the results showed that these micelles could give continuous release for as long as ten days in vitro, with sustained plasma level and increased full accessibility of the medication under in vivo settings.

Doxorubicin (DOX) is a naturally occurring compound produced from various distinct wild-type strains of Streptomyces [126] and is widely used in human cancer chemotherapy. A versatile liquid crystal nanoparticle system with transferrin-functionalized nanoparticles was created by Spillmann et al. [147] for doxorubicin delivery and intracellular fluorescence imaging. In HEK 293T/17 cells, cellular absorption, and sustained release were achieved within endocytic vesicles. To monitor the particles and encapsulate medicines intended for intracellular administration, perylene was utilized as a chromophore. Agarwal et al. [148] developed a dendrimer formulation based on dextran and assessed the formulation's hemolytic activity and drug discharge capability in an in vitro setting. They concluded that the dendritic structure only affects the highly permeable area of the afflicted cells, sparing the healthy tissues and making it more practical for use in biomedical research. Doxil, a type of doxorubicin that was the first nano-drug to receive FDA approval in 1995, is delivered via foliate-functionalized iron oxide nanoparticles with superparamagnetic properties that were first created to treat liver cancer [149]. Compared to Doxil® alone, the in vivo trials in rabbits and rats revealed a two- to fourfold decrease, while folate helped and strengthened precise targeting [150]. The most researched nanostructures are liposomes, employed in several formulations to carry natural compounds like resveratrol [151]. It has been claimed that curcumin, a polyphenolic molecule derived from turmeric, is used to treat malignancies of the breast, bone, lung, cervix, liver, and prostate [152]. For the treatment of cancer, liposomal curcumin formulations have been created [153]. Curcumin was encapsulated in liposomes using several techniques by Cheng et al., who then evaluated the results and found that the approach that depended on pH produced stable products that had good efficiency in encapsulation and bioaccessibility that might be used to treat cancer [154]. Overall, it can be stated that continuous release systems of naturally existing therapeutic compounds provide themselves as a key tool for enhancing their biological activity and minimizing their constraints by offering fresh options for treating chronic and fatal diseases. [155].

Recent Trends and Discussion:

There are now 51 products that utilize this technology being used in clinical practice in the present-day medical nanotechnology landscape [118], [156]–[158]. Notably, these nanomedicines are generally created for pharmaceuticals with limited aqueous dissolution and highly toxic effects, and they frequently could increase the pharmacokinetic features of the drug in consideration while lowering its toxicity. Although only a small number of nanomedicines have been subject to FDA regulation, a recent analysis by Caster et al. [159] found that numerous clinical trial programs are presently underway, indicating that many new pharmaceuticals based on nanotechnology will soon be able to enter the market. Among these nanomaterials, 18 are geared toward chemotherapeutics, 15 are for antibacterial drugs, 28 are for various medical uses, including treating autoimmune illnesses, psychological disorders, and many others, and 30 are for nucleic acid-based therapies.

All nations, developed or developing, are expanding their spending on scientific and technological advancement in this field because of the rapid development of nanotechnology in recent years. However, the characterization of these nanomaterials regarding safety and toxicity and the absence of effective regulation provide significant challenges to researchers working on practical uses of nano-drugs. The therapeutic potential of nanomedicine is hampered by the lack of clear regulatory criteria for developing and assessing the properties of these nanomaterials, even though the list of approved nanomedicine is rather long. Different nanomaterials' structure/function relationships, as well as their traits, makeup, and surface coating, interact with biological systems. Additionally, because these nanomedicines do not reflect the characteristics of the individual particle, it is crucial to consider the possibility of aggregate

License: CC BY-NC 4.0

and agglomerate formation when introducing them into biological systems. Depending on the nano-formulation, this could lead to unexpected toxic effects and different results [160].

Many researchers have struggled to determine the toxicity of nano-drugs in the early stages of testing due to the lack of standard protocols for physio-chemical and physiological/biological characterization of nanomedicines. This has led to failures in late-phase clinical trials. Stronger collaboration between regulatory bodies is required to streamline or minimize the approval process for nano-based medicines/drugs, drug-delivery systems, etc. [118], [161].

The safety evaluation, toxicity testing, and compatibility testing of nanomedicines, along with nano-drug delivery systems, are done based on the rules the FDA uses for conventional medications to defend against their lack of regulation. Nanomedicines and nano-drug delivery systems start the clinical trials phase after the FDA grants the designation of new research drugs (Investigational New Drug, IND) to examine their safety and effectiveness in people. Phase 1, which mostly investigates safety, is followed by Phase 2, which primarily evaluates efficacy, and Phase 3, which primarily evaluates safety, efficacy, and dosage. The FDA may submit an IND after receiving approval in each of these three stages to ask for approval of novel nanomedicines or nano-drug delivery systems. However, this method of regulating nanomedicine has been seriously contested [156], [162]

Considering nanotechnology's rapid growth and prospective applications in nanomedicine, a revised and more comprehensive regulatory strategy is urgently needed. To ensure the release of safe and helpful nanomedicine for patients, country governments must collaborate to design new guidelines that must be precise and sufficiently stringent to address any safety issues [162], [163].

Future Aspects with Respect to Nanomedicine and Ayurveda:

In recent years, the convergence of modern scientific breakthroughs and ancient healing traditions has sparked growing interest and exploration in healthcare innovation. One such intriguing intersection lies in the synergistic combination of nanomedicine and Ayurveda. Nanomedicine, with its precision and targeted approach, and Ayurveda, with its holistic wisdom and personalized therapies, offer complementary strengths that hold the potential to reshape the landscape of medical treatment. As researchers delve deeper into this interdisciplinary collaboration, a horizon of promising future aspects emerges, poised to revolutionize drug delivery, diagnostics, and holistic well-being. A few of the possible future aspects have been discussed as follows:

Personalized Healthcare: Ayurveda emphasizes individualized treatments based on one's unique constitution (dosha) and imbalances. A new era of personalized healthcare could emerge when combined with nanomedicine, which enables targeted drug delivery and precise diagnostics at the molecular level. Nanotechnology could enhance Ayurvedic therapies by delivering herbs or compounds directly to specific cells or tissues, optimizing treatment effectiveness while minimizing adverse effects.

Enhanced Drug Delivery: Nanotechnology offers the ability to encapsulate and deliver bioactive compounds from Ayurvedic herbs in a controlled and targeted manner. This could lead to improved bioavailability, prolonged release, reduced side effects, and less toxicity of herbal remedies. Nano-sized carriers could transport these compounds across barriers like the blood-brain barrier, enabling more effective treatment of neurological disorders.

Combating Antibiotic Resistance: Ayurveda has a rich history of using natural substances with antimicrobial properties. By utilizing nanotechnology, these natural compounds could be encapsulated in nanoparticles to create potent antimicrobial agents. This could address the global challenge of antibiotic resistance by providing alternative treatment options.

Chronic Disease Management: Ayurveda balances the body's systems to prevent and manage chronic diseases. Nanomedicine could enhance Ayurvedic treatments for diabetes, cardiovascular diseases, and cancer. Nanoparticles could deliver therapeutic agents directly to affected tissues, improving efficacy and reducing side effects.

Diagnostics and Monitoring: Ayurvedic diagnostics, which include pulse analysis and tongue examination, could be complemented by advanced nanosensors. These sensors could

License: CC BY-NC 4.0

detect biomarkers and provide real-time information about the body's physiological state. Integrating Ayurvedic diagnostic techniques with nanotechnology could offer a holistic and data-driven approach to health assessment. It also promises to enable early cancer detection through innovative nanoparticle-based diagnostic approaches, enhancing the potential for timely intervention and improved patient outcomes.

Regenerative Medicine: Ayurveda emphasizes rejuvenation and revitalization. Nanotechnology could facilitate tissue engineering and regenerative medicine by delivering growth factors or stem cells to promote tissue repair and regeneration, aligning with Ayurvedic principles of restoring balance and vitality. Nanoparticles enhance stem cell therapies for anti-aging by optimizing delivery and rejuvenation, showing potential for transformative outcomes.

Natural Product Standardization: Ayurveda often employs natural ingredients with variable compositions. Nanotechnology could enable the standardization of herbal products by encapsulating bioactive compounds in nanoparticles with consistent concentrations. This would ensure reproducible and reliable therapeutic effects.

Global Healthcare Accessibility: The fusion of Ayurveda and nanomedicine could contribute to affordable and accessible healthcare solutions, especially in resource-constrained regions. Nanotechnology-based Ayurvedic therapies could provide effective treatments with lower doses and reduced side effects, making them more accessible to a wider population.

Stress Management: Nanoparticles can optimize the delivery of Ayurvedic remedies, enhancing their effectiveness in combating stress. This collaboration also holds the potential for personalized stress assessment, targeted neurological interventions, and reduced side effects. By integrating Ayurvedic practices with nanotechnology, a comprehensive approach to stress relief emerges, potentially promoting emotional balance, resilience, and overall well-being. Ethical considerations ensure this fusion respects cultural values while advancing innovative solutions for modern-day stress challenges.

Conclusion:

This review highlights the scope for integrating green nanoparticle-based drug-delivery systems with Ayurveda and presents a compelling opportunity to bridge ancient healing wisdom with modern scientific advancements by bringing forward the recent advancements in the field of Ayurveda and nanomedicine. Combining the principles of Ayurveda with green nanoparticles offers an eco-friendly approach to drug delivery, aligning with Ayurvedic emphasis on natural remedies and sustainable practices. This convergence could lead to the development of environmentally conscious therapeutic solutions. The potential for enhanced therapeutic efficacy through targeted delivery of Ayurvedic bioactive compounds using green nanoparticles holds promise. This could potentially optimize treatment outcomes and reduce side effects, aligning with Ayurveda's holistic approach to healing. By encapsulating Ayurvedic ingredients within green nanoparticles, the bioavailability and stability of herbal compounds can be addressed, potentially unlocking their full therapeutic potential. This aligns with Ayurvedic teachings on optimal absorption and assimilation of remedies. The personalized and targeted approach of Ayurveda, combined with the precision of green nanoparticle-based drug delivery, could usher in a new era of individualized medicine. This convergence represents a powerful example of how the synergy between traditional knowledge and scientific progress can drive transformative advancements in medicine.

Conflict of interests

The authors declare no conflicts of interest. For a signed statement, please contact the journal office at editor@precisionnanomedicine.com.

Funding:

No External Funding was applied to this article.

License: CC BY-NC 4.0

Acknowledgments

The authors are grateful to the Amity Institute of Biotechnology, Amity University Noida & Department of Biotechnology, for providing us with the facilities and infrastructure for working on this review article.

Quote this article as Kaushik A, Singh RK, Tyagi PK, Green Synthesized Nanoparticle-Based Drug Delivery: Recent Trends and Future Prospects, Precis. Nanomed. 2023, 6(3):1109-1132, https://doi.org/10.33218/001c.89165

References

[1] M. L. Cohen, "Changing patterns of infectious disease," *Nature*, vol. 406, no. 6797, pp. 762–767, Aug. 2000, doi: 10.1038/35021206.

[2] P. W. Taylor, P. D. Stapleton, and J. Paul Luzio, "New ways to treat bacterial infections," *Drug Discov Today*, vol. 7, no. 21, pp. 1086–1091, Nov. 2002, doi: 10.1016/S1359-6446(02)02498-4.

[3] M. Ferrari, "Cancer nanotechnology: opportunities and challenges," *Nat Rev Cancer*, vol. 5, no. 3, pp. 161–171, Mar. 2005, doi: 10.1038/nrc1566.

[4] C. M. Niemeyer, "Nanoparticles, Proteins, and Nucleic Acids: Biotechnology Meets Materials Science," *Angewandte Chemie International Edition*, vol. 40, no. 22, pp. 4128–4158, Nov. 2001, doi: 10.1002/1521-3773(20011119)40:22<4128::AID-ANIE4128>3.0.CO;2-S.

[5] J. O. Metzger, "Book Review: Handbook of Green Chemistry and Technology. Edited by James Clark and Duncan Macquarrie," *Angewandte Chemie International Edition*, vol. 42, no. 6, pp. 601–602, Feb. 2003, doi: 10.1002/anie.200390172.

[6] K. W. Robert, T. M. Parris, and A. A. Leiserowitz, "What is Sustainable Development? Goals, Indicators, Values, and Practice," *Environment: Science and Policy for Sustainable Development*, vol. 47, no. 3, pp. 8–21, Apr. 2005, doi: 10.1080/00139157.2005.10524444.

[7] A. M. Omer, "Energy, environment and sustainable development," *Renewable and Sustainable Energy Reviews*, vol. 12, no. 9, pp. 2265–2300, Dec. 2008, doi: 10.1016/j.rser.2007.05.001.

[8] D. Nath and P. Banerjee, "Green nanotechnology – A new hope for medical biology," *Environ Toxicol Pharmacol*, vol. 36, no. 3, pp. 997–1014, Nov. 2013, doi: 10.1016/j.etap.2013.09.002.

[9] S. E. , F. M. , Y. M. , V. D. , T. L. Razavi M., *Green Processes for Nanotechnology*. Cham: Springer International Publishing, 2015. doi: 10.1007/978-3-319-15461-9.

[10] K. B. Narayanan and N. Sakthivel, "Green synthesis of biogenic metal nanoparticles by terrestrial and aquatic phototrophic and heterotrophic eukaryotes and biocompatible agents," *Adv Colloid Interface Sci*, vol. 169, no. 2, pp. 59–79, Dec. 2011, doi: 10.1016/j.cis.2011.08.004.

[11] C. Hano and B. H. Abbasi, "Plant-Based Green Synthesis of Nanoparticles: Production, Characterization and Applications," *Biomolecules*, vol. 12, no. 1, p. 31, Dec. 2021, doi: 10.3390/biom12010031.

[12] L. S. Mbatha, J. Akinyelu, C. I. Chukwuma, M. P. Mokoena, and T. Kudanga, "Current Trends and Prospects for Application of Green Synthesized Metal Nanoparticles in Cancer and COVID-19 Therapies," *Viruses*, vol. 15, no. 3, p. 741, Mar. 2023, doi: 10.3390/v15030741.

[13] A. S. Schwartz-Duval *et al.*, "Intratumoral generation of photothermal gold nanoparticles through a vectorized biomineralization of ionic gold," *Nat Commun*, vol. 11, no. 1, p. 4530, Sep. 2020, doi: 10.1038/s41467-020-17595-6.

[14] G. Marslin, C. J. Sheeba, and G. Franklin, "Nanoparticles Alter Secondary Metabolism in Plants via ROS Burst," *Front Plant Sci*, vol. 8, May 2017, doi: 10.3389/fpls.2017.00832.

[15] D. C. Luther *et al.*, "Delivery of drugs, proteins, and nucleic acids using inorganic nanoparticles," *Adv Drug Deliv Rev*, vol. 156, pp. 188–213, 2020, doi: 10.1016/j.addr.2020.06.020.

[16] G. Marslin *et al.*, "Secondary Metabolites in the Green Synthesis of Metallic Nanoparticles," *Materials*, vol. 11, no. 6, p. 940, Jun. 2018, doi: 10.3390/ma11060940.

[17] I. de Lázaro and D. J. Mooney, "Obstacles and opportunities in a forward vision for cancer nanomedicine," *Nat Mater*, vol. 20, no. 11, pp. 1469–1479, Nov. 2021, doi: 10.1038/s41563-021-01047-7.

[18] W. Jiang, Y. Wang, J. A. Wargo, F. F. Lang, and B. Y. S. Kim, "Considerations for designing preclinical cancer immune nanomedicine studies," *Nat Nanotechnol*, vol. 16, no. 1, pp. 6–15, Jan. 2021, doi: 10.1038/s41565-020-00817-9.

[19] H. Barabadi *et al.*, "Nanobiotechnology as an emerging approach to combat malaria: A systematic review," *Nanomedicine*, vol. 18, pp. 221–233, Jun. 2019, doi: 10.1016/j.nano.2019.02.017.

License: CC BY-NC 4.0

[20] M. Sousa de Almeida, E. Susnik, B. Drasler, P. Taladriz-Blanco, A. Petri-Fink, and B. Rothen-Rutishauser, "Understanding nanoparticle endocytosis to improve targeting strategies in nanomedicine," *Chem Soc Rev*, vol. 50, no. 9, pp. 5397–5434, 2021, doi: 10.1039/D0CS01127D.
[21] S. Sindhwani and W. C. W. Chan, "Nanotechnology for modern medicine: next step towards clinical translation," *J Intern Med*, vol. 290, no. 3, pp. 486–498, Sep. 2021, doi: 10.1111/joim.13254.
[22] S. Kantak, N. Rajurkar, and P. Adhyapak, "Synthesis and characterization of Abhraka (mica) bhasma by two different methods," *J Ayurveda Integr Med*, vol. 11, no. 3, pp. 236–242, Jul. 2020, doi: 10.1016/j.jaim.2018.11.003.
[23] N. Singh and K. R. C. Reddy, "Pharmaceutical study of Lauha Bhasma," *AYU (An International Quarterly Journal of Research in Ayurveda)*, vol. 31, no. 3, p. 387, 2010, doi: 10.4103/0974-8520.77157.
[24] S. Rai, S. Singh, D. N. S. Gautam, and M. Kumar, "Synthesis, characterization and histopathological study of a lead-based Indian traditional drug: *Naga Bhasma*," *Indian J Pharm Sci*, vol. 72, no. 1, p. 24, 2010, doi: 10.4103/0250-474X.62232.
[25] R. Chaturvedi and C. Jha, "Standard manufacturing procedure of Rajata Bhasma," *AYU (An International Quarterly Journal of Research in Ayurveda)*, vol. 32, no. 4, p. 566, 2011, doi: 10.4103/0974-8520.96135.
[26] D. Pal, C. Sahu, and A. Haldar, "Bhasma : The ancient Indian nanomedicine," *J Adv Pharm Technol Res*, vol. 5, no. 1, p. 4, 2014, doi: 10.4103/2231-4040.126980.
[27] Singh SK, Chaudhary A, Rai DK, and Rai SB, "Preparation and characterization of a mercury based Indian traditional drugRas-Sindoor," *Indian J Tradit Knowl*, 2009.
[28] Singh RK, Kumar S, Aman AK, Kr S, and Kar M, "Physical properties of an Indian Ayurvedic medicine (Shankh Bhasma) as nano materials for its application. ," *Indian J Tradit Knowl.* , 2019.
[29] D. Beaudet *et al.*, "Comparative study on cellular entry of incinerated ancient gold particles (Swarna Bhasma) and chemically synthesized gold particles," *Sci Rep*, vol. 7, no. 1, p. 10678, Sep. 2017, doi: 10.1038/s41598-017-10872-3.
[30] S. Biswas *et al.*, "Physicochemical characterization of Suvarna Bhasma, its toxicity profiling in rat and behavioural assessment in zebrafish model," *J Ethnopharmacol*, vol. 249, p. 112388, Mar. 2020, doi: 10.1016/j.jep.2019.112388.
[31] S. Mohaptra and C. Jha, "Physicochemical characterization of Ayurvedic bhasma (Swarna makshika bhasma): An approach to standardization," *Int J Ayurveda Res*, vol. 1, no. 2, p. 82, 2010, doi: 10.4103/0974-7788.64409.
[32] S. Y. Chaudhari, M. B. Nariya, R. Galib, and P. K. Prajapati, "Acute and subchronic toxicity study of Tamra Bhasma (incinerated copper) prepared with and without Amritikarana," *J Ayurveda Integr Med*, vol. 7, no. 1, pp. 23–29, Mar. 2016, doi: 10.1016/j.jaim.2015.11.001.
[33] P. Jamadagni, S. Jamadagni, R. Singh, S. Upadhyay, S. Gaidhani, and J. Hazra, "Repeated dose oral toxicity of Trivanga Bhasma in Swiss albino mice," *AYU (An International Quarterly Journal of Research in Ayurveda)*, vol. 34, no. 1, p. 118, 2013, doi: 10.4103/0974-8520.115449.
[34] B. Kale and N. Rajurkar, "Synthesis and characterization of Vanga bhasma," *J Ayurveda Integr Med*, vol. 10, no. 2, pp. 111–118, Apr. 2019, doi: 10.1016/j.jaim.2017.05.003.
[35] R. Tripathi, A. Rathore, B. Mehra, and R. Raghubir, "Physico-chemical study of Vaikrānta bhasma," *Anc Sci Life*, vol. 32, no. 4, p. 199, 2013, doi: 10.4103/0257-7941.131971.
[36] A. Pareek and N. Bhatnagar, "Physico-chemical characterization of traditionally prepared Yashada bhasma," *J Ayurveda Integr Med*, vol. 11, no. 3, pp. 228–235, Jul. 2020, doi: 10.1016/j.jaim.2018.11.004.
[37] A. Wele, S. De, M. Dalvi, N. Devi, and V. Pandit, "Nanoparticles of biotite mica as Krishna Vajra Abhraka Bhasma: synthesis and characterization," *J Ayurveda Integr Med*, vol. 12, no. 2, pp. 269–282, Apr. 2021, doi: 10.1016/j.jaim.2020.09.004.
[38] G. Orive, A. R. Gascón, R. M. Hernández, A. Domínguez-Gil, and J. L. Pedraz, "Techniques: New approaches to the delivery of biopharmaceuticals," *Trends Pharmacol Sci*, vol. 25, no. 7, pp. 382–387, Jul. 2004, doi: 10.1016/j.tips.2004.05.006.
[39] S. Zafar Razzacki, "Integrated microsystems for controlled drug delivery," *Adv Drug Deliv Rev*, vol. 56, no. 2, pp. 185–198, Feb. 2004, doi: 10.1016/j.addr.2003.08.012.
[40] R. R. Joseph and S. S. Venkatraman, "Drug delivery to the eye: what benefits do nanocarriers offer?," *Nanomedicine*, vol. 12, no. 6, pp. 683–702, Mar. 2017, doi: 10.2217/nnm-2016-0379.

License: CC BY-NC 4.0

[41] G. Rudramurthy, M. Swamy, U. Sinniah, and A. Ghasemzadeh, "Nanoparticles: Alternatives Against Drug-Resistant Pathogenic Microbes," *Molecules*, vol. 21, no. 7, p. 836, Jun. 2016, doi: 10.3390/molecules21070836.
[42] P.-L. Lam, W.-Y. Wong, Z. Bian, C.-H. Chui, and R. Gambari, "Recent advances in green nanoparticulate systems for drug delivery: efficient delivery and safety concern," *Nanomedicine*, vol. 12, no. 4, pp. 357–385, Feb. 2017, doi: 10.2217/nnm-2016-0305.
[43] Y. Haba, C. Kojima, A. Harada, T. Ura, H. Horinaka, and K. Kono, "Preparation of Poly(ethylene glycol)-Modified Poly(amido amine) Dendrimers Encapsulating Gold Nanoparticles and Their Heat-Generating Ability," *Langmuir*, vol. 23, no. 10, pp. 5243–5246, May 2007, doi: 10.1021/la0700826.
[44] X. Shi, K. Sun, and J. R. Baker, "Spontaneous Formation of Functionalized Dendrimer-Stabilized Gold Nanoparticles," *The Journal of Physical Chemistry C*, vol. 112, no. 22, pp. 8251–8258, Jun. 2008, doi: 10.1021/jp801293a.
[45] S.-H. Park, S.-G. Oh, J.-Y. Mun, and S.-S. Han, "Loading of gold nanoparticles inside the DPPC bilayers of liposome and their effects on membrane fluidities," *Colloids Surf B Biointerfaces*, vol. 48, no. 2, pp. 112–118, Mar. 2006, doi: 10.1016/j.colsurfb.2006.01.006.
[46] A. P. K. G. de Villiers MM, *Nanotechnology in drug delivery.* 2008.
[47] A. V Kabanov, P. Lemieux, S. Vinogradov, and V. Alakhov, "Pluronic® block copolymers: novel functional molecules for gene therapy," *Adv Drug Deliv Rev*, vol. 54, no. 2, pp. 223–233, Feb. 2002, doi: 10.1016/S0169-409X(02)00018-2.
[48] B. Ouattara, R. E. Simard, R. A. Holley, G. J.-P. Piette, and A. Bégin, "Antibacterial activity of selected fatty acids and essential oils against six meat spoilage organisms," *Int J Food Microbiol*, vol. 37, no. 2–3, pp. 155–162, Jul. 1997, doi: 10.1016/S0168-1605(97)00070-6.
[49] G. Sharma, K. Raturi, S. Dang, S. Gupta, and R. Gabrani, "Combinatorial antimicrobial effect of curcumin with selected phytochemicals on *Staphylococcus epidermidis*," *J Asian Nat Prod Res*, vol. 16, no. 5, pp. 535–541, May 2014, doi: 10.1080/10286020.2014.911289.
[50] S. I. Abdelwahab *et al.*, "Thymoquinone-loaded nanostructured lipid carriers: preparation, gastroprotection, in vitro toxicity, and pharmacokinetic properties after extravascular administration," *Int J Nanomedicine*, p. 2163, Jun. 2013, doi: 10.2147/IJN.S44108.
[51] K. Krauel, T. Pitaksuteepong, N. M. Davies, and T. Rades, "Entrapment of Bioactive Molecules in Poly (Alkylcyanoacrylate) Nanoparticles," *American Journal of Drug Delivery*, vol. 2, no. 4, pp. 251–259, 2004, doi: 10.2165/00137696-200402040-00005.
[52] G. Zhai, Guo, Tan, and Liu, "Preparation and evaluation of quercetin-loaded lecithin-chitosan nanoparticles for topical delivery," *Int J Nanomedicine*, p. 1621, Aug. 2011, doi: 10.2147/IJN.S22411.
[53] M. Sechi *et al.*, "Development of novel cationic chitosan- and anionic alginate–coated poly(D,L-lactide-co-glycolide) nanoparticles for controlled release and light protection of resveratrol," *Int J Nanomedicine*, p. 5501, Oct. 2012, doi: 10.2147/IJN.S36684.
[54] L. Casettari and L. Illum, "Chitosan in nasal delivery systems for therapeutic drugs," *Journal of Controlled Release*, vol. 190, pp. 189–200, Sep. 2014, doi: 10.1016/j.jconrel.2014.05.003.
[55] B. Xu, R. Watkins, L. Wu, C. Zhang, and R. Davis, "Natural product-based nanomedicine: recent advances and issues," *Int J Nanomedicine*, p. 6055, Sep. 2015, doi: 10.2147/IJN.S92162.
[56] Y. Saadeh and D. Vyas, "Nanorobotic Applications in Medicine: Current Proposals and Designs," *Am J Robot Surg*, vol. 1, no. 1, pp. 4–11, Jun. 2014, doi: 10.1166/ajrs.2014.1010.
[57] A. Z. Mirza and F. A. Siddiqui, "Nanomedicine and drug delivery: a mini review," *Int Nano Lett*, vol. 4, no. 1, p. 94, Mar. 2014, doi: 10.1007/s40089-014-0094-7.
[58] H. Lu, J. Wang, T. Wang, J. Zhong, Y. Bao, and H. Hao, "Recent Progress on Nanostructures for Drug Delivery Applications," *J Nanomater*, vol. 2016, pp. 1–12, 2016, doi: 10.1155/2016/5762431.
[59] E. Blanco, H. Shen, and M. Ferrari, "Principles of nanoparticle design for overcoming biological barriers to drug delivery," *Nat Biotechnol*, vol. 33, no. 9, pp. 941–951, Sep. 2015, doi: 10.1038/nbt.3330.
[60] A. Kumari, V. Kumar, and S. K. Yadav, "Nanotechnology: A Tool to Enhance Therapeutic Values of Natural Plant Products," *Trends in Medical Research*, vol. 7, no. 2, pp. 34–42, Feb. 2012, doi: 10.3923/tmr.2012.34.42.
[61] S. Mignani, S. El Kazzouli, M. Bousmina, and J.-P. Majoral, "Expand classical drug administration ways by emerging routes using dendrimer drug delivery systems: A concise overview," *Adv Drug Deliv Rev*, vol. 65, no. 10, pp. 1316–1330, Oct. 2013, doi: 10.1016/j.addr.2013.01.001.

License: CC BY-NC 4.0

[62] V. Lounnas, T. Ritschel, J. Kelder, R. McGuire, R. P. Bywater, and N. Foloppe, "CURRENT PROGRESS IN STRUCTURE-BASED RATIONAL DRUG DESIGN MARKS A NEW MINDSET IN DRUG DISCOVERY," *Comput Struct Biotechnol J*, vol. 5, no. 6, p. e201302011, Feb. 2013, doi: 10.5936/csbj.201302011.

[63] T. Mavromoustakos *et al.*, "Strategies in the Rational Drug Design," *Curr Med Chem*, vol. 18, no. 17, pp. 2517–2530, Jun. 2011, doi: 10.2174/092986711795933731.

[64] P. T. Wong and S. K. Choi, "Mechanisms of Drug Release in Nanotherapeutic Delivery Systems," *Chem Rev*, vol. 115, no. 9, pp. 3388–3432, May 2015, doi: 10.1021/cr5004634.

[65] V. Prachayasittikul *et al.*, "Computer-Aided Drug Design of Bioactive Natural Products," *Curr Top Med Chem*, vol. 15, no. 18, pp. 1780–1800, Jun. 2015, doi: 10.2174/1568026615666150506151101.

[66] G. Chen, I. Roy, C. Yang, and P. N. Prasad, "Nanochemistry and Nanomedicine for Nanoparticle-based Diagnostics and Therapy," *Chem Rev*, vol. 116, no. 5, pp. 2826–2885, Mar. 2016, doi: 10.1021/acs.chemrev.5b00148.

[67] T. Rodrigues, D. Reker, P. Schneider, and G. Schneider, "Counting on natural products for drug design," *Nat Chem*, vol. 8, no. 6, pp. 531–541, Jun. 2016, doi: 10.1038/nchem.2479.

[68] B. Pelaz *et al.*, "Diverse Applications of Nanomedicine," *ACS Nano*, vol. 11, no. 3, pp. 2313–2381, Mar. 2017, doi: 10.1021/acsnano.6b06040.

[69] B. D. Mattos, O. J. Rojas, and W. L. E. Magalhães, "Biogenic silica nanoparticles loaded with neem bark extract as green, slow-release biocide," *J Clean Prod*, vol. 142, pp. 4206–4213, Jan. 2017, doi: 10.1016/j.jclepro.2016.11.183.

[70] C. Kinnear, T. L. Moore, L. Rodriguez-Lorenzo, B. Rothen-Rutishauser, and A. Petri-Fink, "Form Follows Function: Nanoparticle Shape and Its Implications for Nanomedicine," *Chem Rev*, vol. 117, no. 17, pp. 11476–11521, Sep. 2017, doi: 10.1021/acs.chemrev.7b00194.

[71] M. Sethi *et al.*, "Effect of drug release kinetics on nanoparticle therapeutic efficacy and toxicity," *Nanoscale*, vol. 6, no. 4, pp. 2321–2327, 2014, doi: 10.1039/C3NR05961H.

[72] N. Kamaly, B. Yameen, J. Wu, and O. C. Farokhzad, "Degradable Controlled-Release Polymers and Polymeric Nanoparticles: Mechanisms of Controlling Drug Release," *Chem Rev*, vol. 116, no. 4, pp. 2602–2663, Feb. 2016, doi: 10.1021/acs.chemrev.5b00346.

[73] V. TORCHILIN, "Multifunctional nanocarriers☆," *Adv Drug Deliv Rev*, vol. 58, no. 14, pp. 1532–1555, Dec. 2006, doi: 10.1016/j.addr.2006.09.009.

[74] A. Almalik *et al.*, "Hyaluronic Acid Coated Chitosan Nanoparticles Reduced the Immunogenicity of the Formed Protein Corona," *Sci Rep*, vol. 7, no. 1, p. 10542, Sep. 2017, doi: 10.1038/s41598-017-10836-7.

[75] T. F. Martens *et al.*, "Coating nanocarriers with hyaluronic acid facilitates intravitreal drug delivery for retinal gene therapy," *Journal of Controlled Release*, vol. 202, pp. 83–92, Mar. 2015, doi: 10.1016/j.jconrel.2015.01.030.

[76] B. Pelaz *et al.*, "Surface Functionalization of Nanoparticles with Polyethylene Glycol: Effects on Protein Adsorption and Cellular Uptake," *ACS Nano*, vol. 9, no. 7, pp. 6996–7008, Jul. 2015, doi: 10.1021/acsnano.5b01326.

[77] P. Kolhar *et al.*, "Using shape effects to target antibody-coated nanoparticles to lung and brain endothelium," *Proceedings of the National Academy of Sciences*, vol. 110, no. 26, pp. 10753–10758, Jun. 2013, doi: 10.1073/pnas.1308345110.

[78] J. Müller *et al.*, "Coating nanoparticles with tunable surfactants facilitates control over the protein corona," *Biomaterials*, vol. 115, pp. 1–8, Jan. 2017, doi: 10.1016/j.biomaterials.2016.11.015.

[79] W. Gao and L. Zhang, "Coating nanoparticles with cell membranes for targeted drug delivery," *J Drug Target*, vol. 23, no. 7–8, pp. 619–626, Sep. 2015, doi: 10.3109/1061186X.2015.1052074.

[80] H. Gao *et al.*, "Ligand modified nanoparticles increases cell uptake, alters endocytosis and elevates glioma distribution and internalization," *Sci Rep*, vol. 3, no. 1, p. 2534, Aug. 2013, doi: 10.1038/srep02534.

[81] A. Jain and S. K. Jain, "Ligand-Appended BBB-Targeted Nanocarriers (LABTNs)," *Crit Rev Ther Drug Carrier Syst*, vol. 32, no. 2, pp. 149–180, 2015, doi: 10.1615/CritRevTherDrugCarrierSyst.2015010903.

[82] X. Gao, J. Zhang, Q. Xu, Z. Huang, Y. Wang, and Q. Shen, "Hyaluronic acid-coated cationic nanostructured lipid carriers for oral vincristine sulfate delivery," *Drug Dev Ind Pharm*, vol. 43, no. 4, pp. 661–667, Apr. 2017, doi: 10.1080/03639045.2016.1275671.

License: CC BY-NC 4.0

[83] H. Shen, S. Shi, Z. Zhang, T. Gong, and X. Sun, "Coating Solid Lipid Nanoparticles with Hyaluronic Acid Enhances Antitumor Activity against Melanoma Stem-like Cells," *Theranostics*, vol. 5, no. 7, pp. 755–771, 2015, doi: 10.7150/thno.10804.

[84] T. Wang, J. Hou, C. Su, L. Zhao, and Y. Shi, "Hyaluronic acid-coated chitosan nanoparticles induce ROS-mediated tumor cell apoptosis and enhance antitumor efficiency by targeted drug delivery via CD44," *J Nanobiotechnology*, vol. 15, no. 1, p. 7, Dec. 2017, doi: 10.1186/s12951-016-0245-2.

[85] S. Muro, "Challenges in design and characterization of ligand-targeted drug delivery systems," *Journal of Controlled Release*, vol. 164, no. 2, pp. 125–137, Dec. 2012, doi: 10.1016/j.jconrel.2012.05.052.

[86] L. Kou, J. Sun, Y. Zhai, and Z. He, "The endocytosis and intracellular fate of nanomedicines: Implication for rational design," *Asian J Pharm Sci*, vol. 8, no. 1, pp. 1–10, Feb. 2013, doi: 10.1016/j.ajps.2013.07.001.

[87] Z. Li *et al.*, "Transporting carriers for intracellular targeting delivery via non-endocytic uptake pathways," *Drug Deliv*, vol. 24, no. 2, pp. 45–55, Nov. 2017, doi: 10.1080/10717544.2017.1391889.

[88] S. Salatin and A. Yari Khosroushahi, "Overviews on the cellular uptake mechanism of polysaccharide colloidal nanoparticles," *J Cell Mol Med*, vol. 21, no. 9, pp. 1668–1686, Sep. 2017, doi: 10.1111/jcmm.13110.

[89] Z. Al-Ahmady and K. Kostarelos, "Chemical Components for the Design of Temperature-Responsive Vesicles as Cancer Therapeutics," *Chem Rev*, vol. 116, no. 6, pp. 3883–3918, Mar. 2016, doi: 10.1021/acs.chemrev.5b00578.

[90] Y. Bai, F.-Y. Xie, and W. Tian, "Controlled Self-assembly of Thermo-responsive Amphiphilic H-shaped Polymer for Adjustable Drug Release," *Chinese Journal of Polymer Science*, vol. 36, no. 3, pp. 406–416, Mar. 2018, doi: 10.1007/s10118-018-2086-y.

[91] Z. Zhang *et al.*, "Temperature responsive fluorescent polymer nanoparticles (TRFNPs) for cellular imaging and controlled releasing of drug to living cells," *Colloids Surf B Biointerfaces*, vol. 159, pp. 905–912, Nov. 2017, doi: 10.1016/j.colsurfb.2017.08.060.

[92] T. S. Anirudhan and A. S. Nair, "Temperature and ultrasound sensitive gatekeepers for the controlled release of chemotherapeutic drugs from mesoporous silica nanoparticles," *J Mater Chem B*, vol. 6, no. 3, pp. 428–439, 2018, doi: 10.1039/C7TB02292A.

[93] Y. Guo *et al.*, "Light/magnetic hyperthermia triggered drug released from multi-functional thermo-sensitive magnetoliposomes for precise cancer synergetic theranostics," *Journal of Controlled Release*, vol. 272, pp. 145–158, Feb. 2018, doi: 10.1016/j.jconrel.2017.04.028.

[94] A. Hervault and N. T. K. Thanh, "Magnetic nanoparticle-based therapeutic agents for thermo-chemotherapy treatment of cancer," *Nanoscale*, vol. 6, no. 20, pp. 11553–11573, 2014, doi: 10.1039/C4NR03482A.

[95] L. Xu *et al.*, "Biodegradable pH-responsive hydrogels for controlled dual-drug release," *J Mater Chem B*, vol. 6, no. 3, pp. 510–517, 2018, doi: 10.1039/C7TB01851G.

[96] M. Mathiyazhakan, C. Wiraja, and C. Xu, "A Concise Review of Gold Nanoparticles-Based Photo-Responsive Liposomes for Controlled Drug Delivery," *Nanomicro Lett*, vol. 10, no. 1, p. 10, Jan. 2018, doi: 10.1007/s40820-017-0166-0.

[97] G. Ma *et al.*, "Development of ionic strength/pH/enzyme triple-responsive zwitterionic hydrogel of the mixed <scp>l</scp> -glutamic acid and <scp>l</scp> -lysine polypeptide for site-specific drug delivery," *J Mater Chem B*, vol. 5, no. 5, pp. 935–943, 2017, doi: 10.1039/C6TB02407F.

[98] J. Alonso *et al.*, "Superparamagnetic nanoparticles encapsulated in lipid vesicles for advanced magnetic hyperthermia and biodetection," *J Appl Phys*, vol. 119, no. 8, Feb. 2016, doi: 10.1063/1.4942618.

[99] K. Ulbrich, K. Holá, V. Šubr, A. Bakandritsos, J. Tuček, and R. Zbořil, "Targeted Drug Delivery with Polymers and Magnetic Nanoparticles: Covalent and Noncovalent Approaches, Release Control, and Clinical Studies," *Chem Rev*, vol. 116, no. 9, pp. 5338–5431, May 2016, doi: 10.1021/acs.chemrev.5b00589.

[100] C.-W. Chen *et al.*, "Encapsulation of Au/Fe_3O_4 nanoparticles into a polymer nanoarchitecture with combined near infrared-triggered chemo-photothermal therapy based on intracellular secondary protein understanding," *J Mater Chem B*, vol. 5, no. 29, pp. 5774–5782, 2017, doi: 10.1039/C7TB00944E.

License: CC BY-NC 4.0

[101] H. Jahangirian, E. Ghasemian lemraski, T. J. Webster, R. Rafiee-Moghaddam, and Y. Abdollahi, "A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine," *Int J Nanomedicine*, vol. Volume 12, pp. 2957–2978, Apr. 2017, doi: 10.2147/IJN.S127683.
[102] Robinson M and Zhang X, *The world medicines situation. Traditional medicines: global situation, issues and challenges.* Geneva: World Health Organization, 2011.
[103] A. G. Atanasov *et al.*, "Discovery and resupply of pharmacologically active plant-derived natural products: A review," *Biotechnol Adv*, vol. 33, no. 8, pp. 1582–1614, Dec. 2015, doi: 10.1016/j.biotechadv.2015.08.001.
[104] B. David, J.-L. Wolfender, and D. A. Dias, "The pharmaceutical industry and natural products: historical status and new trends," *Phytochemistry Reviews*, vol. 14, no. 2, pp. 299–315, Apr. 2015, doi: 10.1007/s11101-014-9367-z.
[105] M. Namdari, A. Eatemadi, M. Soleimaninejad, and A. T. Hammed, "A brief review on the application of nanoparticle enclosed herbal medicine for the treatment of infective endocarditis," *Biomedicine & Pharmacotherapy*, vol. 87, pp. 321–331, Mar. 2017, doi: 10.1016/j.biopha.2016.12.099.
[106] A. D. Kinghorn, L. Pan, J. N. Fletcher, and H. Chai, "The Relevance of Higher Plants in Lead Compound Discovery Programs," *J Nat Prod*, vol. 74, no. 6, pp. 1539–1555, Jun. 2011, doi: 10.1021/np200391c.
[107] H. Yuan, Q. Ma, L. Ye, and G. Piao, "The Traditional Medicine and Modern Medicine from Natural Products," *Molecules*, vol. 21, no. 5, p. 559, Apr. 2016, doi: 10.3390/molecules21050559.
[108] J. K. Patra, G. Das, and K.-H. Baek, "TOWARDS A GREENER ENVIRONMENT: SYNTHESIS AND APPLICATIONS OF GREEN NANOPARTICLES," *Pak J Agric Sci*, vol. 53, no. 02, pp. 345–354, Jun. 2016, doi: 10.21162/PAKJAS/16.3027.
[109] K. V. Ramana, S. S. Singhal, and A. B. Reddy, "Therapeutic Potential of Natural Pharmacological Agents in the Treatment of Human Diseases," *Biomed Res Int*, vol. 2014, pp. 1–4, 2014, doi: 10.1155/2014/573452.
[110] Guo W, *Green technology for nanoparticles in biomedical applications. In: Rai M, Posten C, editors. Green biosynthesis of nanoparticles: mechanisms and applications.* . 2013.
[111] A. Wicki, D. Witzigmann, V. Balasubramanian, and J. Huwyler, "Nanomedicine in cancer therapy: Challenges, opportunities, and clinical applications," *Journal of Controlled Release*, vol. 200, pp. 138–157, Feb. 2015, doi: 10.1016/j.jconrel.2014.12.030.
[112] D. Yohan and B. D. Chithrani, "Applications of Nanoparticles in Nanomedicine," *J Biomed Nanotechnol*, vol. 10, no. 9, pp. 2371–2392, Sep. 2014, doi: 10.1166/jbn.2014.2015.
[113] P. Ambesh *et al.*, "Nanomedicine in coronary artery disease," *Indian Heart J*, vol. 69, no. 2, pp. 244–251, Mar. 2017, doi: 10.1016/j.ihj.2017.02.007.
[114] M. A. Obeid, M. M. Al Qaraghuli, M. Alsaadi, A. R. Alzahrani, K. Niwasabutra, and V. A. Ferro, "Delivering natural products and biotherapeutics to improve drug efficacy," *Ther Deliv*, vol. 8, no. 11, pp. 947–956, Nov. 2017, doi: 10.4155/tde-2017-0060.
[115] V. Grazú, M. Moros, and C. Sánchez-Espinel, "Nanocarriers as Nanomedicines," 2012, pp. 337–440. doi: 10.1016/B978-0-12-415769-9.00014-5.
[116] L. Y. Rizzo, B. Theek, G. Storm, F. Kiessling, and T. Lammers, "Recent progress in nanomedicine: therapeutic, diagnostic and theranostic applications," *Curr Opin Biotechnol*, vol. 24, no. 6, pp. 1159–1166, Dec. 2013, doi: 10.1016/j.copbio.2013.02.020.
[117] Devasena T., *Diagnostic and therapeutic nanomaterials. In: Therapeutic and diagnostic nanomaterials.* Springer, 2017.
[118] C. L. Ventola, "Progress in Nanomedicine: Approved and Investigational Nanodrugs.," *P T*, vol. 42, no. 12, pp. 742–755, Dec. 2017.
[119] H. Havel *et al.*, "Nanomedicines: From Bench to Bedside and Beyond," *AAPS J*, vol. 18, no. 6, pp. 1373–1378, Nov. 2016, doi: 10.1208/s12248-016-9961-7.
[120] A. Kumar *et al.*, "Innovative pharmaceutical development based on unique properties of nanoscale delivery formulation," *Nanoscale*, vol. 5, no. 18, p. 8307, 2013, doi: 10.1039/c3nr01525d.
[121] A. Boroumand Moghaddam, F. Namvar, M. Moniri, P. Md. Tahir, S. Azizi, and R. Mohamad, "Nanoparticles Biosynthesized by Fungi and Yeast: A Review of Their Preparation, Properties, and Medical Applications," *Molecules*, vol. 20, no. 9, pp. 16540–16565, Sep. 2015, doi: 10.3390/molecules200916540.
[122] S. Iravani, "Bacteria in Nanoparticle Synthesis: Current Status and Future Prospects," *Int Sch Res Notices*, vol. 2014, pp. 1–18, Oct. 2014, doi: 10.1155/2014/359316.

License: CC BY-NC 4.0

[123] A. K. Mittal, Y. Chisti, and U. C. Banerjee, "Synthesis of metallic nanoparticles using plant extracts," *Biotechnol Adv*, vol. 31, no. 2, pp. 346–356, Mar. 2013, doi: 10.1016/j.biotechadv.2013.01.003.

[124] A. B. Balaji, H. Pakalapati, M. Khalid, R. Walvekar, and H. Siddiqui, "Natural and synthetic biocompatible and biodegradable polymers," in *Biodegradable and Biocompatible Polymer Composites*, Elsevier, 2018, pp. 3–32. doi: 10.1016/B978-0-08-100970-3.00001-8.

[125] M. Bassas-Galia, S. Follonier, M. Pusnik, and M. Zinn, "Natural polymers," in *Bioresorbable Polymers for Biomedical Applications*, Elsevier, 2017, pp. 31–64. doi: 10.1016/B978-0-08-100262-9.00002-1.

[126] H. A. Khan, M. K. Sakharkar, A. Nayak, U. Kishore, and A. Khan, "Nanoparticles for biomedical applications: An overview," in *Nanobiomaterials*, Elsevier, 2018, pp. 357–384. doi: 10.1016/B978-0-08-100716-7.00014-3.

[127] A. Aravamudhan, D. M. Ramos, A. A. Nada, and S. G. Kumbar, "Natural Polymers," in *Natural and Synthetic Biomedical Polymers*, Elsevier, 2014, pp. 67–89. doi: 10.1016/B978-0-12-396983-5.00004-1.

[128] M. Swierczewska, H. S. Han, K. Kim, J. H. Park, and S. Lee, "Polysaccharide-based nanoparticles for theranostic nanomedicine," *Adv Drug Deliv Rev*, vol. 99, pp. 70–84, Apr. 2016, doi: 10.1016/j.addr.2015.11.015.

[129] G. Franci *et al.*, "Silver Nanoparticles as Potential Antibacterial Agents," *Molecules*, vol. 20, no. 5, pp. 8856–8874, May 2015, doi: 10.3390/molecules20058856.

[130] G. Pajardi *et al.*, "Skin substitutes based on allogenic fibroblasts or keratinocytes for chronic wounds not responding to conventional therapy: a retrospective observational study," *Int Wound J*, vol. 13, no. 1, pp. 44–52, Feb. 2016, doi: 10.1111/iwj.12223.

[131] G. Rahimi, F. Alizadeh, and A. Khodavandi, "Mycosynthesis of Silver Nanoparticles from <i>Candida albicans</i> and its Antibacterial Activity against <i>Escherichia coli</i> and <i>Staphylococcus aureus</i>," *Tropical Journal of Pharmaceutical Research*, vol. 15, no. 2, p. 371, Mar. 2016, doi: 10.4314/tjpr.v15i2.21.

[132] M. Ali, B. Kim, K. D. Belfield, D. Norman, M. Brennan, and G. S. Ali, "Inhibition of Phytophthora parasitica and P. capsici by Silver Nanoparticles Synthesized Using Aqueous Extract of Artemisia absinthium," *Phytopathology*, vol. 105, no. 9, pp. 1183–1190, Sep. 2015, doi: 10.1094/PHYTO-01-15-0006-R.

[133] V. Malapermal, I. Botha, S. B. N. Krishna, and J. N. Mbatha, "Enhancing antidiabetic and antimicrobial performance of Ocimum basilicum, and Ocimum sanctum (L.) using silver nanoparticles," *Saudi J Biol Sci*, vol. 24, no. 6, pp. 1294–1305, Sep. 2017, doi: 10.1016/j.sjbs.2015.06.026.

[134] R. Sankar, A. Karthik, A. Prabu, S. Karthik, K. S. Shivashangari, and V. Ravikumar, "Origanum vulgare mediated biosynthesis of silver nanoparticles for its antibacterial and anti-cancer activity," *Colloids Surf B Biointerfaces*, vol. 108, pp. 80–84, Aug. 2013, doi: 10.1016/j.colsurfb.2013.02.033.

[135] K. Baek and J. K. Patra, "Comparative study of proteasome inhibitory, synergistic antibacterial, synergistic anticandidal, and antioxidant activities of gold nanoparticles biosynthesized using fruit waste materials," *Int J Nanomedicine*, vol. Volume 11, pp. 4691–4705, Sep. 2016, doi: 10.2147/IJN.S108920.

[136] J. K. Patra, Y. Kwon, and K.-H. Baek, "Green biosynthesis of gold nanoparticles by onion peel extract: Synthesis, characterization and biological activities," *Advanced Powder Technology*, vol. 27, no. 5, pp. 2204–2213, Sep. 2016, doi: 10.1016/j.apt.2016.08.005.

[137] J. K. Patra and K. Baek, "Biosynthesis of silver nanoparticles using aqueous extract of silky hairs of corn and investigation of its antibacterial and anticandidal synergistic activity and antioxidant potential," *IET Nanobiotechnol*, vol. 10, no. 5, pp. 326–333, Oct. 2016, doi: 10.1049/iet-nbt.2015.0102.

[138] J. K. Patra and K.-H. Baek, "Green synthesis of silver chloride nanoparticles using Prunus persica L. outer peel extract and investigation of antibacterial, anticandidal, antioxidant potential," *Green Chem Lett Rev*, vol. 9, no. 2, pp. 132–142, Apr. 2016, doi: 10.1080/17518253.2016.1192692.

[139] J. K. Patra, G. Das, and K.-H. Baek, "Phyto-mediated biosynthesis of silver nanoparticles using the rind extract of watermelon (Citrullus lanatus) under photo-catalyzed condition and investigation of its antibacterial, anticandidal and antioxidant efficacy," *J Photochem Photobiol B*, vol. 161, pp. 200–210, Aug. 2016, doi: 10.1016/j.jphotobiol.2016.05.021.

License: CC BY-NC 4.0

[140] A. Z. Wilczewska, K. Niemirowicz, K. H. Markiewicz, and H. Car, "Nanoparticles as drug delivery systems," *Pharmacological Reports*, vol. 64, no. 5, pp. 1020–1037, Sep. 2012, doi: 10.1016/S1734-1140(12)70901-5.

[141] Z. Zhu, Y. Li, X. Yang, W. Pan, and H. Pan, "The reversion of anti-cancer drug antagonism of tamoxifen and docetaxel by the hyaluronic acid-decorated polymeric nanoparticles," *Pharmacol Res*, vol. 126, pp. 84–96, Dec. 2017, doi: 10.1016/j.phrs.2017.07.011.

[142] D. A. Dias, S. Urban, and U. Roessner, "A Historical Overview of Natural Products in Drug Discovery," *Metabolites*, vol. 2, no. 2, pp. 303–336, Apr. 2012, doi: 10.3390/metabo2020303.

[143] U. Gupta *et al.*, "Enhanced apoptotic and anti-cancer potential of paclitaxel loaded biodegradable nanoparticles based on chitosan," *Int J Biol Macromol*, vol. 98, pp. 810–819, May 2017, doi: 10.1016/j.ijbiomac.2017.02.030.

[144] C.-H. Chang *et al.*, "Development of novel nanoparticles shelled with heparin for berberine delivery to treat Helicobacter pylori," *Acta Biomater*, vol. 7, no. 2, pp. 593–603, Feb. 2011, doi: 10.1016/j.actbio.2010.08.028.

[145] H. M. Aldawsari and K. M. Hosny, "Solid lipid nanoparticles of Vancomycin loaded with Ellagic acid as a tool for overcoming nephrotoxic side effects: Preparation, characterization, and nephrotoxicity evaluation," *J Drug Deliv Sci Technol*, vol. 45, pp. 76–80, Jun. 2018, doi: 10.1016/j.jddst.2018.02.016.

[146] L. Dian *et al.*, "Enhancing oral bioavailability of quercetin using novel soluplus polymeric micelles," *Nanoscale Res Lett*, vol. 9, no. 1, p. 684, Dec. 2014, doi: 10.1186/1556-276X-9-684.

[147] C. M. Spillmann, J. Naciri, W. R. Algar, I. L. Medintz, and J. B. Delehanty, "Multifunctional Liquid Crystal Nanoparticles for Intracellular Fluorescent Imaging and Drug Delivery," *ACS Nano*, vol. 8, no. 7, pp. 6986–6997, Jul. 2014, doi: 10.1021/nn501816z.

[148] A. Agarwal, U. Gupta, A. Asthana, and N. K. Jain, "Dextran conjugated dendritic nanoconstructs as potential vectors for anti-cancer agent," *Biomaterials*, vol. 30, no. 21, pp. 3588–3596, Jul. 2009, doi: 10.1016/j.biomaterials.2009.03.016.

[149] Y. (Chezy) Barenholz, "Doxil® — The first FDA-approved nano-drug: Lessons learned," *Journal of Controlled Release*, vol. 160, no. 2, pp. 117–134, Jun. 2012, doi: 10.1016/j.jconrel.2012.03.020.

[150] J. H. Maeng *et al.*, "Multifunctional doxorubicin loaded superparamagnetic iron oxide nanoparticles for chemotherapy and magnetic resonance imaging in liver cancer," *Biomaterials*, vol. 31, no. 18, pp. 4995–5006, Jun. 2010, doi: 10.1016/j.biomaterials.2010.02.068.

[151] C. Bonechi *et al.*, "Using Liposomes as Carriers for Polyphenolic Compounds: The Case of Trans-Resveratrol," *PLoS One*, vol. 7, no. 8, p. e41438, Aug. 2012, doi: 10.1371/journal.pone.0041438.

[152] A. Noorafshan and S. Ashkani-Esfahani, "A review of therapeutic effects of curcumin.," *Curr Pharm Des*, vol. 19, no. 11, pp. 2032–46, 2013.

[153] T. Feng, Y. Wei, R. Lee, and L. Zhao, "Liposomal curcumin and its application in cancer," *Int J Nanomedicine*, vol. Volume 12, pp. 6027–6044, Aug. 2017, doi: 10.2147/IJN.S132434.

[154] C. Cheng, S. Peng, Z. Li, L. Zou, W. Liu, and C. Liu, "Improved bioavailability of curcumin in liposomes prepared using a pH-driven, organic solvent-free, easily scalable process," *RSC Adv*, vol. 7, no. 42, pp. 25978–25986, 2017, doi: 10.1039/C7RA02861J.

[155] A. R. Bilia, C. Guccione, B. Isacchi, C. Righeschi, F. Firenzuoli, and M. C. Bergonzi, "Essential Oils Loaded in Nanosystems: A Developing Strategy for a Successful Therapeutic Approach," *Evidence-Based Complementary and Alternative Medicine*, vol. 2014, pp. 1–14, 2014, doi: 10.1155/2014/651593.

[156] V. Sainz *et al.*, "Regulatory aspects on nanomedicines," *Biochem Biophys Res Commun*, vol. 468, no. 3, pp. 504–510, Dec. 2015, doi: 10.1016/j.bbrc.2015.08.023.

[157] S. Hassan *et al.*, "Evolution and clinical translation of drug delivery nanomaterials," *Nano Today*, vol. 15, pp. 91–106, Aug. 2017, doi: 10.1016/j.nantod.2017.06.008.

[158] V. Agrahari and V. Agrahari, "Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities," *Drug Discov Today*, vol. 23, no. 5, pp. 974–991, May 2018, doi: 10.1016/j.drudis.2018.01.047.

[159] J. M. Caster, A. N. Patel, T. Zhang, and A. Wang, "Investigational nanomedicines in 2016: a review of nanotherapeutics currently undergoing clinical trials," *WIREs Nanomedicine and Nanobiotechnology*, vol. 9, no. 1, Jan. 2017, doi: 10.1002/wnan.1416.

License: CC BY-NC 4.0

[160] M. G. Wacker, A. Proykova, and G. M. L. Santos, “Dealing with nanosafety around the globe—Regulation vs. innovation,” *Int J Pharm*, vol. 509, no. 1–2, pp. 95–106, Jul. 2016, doi: 10.1016/j.ijpharm.2016.05.015.

[161] P.-C. Lin, S. Lin, P. C. Wang, and R. Sridhar, “Techniques for physicochemical characterization of nanomaterials,” *Biotechnol Adv*, vol. 32, no. 4, pp. 711–726, Jul. 2014, doi: 10.1016/j.biotechadv.2013.11.006.

[162] J. H. Grossman, R. M. Crist, and J. D. Clogston, “Early Development Challenges for Drug Products Containing Nanomaterials,” *AAPS J*, vol. 19, no. 1, pp. 92–102, Jan. 2017, doi: 10.1208/s12248-016-9980-4.

[163] S. Tinkle *et al.*, “Nanomedicines: addressing the scientific and regulatory gap,” *Ann N Y Acad Sci*, vol. 1313, no. 1, pp. 35–56, Apr. 2014, doi: 10.1111/nyas.12403.

License: CC BY-NC 4.0