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# ADVANCING THERAPEUTICS THROUGH NANOPHARMACEUTICALS: INTEGRATING PHARMACOLOGICAL MECHANISMS AND NATURAL PRODUCT RESEARCH

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## ABSTRACT

The field of therapeutic innovation is changing as a result of the combination of nanotechnology with drug science and natural product research. Nanoparticles, nanoliposomes, dendrimers, and polymeric nanocarriers are examples of nanotechnology-based drug delivery systems that have become effective instruments for overcoming the drawbacks of traditional formulations, such as low solubility, instability, and non-specific dispersion. Enhanced bioavailability, targeted distribution, and controlled release are made possible by these nanosystems, which improve therapeutic results while reducing side effects. Ensuring efficacy and safety requires a greater comprehension of how these sophisticated formulations interact with biological systems. The scientific basis for improving nanomedicine is provided by studies of absorption, distribution, metabolism, and excretion (ADME) as well as research into toxicity and mechanisms of action. However, natural sources continue to be an essential supply of bioactive substances. Despite their potential for medicinal use, many plant-derived compounds have drawbacks such poor water solubility, quick metabolism, or low bioavailability. By shielding these substances from deterioration and enabling targeted administration to certain regions, encapsulation within nanocarriers provides answers. Nature-inspired compounds and nanotechnology work together to improve their therapeutic relevance and connect conventional knowledge with contemporary biomedical science. When combined, these methods produce a multidisciplinary framework that speeds up medication development and creates new opportunities for customized medicine. In areas where traditional treatments frequently fail, such as cancer, infectious illnesses, neurological disorders, and chronic inflammatory conditions, applications are especially promising. Researchers can create next-generation treatments that are sustainable, efficient, and customized to each patient's needs by fusing the knowledge of natural bioactives with the accuracy of nanotechnology and thorough biological testing. The present developments, difficulties, and prospects for combining nanotechnology with drug science and natural product research are highlighted in this study. In the end, it contributes to a new age of comprehensive and technologically advanced healthcare by highlighting the significance of teamwork in converting laboratory advances into clinical practice.

**KEYWORDS:** Nanotechnology, ADME, Natural bioactives, Product research, Advanced healthcare.

## INTRODUCTION

Offering complementary therapies and natural alternatives for illness prevention and treatment, herbal medicine continues to be a pillar of global healthcare. The importance of herbal medicine is highlighted by many modern pharmaceuticals, such as aspirin (from Salix alba bark) and artemisinin (from Artemisia annua), which are derived from plant bioactive compounds. (1) Herbs like Gymnema sylvestre, garlic (Allium sativum), and turmeric (Curcuma longa) demonstrate pharmacological benefits and often have fewer side effects than synthetic drugs. This makes them valuable in managing chronic conditions such as diabetes, cardiovascular disease, and inflammation. Additionally, the widespread availability and affordability of herbal medicines, especially in resource-limited regions, strengthen their role within diverse healthcare systems. The World Health Organization (WHO) estimates that approximately 80% of people globally rely on herbal medicine for primary healthcare (WHO, 2023). A 2023 WHO survey of 170 member states found that 88% reported explicit use of traditional and complementary medicine (TCM), with herbal medicines being the most common modality, underscoring their deep integration into national health systems (WHO Global Report on Traditional and Complementary Medicine, 2023). In the United States, consumer spending on herbal supplements reached USD 16.8 billion in 2024, reflecting a significant shift toward natural health products in developed economies. (2) The clinical utility of traditional

herbal preparations is limited by poor absorption and instability of plant-derived compounds such as flavonoids and polyphenols, which have low water solubility, rapid metabolism, and limited gastrointestinal absorption, reducing the amount that reaches systemic circulation and target sites. These bioactive compounds are also susceptible to degradation from light, heat, moisture, and microbial contamination during storage and processing, which diminishes their potency over time. Furthermore, inconsistent efficacy and lack of standardization—due to variations in plant species, cultivation conditions, harvesting times, extraction methods, and absence of precise dosage control—cause significant batch-to-batch variability in active ingredient content. This inconsistency leads to unpredictable therapeutic outcomes and limits reliable clinical use. These challenges emphasize the need for modern technological strategies such as nano formulation, advanced extraction methods, and strict quality control to improve the stability, bioavailability, and effectiveness of herbal medicines and successfully integrate them into contemporary healthcare systems. Figure 1 illustrates how natural bioactive compounds (with antiviral, antioxidant, immunomodulatory, and anti-inflammatory activities) are incorporated into a nanoparticle delivery system to improve their therapeutic performance. (3) Nanoparticles enhance the physicochemical properties of these compounds by increasing solubility, enabling controlled drug release, and improving bioavailability. In addition, they facilitate targeted drug delivery, resulting in greater cellular uptake, reduced drug resistance, and enhanced pharmacological effects. Overall, nanoparticle-based delivery systems improve the efficacy, stability, and safety of natural products, making them more effective for disease treatment. (4)

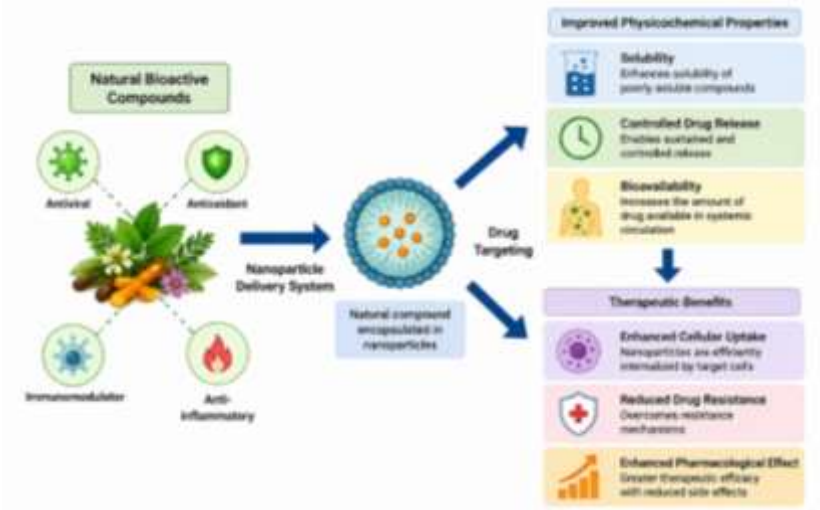


**Figure 1: Nanoparticle-mediated delivery of natural bioactive compounds significantly improves their therapeutic potential by encapsulating these compounds within nanoscale carriers. This encapsulation enhances key physicochemical characteristics such as solubility, stability, and controlled drug release, which together increase bioavailability. Moreover, nanoparticles enable targeted delivery to specific tissues or cells, promoting greater cellular uptake and minimizing drug resistance. These improvements collectively lead to enhanced treatment efficacy and reduced side effects, making nanoparticle-based delivery a promising strategy for natural product therapeutics. (5)**

Nanotechnology presents a revolutionary solution to these challenges. It involves designing and using materials and delivery systems at the nanoscale (1–100 nm) specifically for herbal bioactive compounds. Nanocarriers can be engineered to accumulate at disease sites, such as tumors or inflamed tissues, enhancing efficacy while reducing off-target effects. They also allow precise loading of active substances and controlled release, resulting in more consistent therapeutic blood levels and predictable outcomes. (6)

This review aims to investigate the potential of nanotechnology to improve the safety, effectiveness, and standardization of herbal medicines. By combining traditional knowledge with modern scientific methods, we can enhance health outcomes and ensure herbal therapies are both safe and effective. Addressing regulatory challenges and understanding pathways for clinical acceptance will further support the integration of nanotechnology into herbal medicine. In summary, while traditional herbal medicine offers promising therapeutic options, overcoming its limitations with advanced technologies like nanotechnology is essential for maximizing benefits and ensuring safe clinical use. (7,102)

Since ancient times, natural substances have been used for healing. However, many still fail clinical trials due to challenges with using large materials for drug delivery, including in vivo instability, poor absorption, low solubility and bioavailability, lack of target-specific delivery, and potential harmful effects. Innovative drug delivery methods targeting specific medications may offer solutions to these issues. Nanoparticles (NPs) have revolutionized drug delivery by enhancing the potency, targeting, and controlled release of therapeutic agents. Typically sized between 1 and 1000 nanometers, nanoparticles provide significant benefits such as improved stability, precise targeting, and controlled release. (8) This precision allows for tailored treatments for specific diseases, reducing side effects and improving outcomes. Consequently, nanoparticle drug delivery systems hold promise for overcoming the limitations of conventional methods, especially for complex diseases like cancer, viral infections, and genetic disorders.

In drug delivery, nanoparticles can be designed to specifically target certain tissues or cells, reducing side effects and enhancing treatment precision. This targeted approach is particularly effective in antibacterial therapies, gene delivery,

and cancer treatment. Additionally, the use of multifunctional nanoparticles enables simultaneous diagnosis and therapy, known as theranostics, making them essential tools in personalized medicine. (101) Novel nano-based drug delivery systems (NDDS) leverage the unique properties of nanoscale materials to maximize drug absorption, minimize side effects, and improve therapeutic efficacy. This review highlights recent advances in the development and optimization of materials such as nanoparticles, liposomes, dendrimers, and micelles aimed at enhancing patient outcomes. (9) It also addresses ongoing challenges including toxicity, scalability, and regulatory barriers. The promising applications of NDDS, including gene therapy, personalized medicine, and multidrug delivery systems, are explored. Continuous progress in nanotechnology has the potential to revolutionize treatment approaches across fields like cancer, infectious diseases, and chronic illnesses. By integrating insights from recent clinical trials and regulatory approvals, this review offers a comprehensive and forward-looking perspective on the evolving landscape of NDDS, bridging advances in materials science with clinical validation. (10)

**2.Natural compounds:**

Natural compounds, also known as natural products, are complex chemical molecules found in plants and microorganisms. Many possess pharmacological or biological activities that offer therapeutic benefits in treating human diseases. These compounds have been explored for use in cancer, infectious diseases, and various other conditions within complementary and alternative medicine. (11) This review highlights several commonly studied natural compounds, particularly those investigated in combination with nanoparticles for use as nanomedicine. Over the past 30 years, the US Food and Drug Administration (FDA) and other regulatory agencies worldwide have approved approximately 61% of developed natural compounds for cancer treatment and 49% for treating infections. This review will also cover the mechanisms of action of these natural compounds. The structures of selected natural compounds discussed here are shown in Figure 2, and their relevant physicochemical properties are listed in Table 1.

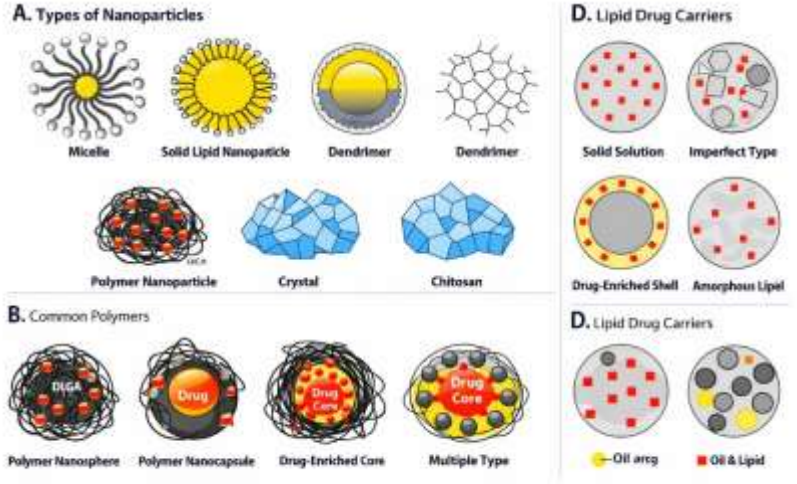


**Figure 2: Schematic representations of nanoparticles: (A) Graphical depictions of the most common types of nanoparticles. Polymer charges are shown as red and blue circles for certain polymer nanoparticles. (B) Chemical structures of the most commonly used polymers in polymer nanoparticles. (C) Graphical representations of the two types of polymer nanoparticles, with drugs incorporated shown in red. (D) Drug-incorporation models in solid lipid nanoparticles (left) and various types of nanostructured carriers (right).**

**Abbreviations:** PLGA: poly (lactic-co-glycolic acid), PEG: polyethylene glycol, PVA: polyvinyl alcohol, PLA: poly-l-lactic acid, PCL: polycaprolactone. (9,12,100)

**Table 1: Physicochemical properties of selected natural compounds (13)**

| Natural Compound | Partition Coefficient (log P) | Polar Surface Area / Molecular Surface Area (Å²) |
|---|---|---|
| Apigenin | 2.71 | 86.99 / 326.60 |
| Baicalein | 2.71 | 86.99 / 325.74 |
| Berberine | 1.28 | 40.84 / 373.39 |
| Caffeic acid | 1.53 | 77.76 / 212.76 |
| Caffeine | −0.55 | 58.44 / 167.09 |
| Catechin | 1.80 | 110.38 / 373.00 |
| Cinnamaldehyde | 1.98 | 17.07 / 194.07 |
| Curcumin | 4.12, 3.29[b] | 93.60 / 509.73 |
| Epigallocatechin gallate | 3.08 | 197.37 / 515.67 |
| Ellagic acid | 2.32 | 133.52 / 319.41 |

| | | |
|---|---|---|
| Epicatechin | 1.80 | 110.38 / 373.00 |
| Eugenol | 2.61 | 29.46 / 257.78 |
| Gambogic acid | 7.78 | 119.36 / 906.97 |
| Genistein | 3.08, 3.04[c] | 86.99 / 325.74 |
| 6-Gingerol | 3.62 | 66.76 / 507.34 |
| Hydroxytyrosol | 0.89 | 60.69 / 174.64 |
| Kaempferol | 2.46, 3.11[c] | 107.22 / 337.38 |
| Luteolin | 2.40 | 107.22 / 337.38 |
| Morin | 2.16 | 127.45 / 348.34 |
| Naringenin | 2.84, 2.6[c] | 86.99 / 351.94 |
| Oleuropein | 0.11 | 201.67 / 777.31 |
| Paeonol | 1.72 | 46.53 / 251.94 |
| Quercetin | 2.16, 1.82[c] | 127.45 / 348.34 |
| Resveratrol | 3.40 | 60.69 / 308.38 |
| Rosmarinic acid | 3.00 | 144.51 / 524.64 |
| Salidroside | −0.58 | 119.61 / 426.44 |
| Salvianolic acid B | pH-dependent[d] | Not Available (N/A) |
| Silibinin | 2.63 | 155.14 / 614.71 |
| Tanshinone I | 4.00 | 47.28 / 368.37 |
| Taxifolin | 1.82 | 127.45 / 387.07 |
| Thymoquinone | 2.55 | 34.14 / 425.97 |
| Tyrosol | 0.40 | 19.12 / 179.74 |
| Ursolic acid | 6.58 | 57.53 / 795.27 |

**Notes:** aLogP and surface area values were obtained from http://www.chemicalize.org unless otherwise specified, bData from Grynkiewicz G, Ślifirski P. Curcumin and curcuminoids in quest for medicinal status. Acta Biochim Pol. 2012;59(2):201–212, cData from Rothwell JA, Day AJ, Morgan MR. Experimental determination of octanol-water partition coefficients of quercetin and related flavonoids. J Agric Food Chem. 2005;53(11):4355–4360, dData from Li J, Liu P, Liu JP, et al. Bioavailability and foam cells permeability enhancement of Salvianolic acid B pellets based on drug-phospholipids complex technique. Eur J Pharm Biopharm. 2013;83(1):76–86. (99)

**3. Application to cancer:**

Extensive research has been conducted on natural compounds for cancer treatment. Many of these compounds fight cancer by inducing tumor-suppressing autophagy, with around fifty different substances identified to act this way. Curcumin and caffeine are among the most well-known. Curcumin can trigger autophagy linked to cell death and induces this process in lung adenocarcinoma cells through the AMP-activated protein kinase signaling pathway, without affecting healthy lung tissue. (99) Caffeine induces autophagy through a different mechanism; when combined with rapamycin, it increases autophagosome levels by inhibiting key signaling pathways, including phosphoinositide 3-kinase, protein kinase B (Akt), mammalian target of rapamycin (mTOR), and p70S6 kinase. This mechanism is similar to that of several anticancer drugs. Additionally, between 15 and 20 natural compounds exhibit cytoprotective autophagy. Resveratrol is the most studied of these, shown to induce protective autophagy in melanoma and glioma cells. (14)

Resveratrol has been shown to induce protective autophagy in melanoma B16 cells through the ceramide/Akt/mTOR pathway. Flavonoid extracts also promote autophagy by activating caspase-dependent signaling pathways and inhibiting sirtuin 1/p53-mediated mitochondrial and Akt pathways. Natural compounds have been found to inhibit P-glycoprotein (P-gp) in cancer cells. P-gp receptors pump foreign substances out of cells and are often overexpressed in tumor cells, which lowers intracellular drug levels and reduces the effectiveness of chemotherapy. Certain flavonoids, coumarins, terpenoids, alkaloids, and saponins exhibit P-gp inhibition. (15) Flavonoids and stilbenes can also inhibit ATP-binding cassette transporters like P-gp, multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein.

Common flavonoids with these properties include epigallocatechin gallate (EGCG), quercetin, genistein, morin, and kaempferol. EGCG can downregulate P-gp and breast cancer resistance protein, while quercetin reduces P-gp expression in gastric carcinoma cells. A combination of genistein, quercetin, morin, and kaempferol has been shown to decrease MRP1-mediated transport in Panc-1 cells. (16) Figure 3 represents the Chemical structures of the selected natural compounds discussed in this review. The effects of curcuminoids on the cell cycle have been studied in lung cancer cell lines A549 and H460. Increasing curcuminoid concentrations led to a rise in sub-G1 cells and a decrease in G0/G1 phase cells, with no significant impact on the S phase. Only the highest curcuminoid concentration caused an increase in G2/M phase cells, possibly indicating cell cycle arrest due to apoptosis. While both cell lines appear to arrest in the G2/M phase, this effect may vary by cell type. Previous studies found that the breast cancer cell line MCF-7 arrests in the G1 phase. (17)

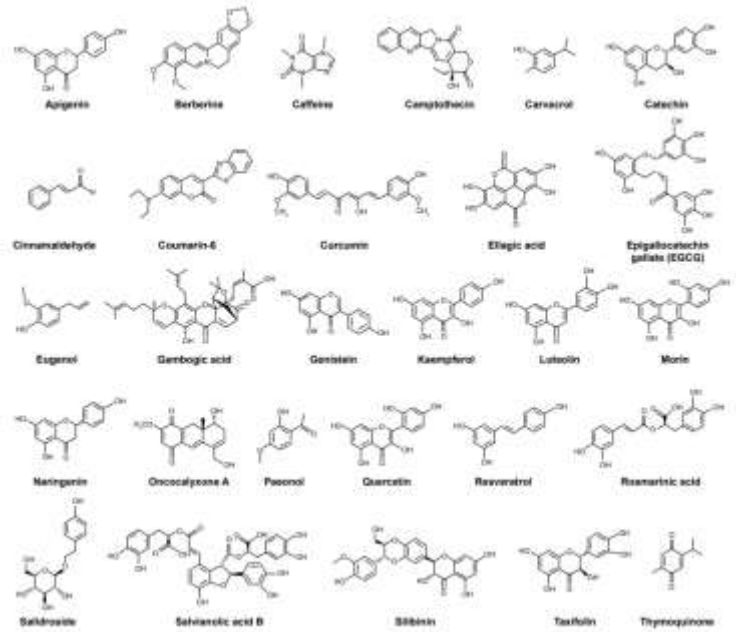


**Figure 3: Chemical structures of the selected natural compounds discussed in this review.**

The figure categorizes major nanoparticle-based delivery systems for cancer gene therapy into four groups: lipid-based nanoparticles (liposomes, emulsions, lipid nanoparticles, lipid micelles), extracellular vesicles (exosomes, microvesicles, outer membrane vesicles), polymeric nanoparticles (polymersomes, polymer micelles, dendrimers, nanospheres), and inorganic nanoparticles (silica nanoparticles, gold nanoparticles, quantum dots, layered double hydroxides). These nanocarriers transport therapeutic genetic materials such as siRNA, miRNA, mRNA, plasmid DNA, CRISPR-Cas9 systems, and CAR-T gene therapy components. (18)

Nanoparticles protect these nucleic acids from degradation, enhance targeted delivery and cellular uptake in tumor cells, and reduce systemic toxicity, collectively improving the safety and efficacy of cancer gene therapy. Figure 4 illustrates the major nanoparticle-based delivery systems employed in cancer gene therapy, dividing them into four main categories: lipid-based nanoparticles including liposomes, emulsions, lipid nanoparticles, and lipid micelles; extracellular vesicles such as exosomes, microvesicles, and outer membrane vesicles; polymeric nanoparticles including polymersomes, polymer micelles, dendrimers, and nanospheres; and inorganic nanoparticles like silica nanoparticles, gold nanoparticles, quantum dots, and layered double hydroxides. (22) These diverse nanocarriers are engineered to deliver a variety of therapeutic genetic materials, including small interfering RNA (siRNA), microRNA (miRNA), messenger RNA (mRNA), plasmid DNA, CRISPR-Cas9 gene-editing components, and chimeric antigen receptor T-cell (CAR-T) gene therapy elements. By encapsulating and protecting these nucleic acids from enzymatic degradation within the body, nanoparticles improve their stability and bioavailability. Furthermore, they facilitate enhanced targeting of tumor cells and promote efficient cellular uptake, which together reduce off-target effects and systemic toxicity. This targeted and efficient delivery system ultimately increases the therapeutic effectiveness and safety profile of cancer gene therapies, making nanoparticle carriers a crucial tool in advancing precision oncology. (19,20,21)


**Figure 4: The major nanoparticle-based delivery systems employed in cancer gene therapy, dividing them into four main categories: lipid-based nanoparticles including liposomes, emulsions, lipid nanoparticles, and lipid micelles; extracellular vesicles such as exosomes, microvesicles, and outer membrane vesicles; polymeric nanoparticles including polymersomes, polymer micelles, dendrimers, and nanospheres; and inorganic nanoparticles like silica nanoparticles, gold nanoparticles, quantum dots, and layered double hydroxides. (23)**

**4. Application to bacterial infection:**
Most antibiotics used today are natural products or their derivatives. Although larger pharmaceutical companies have recently reduced efforts in developing and screening natural antibiotics, smaller biotechnology firms have taken on this work. Three natural product-derived antibiotics recently approved for use in the USA are daptomycin, retapamulin, and fidaxomicin. Several natural compounds, including those mentioned in the cancer section, are also used as antimicrobial agents. Compounds such as curcumin, cinnamaldehyde, eugenol, and carvacrol have demonstrated antimicrobial properties. Cinnamaldehyde is extracted from cinnamon, eugenol comes from cloves, oregano, cinnamon, basil, and bay leaves, while carvacrol is sourced from oregano. Although detailed mechanistic studies on these compounds are limited, some research indicates that essential oils from oregano and basil disrupt bacterial cell membranes, leading to cell death. Additionally, cinnamaldehyde and eugenol have been shown to inhibit bacterial cell wall synthesis. (24)

**5. Application to other conditions:**
The use of natural compounds for various health conditions is growing and gaining more attention. (98) Some compounds used as anticancer agents, such as curcumin, quercetin, eugenol, rosmarinic acid, and kaempferol, also possess anti-inflammatory properties. They work by suppressing proinflammatory pathways, including transcription factors NF-kappaB and AP-1, as well as the enzyme cyclooxygenase-2, which is involved in inflammation. These compounds have been incorporated into nanoparticles for cancer treatment but could also potentially be applied to other inflammatory diseases, such as type 2 diabetes. (25)
Many natural products possess antioxidant properties that offer health benefits. Examples include quercetin, catechin, ellagic acid, extracts from Merremia emarginata, curcumin, luteolin, and taxifolin. These compounds achieve their antioxidant effects through different mechanisms. For instance, quercetin, catechin, curcumin, luteolin, and taxifolin form phenoxyl radicals when exposed to free radicals in the body. Salvianolic acid B is another potent antioxidant known for its strong radical-scavenging ability. (26)
Natural products have also demonstrated potential in treating various diseases. Berberine, a quaternary ammonium salt derived from plants in the Berberis genus, has shown promise for treating hepatosteatosis when delivered via solid lipid nanoparticles (SLNs). Berberine SLNs may help by downregulating key lipogenesis proteins, including fatty acid synthase, stearoyl-coenzyme A desaturase, and sterol regulatory element-binding protein 1c. (27)
Thymoquinone, extracted from Nigella sativa, offers protective effects for the gastrointestinal system. Its protective mechanism involves binding free radicals, which are excessively produced after ethanol consumption and can cause mucosal damage and lesions. By neutralizing these free radicals, thymoquinone helps prevent ethanol-induced gastric ulcers.
Additionally, paeonol, found in plants of the Paeonia genus, protects against ultraviolet B (UVB)-induced melanogenesis by inhibiting tyrosinase, an enzyme activated by UVB that promotes melanin production. (28)

**6. Bioavailability:**
Nanoparticles can enhance the effectiveness of natural compounds in disease treatment and prevention by improving their bioavailability. Many studied natural compounds, such as curcumin, resveratrol, and EGCG, are highly lipophilic (Table 1), which limits their solubility in the bloodstream and results in low bioavailability. Consequently, higher doses are often required to achieve therapeutic effects, which may cause toxicity or reduce patient compliance. Encapsulating these lipophilic compounds in nanoparticles improves their water solubility and efficiency. (29) For example, bergamot essential oil encapsulated in liposomes showed enhanced solubility and increased cancer cell death in vitro. Similarly, nanoemulsified berberine dissolved more efficiently than free berberine in a phosphate buffer. On the other hand, highly hydrophilic natural compounds like tannins and terpenoids often have low bioavailability because they cannot easily cross biological membranes. In both cases, using nanoparticles to deliver these natural compounds can improve bioavailability and reduce the dose needed for therapeutic effects. (30)
Table 2 highlights several examples of nanoparticle formulations and adjuvants that enhance the bioavailability (drug concentration in plasma) of selected natural compounds. Curcumin, a diarylheptanoid from turmeric, has attracted significant attention as a potential treatment for various health issues, including cancer, inflammation, microbial infections, angiogenesis, amyloidosis, wound healing, and morphine tolerance reduction. However, its poor bioavailability limits its therapeutic effectiveness in clinical trials. In one animal study, 75% of an orally administered 1 g/kg dose of curcumin was excreted in feces. Recently, many animal studies have focused on improving the bioavailability of curcumin through different strategies.

**Table 2: Comparison of plasma concentrations of natural compounds with the use of nanoparticles or adjuvants and in free drug form (31,32,33,34,35)**

| Natural Compound | Nanoparticle Type | Dose | Plasma Concentration | Plasma Concentration (Free Drug) | Mixture (Free Drug + Empty Nanoparticle) |
|---|---|---|---|---|---|
| Apigenin | Carbon nanopowder solid dispersion | 60 mg/kg b.w. | 3.26 µg/mL | 1.33 µg/mL | 1.43 µg/mL |
| Curcumin | Liposome | 100 mg/kg b.w. | 319.2 µg/L | 64.6 µg/L | 78.3 µg/L |

| | | | | | |
|---|---|---|---|---|---|
| Curcumin | Solid lipid nanoparticle | 50 mg/kg b.w. | 14.29 µg/mL | 0.292 µg/mL | N/A |
| Curcumin | PLGA nanoparticle | 100 mg/kg b.w. | 6.75 µg/mL | 1.55 µg/mL | N/A |
| Curcumin | Piperine (adjuvant, rats) | 2 g/kg curcumin + 20 mg/kg piperine b.w. | 1.8 µg/mL | 1.35 µg/mL | N/A |
| Curcumin | Piperine (adjuvant, humans) | 2 g/kg curcumin + 20 mg/kg piperine b.w. | 0.006 µg/mL | 0.18 µg/mL | N/A |
| EGCG (Epigallocatechin gallate) | Piperine (adjuvant, mice) | 163.8 µmol/kg EGCG + 70.2 µmol/kg piperine b.w. | 0.66 µmol/L | 0.32 µmol/L | N/A |
| Taxifolin | Nanoparticles via liquid antisolvent precipitation | 50 mg/kg b.w. | 13.5 ng/mL | 1.3 ng/mL | N/A |

Takahashi et al. administered liposome-encapsulated curcumin (LEC) nanoparticles orally to Sprague Dawley rats and measured plasma curcumin levels. The area under the curve (AUC) for LEC was nearly 5 times higher than that for free curcumin. Other liposome nanoparticles have also been shown to improve curcumin's bioavailability. Similar enhancements have been observed with solid lipid nanoparticles (SLNs), with one pharmacokinetic study showing a 39-fold increase in bioavailability when 50 mg/kg of curcumin was delivered via SLNs. Polymer nanoparticles also significantly boost curcumin bioavailability. For example, curcumin-loaded PLGA nanoparticles increased oral bioavailability by over 5 times compared to free curcumin. Additionally, less common delivery methods, such as wet milling combined with crystallization, have produced nanosized curcumin particles with higher bioavailability than traditional powder forms. (36)

The mechanism by which PLGA nanoparticles enhance curcumin bioavailability has been investigated. One study proposed that this increase results from the inhibition of P-glycoprotein (P-gp)-mediated drug efflux, as P-gp is highly expressed in the intestinal membrane. To test this, researchers added verapamil (a P-gp inhibitor) to curcumin or PLGA-curcumin nanoparticles and measured curcumin levels in the jejunum after 120 minutes. They found significant differences in curcumin retention between plain curcumin and PLGA-curcumin nanoparticles, regardless of verapamil presence. No significant difference was observed between curcumin with verapamil and PLGA-curcumin nanoparticles without verapamil, suggesting that PLGA nanoparticles inhibit P-gp, improving drug permeability and bioavailability. Another study compared the effects of curcumin encapsulated in PLGA nanoparticles versus PEG-b-PLA nanoparticles on morphine tolerance in mice. Mice given curcumin-PLGA nanoparticles showed significantly greater reduction in morphine tolerance, likely due to better curcumin absorption with PLGA. These findings highlight the promising potential of nanoparticle-mediated drug delivery and emphasize the importance of understanding the mechanisms behind nanoparticle-based delivery systems for natural compounds. (37)

Nanoparticles have also been used to improve the bioavailability of various other natural compounds. Apigenin, a plant-derived flavone with low solubility in both lipids and water, showed enhanced solubility when incorporated into a carbon nanopowder solid dispersion (SD). This technique reduces compound aggregation and improves dispersibility. In Sprague Dawley rats, the oral bioavailability of apigenin increased by 183% with the carbon SD.

Thymoquinone, the main active component of Nigella sativa, exhibited a six-fold increase in bioavailability and enhanced gastrointestinal protective effects when encapsulated in a lipid nanocarrier compared to its free form. (38)

Natamycin, an antifungal agent from Streptomyces natalensis used to treat corneal fungal infections, was delivered using lecithin mucosal adhesive nanoparticles. Compared to the commercial natamycin ophthalmic suspension, this nanoparticle formulation increased bioavailability by 1.47-fold and reduced clearance by 7.4-fold. Icaritin, a flavanol derived from kaempferol and used to prevent osteoporosis, was incorporated into nanocrystals, resulting in a doubling of its AUC value. Similarly, self-nanoemulsifying quercetin showed twice the bioavailability of quercetin alone. (97) Taxifolin, another flavanol plant derivative, demonstrated a sevenfold increase in oral bioavailability when formed into nanoparticles via liquid antisolvent precipitation, with particle size controlled by precipitation conditions. (39)

Polymeric nanoparticles made from materials such as PEG, PVA, and PLA have been used to enhance the bioavailability of luteolin, EGCG, tea polyphenols, and silibinin. EGCG, known to inhibit P-glycoprotein in the intestinal lining, showed significantly increased intestinal absorption when encapsulated in chitosan nanoparticles, leading to improved bioavailability. As discussed, nanoparticles significantly enhance the bioavailability of natural compounds, improving their pharmacokinetics and therapeutic effects while reducing the risk of high-dose toxicity. However, nanoparticles are not the only method to boost bioavailability. The addition of adjuvants like piperine to curcumin has also proven effective. Piperine may increase curcumin's bioavailability through several mechanisms. (40) It inhibits glucuronidation, a metabolic process that attaches glucuronic acid to curcumin, reducing its activity. Piperine also inhibits P-glycoprotein (P-gp), which pumps substances out of the intestinal lining, and cytochrome P450 (CYP) 3A4, a liver enzyme that oxidizes

small molecules, both of which can lower curcumin's activity. Due to these effects, piperine is a valuable adjuvant for enhancing curcumin bioavailability. Studies show that combining piperine with curcumin increased bioavailability by 154% in rats and up to 2,000% in human volunteers. While adjuvants lack some benefits of nanoparticles, piperine can be combined with natural compounds and nanoparticles to further improve bioavailability. It is also possible to employ several kinds of nanomaterials to improve the bioavailability of natural substances. (41) Pharmacokinetic studies have not yet been carried out, however research on special kinds of nano delivery devices and their use with natural chemicals has been done. It is noteworthy that the chemicals' therapeutic effects enhance upon the inclusion of these nanomaterials. To treat breast cancer, for instance, a silk fibroin nanoparticle was created. The nanoparticle was made of a blend of chitosan and silk and included curcumin. The increased bioavailability of curcumin via PLGA nanoparticles is believed to result from the inhibition of P-glycoprotein (P-gp)–mediated efflux, a protein abundant in the intestinal membrane that pumps drugs out of cells. (42) Xie et al. tested this by comparing curcumin alone and PLGA–curcumin nanoparticles with and without verapamil (VRP), a known P-gp inhibitor. They found that the remaining curcumin ratio (RCR) in the jejunum was significantly higher with PLGA nanoparticles, similar to the effect seen with VRP, indicating that PLGA nanoparticles inhibit P-gp, thereby increasing curcumin permeability and bioavailability. In another study, Shen et al. showed that curcumin encapsulated in PLGA nanoparticles orally administered to mice more effectively attenuated morphine tolerance than curcumin in PEG-b-PLA nanoparticles. This suggests better absorption of curcumin with PLGA formulation. (43) These studies highlight the potential of nanoparticle-based drug delivery systems and the importance of understanding their mechanisms to advance natural compound therapeutics. (44) Nanoparticles have been effectively used to increase the bioavailability of several natural compounds; Apigenin, a plant flavone with low lipid and water solubility, showed a 183% increase in bioavailability when incorporated into a carbon nanopowder solid dispersion (SD), which improves solubility by reducing aggregation and increasing dispersibility; Thymoquinone, from Nigella sativa, encapsulated in a lipid nanocarrier, exhibited a six-fold increase in bioavailability along with enhanced gastrointestinal protection; Natamycin, an antifungal agent, delivered via lecithin mucosal adhesive nanoparticles, showed a 1.47-fold increase in bioavailability and a 7.4-fold decrease in clearance compared to commercial formulations; Icaritin, used for osteoporosis prevention, doubled its AUC value when incorporated into nanocrystals; Quercetin in self-nanoemulsifying form had twice the bioavailability of the free compound; Taxifolin nanoparticles, prepared by liquid antisolvent precipitation, exhibited a seven-fold increase in oral bioavailability compared to normal taxifolin; Polymeric nanoparticles using polymers like PEG, PVA, and PLA have been used to enhance bioavailability of luteolin, EGCG, tea polyphenols, and silibinin. Specifically, EGCG encapsulated in chitosan nanoparticles significantly improved intestinal absorption by inhibiting P-gp, leading to increased bioavailability. (45) Nanoparticles improve pharmacokinetic properties and therapeutic effects of natural compounds while reducing dose-related toxicity. Besides nanoparticles, adjuvants like piperine have also been found to enhance curcumin's bioavailability through several mechanisms.

Piperine enhances the bioavailability of curcumin partly by inhibiting glucuronidation, a metabolic process that attaches glucuronic acid to curcumin and reduces its effectiveness. It also inhibits P-glycoprotein (P-gp), a transporter in the intestinal lining that pumps substances out of cells, decreasing absorption, and cytochrome P450 (CYP) 3A4, a liver enzyme involved in drug oxidation that can lower the activity of compounds like curcumin. (46) Due to these combined effects, piperine increases curcumin bioavailability by approximately 154% in rats and up to 2000% in humans. While adjuvants like piperine do not provide all the benefits of nanoparticles, they can be used alongside nanoparticle delivery systems to further improve bioavailability. In addition to PLGA and carbon-based nanoparticles, other nanomaterials have been explored to boost natural compound delivery. For example, silk fibroin nanoparticles made from silk and chitosan, containing curcumin, significantly increased curcumin uptake in breast cancer cells, though pharmacokinetic data is lacking. Quercetin loaded into β-cyclodextrin dodecylcarbonate nanoparticles reduced inflammatory markers in neuronal cells. Other cases include camptothecin encapsulated in liposomes, which enhanced its effectiveness against melanoma cells, and phytochemicals from traditional Chinese medicine formulated as nanoparticles to improve liver protective effects. These examples illustrate how nanoparticles can enhance both the bioavailability and therapeutic potential of natural compounds. (47)

The route of drug administration significantly impacts its bioavailability, which is defined as the fraction of a drug that reaches systemic circulation and exerts a therapeutic effect. Most studies focus on oral delivery due to its convenience and high patient compliance. Another promising route is topical administration, though it typically suffers from very low bioavailability—nonsteroidal anti-inflammatory drugs applied topically often achieve less than 5%–15% bioavailability. (1,96) However, nanotechnology shows promise in enhancing topical delivery. For example, lycopene, a compound found in tomatoes with anti-inflammatory effects and fewer side effects than steroids, has been incorporated into nanocarriers called "transfersomes" and endosomes (vesicle-like structures similar to liposomes). These formulations reduced swelling by 97% and 87% respectively, comparable to the steroid betamethasone. Another study created a nanosphere hydrogel containing salidroside and paeonol for topical protection against UV-induced melanoma, suggesting that natural compound nanoparticles could replace conventional creams. (48)

Transdermal delivery, which also requires skin penetration, is another related method. In one study, PLGA nanoparticles loaded with an ethanolic apple peel extract—known for photoprotective properties—were combined with oleic acid, a permeation enhancer. This nano formulation released 90% of the drug, compared to only 25% release from the free extract in cells, demonstrating enhanced bioavailability. Despite the significant advances in nanoparticle formulations for natural compounds, only a few have reached clinical trial stages. Further research is needed to optimize these delivery systems and to clarify the mechanisms driving improved nanoparticle-based bioavailability. (49)

**7. Targeting:**

A key advantage of using nanoparticles for delivering natural compounds is their ability to specifically target certain tissues or organs. Targeting offers several benefits: it increases drug bioavailability by directing more of the drug to the desired site, and it reduces systemic toxicity by limiting the drug's release mainly to the target area. Targeting strategies generally fall into two categories: active targeting, where nanoparticles are functionalized with ligands such as proteins, peptides, antibodies, or small molecules to bind specific tissues; and passive targeting, which relies on the natural physical properties of nanoparticles—like size, shape, and surface charge—to accumulate in certain tissues without specific biochemical interactions. Active targeting often involves attaching molecules to nanoparticles that facilitate their uptake by target cells. (50) For example, monoclonal antibodies conjugated to nanoparticles show promise for crossing the blood-brain barrier, although this has yet to be applied with natural compounds. Folic acid (FA) has been widely used to target cancer cells that overexpress FA receptors. In one study, quercetin-loaded PLGA nanoparticles stabilized with PEG (which improves biocompatibility and circulation time) were conjugated with FA. These FA-targeted nanoparticles showed significantly higher uptake and greater cytotoxicity against HeLa cancer cells compared to non-targeted controls. Other targeting approaches include modifying lipid nanovesicles with specific ligands such as L-glutamic acid derivatives to direct curcumin-loaded nanoparticles to bone marrow macrophages. (51) Additionally, curcumin encapsulated in PLGA-lecithin-PEG nanoparticles with RNA aptamers targeting epithelial cell adhesion molecules successfully delivered the drug to colorectal cancer cells. Functionalizing nanoparticles with small molecules for natural compound delivery is an emerging area requiring more research. For instance, benzothiazole aniline (BTA), which binds amyloid proteins and inhibits HIV infection enhancers, has been attached to polyacrylate nanoparticles to block HIV infection pathways. Such nanoparticles could be adapted to enhance delivery of anti-Alzheimer's natural compounds like curcumin. External forces can also guide nanoparticle targeting. Magnetic fields, for example, can direct iron oxide nanoparticles loaded with curcumin or plant-derived antitumor agents toward cancer cells, significantly increasing uptake. Passive targeting leverages biological phenomena like the enhanced permeability and retention (EPR) effect in tumors, where leaky blood vessels allow nanoparticles to accumulate preferentially in tumor tissue. (52) This effect has been exploited using PEG-containing telodendrimers nanoparticles carrying gambogic acid and vitamin E for colon cancer treatment, showing high tumor uptake in mice. The reticuloendothelial system (RES) can also be targeted passively. Studies tracking gold nanoparticles of various sizes in rats revealed their distribution to organs such as the liver, spleen, lungs, and kidneys, highlighting the role of particle size in biodistribution. Overall, nanoparticle targeting—whether active, passive, or guided by external forces—holds great potential to improve the precision and safety of natural compound drug delivery. Table 3 represents Summary of Targeting Techniques. (53)

**Table 3: Summary of Targeting Techniques**

| Natural Product | Disease | Nanodevice | Advantages |
|---|---|---|---|
| Curcumin | Macrophage-related diseases (54,55) | SA- and PEG-DSPE-conjugated lipid nanoparticle | Particles are more likely to go to the bone marrow and be phagocytized by macrophages |
| | Cancer (56) | Iron oxide nanoparticles | Uptaken by cancer cells when induced by magnetic field |
| | Colorectal adenocarcinoma cells (57,58,59) | PLGA-lecithin-PEG nanoparticles with RNA aptamers | The RNA aptamers target epithelial cell adhesion molecules that are expressed in colorectal adenocarcinoma cells |
| Eugenol | Fungal skin infections (60) | SA hydrogel containing eugenol-loaded solid lipid nanoparticles | Solid lipid nanoparticles were able to increase the amount of eugenol delivered to the infected cells by at least six-fold compared to other models |
| Gambogic acid | Colon cancer (61) | Vitamin E-containing telodendrimers | EPR effect allows the nanoparticle to be targeted to the tumor cells; Nanoparticles show high uptake rates in cancer cells |
| Oncocalyxone A | Guided by magnetic field (62) | Iron oxide nanoparticles coated in oleic acid and block copolymer | The iron oxide nanoparticles can be guided by magnetic field |
| Quercetin | Tumor cells overexpressing folate receptors (63,64,66) | PEG-conjugated PLGA nanoparticles with folic acid | Contains folic acid on the surface, Nanoparticle will more likely bind with cancer cells, which express more folic acid receptors than healthy cells, Reduces the interaction of the drug with healthy cells |

**8. Controlled Release:**

Controlled release in natural product-based nanomedicine refers to the design of nanoparticle systems that deliver natural compounds gradually over time, improving therapeutic efficacy while minimizing side effects. (65) Recent advances have focused on developing nanocarriers—such as liposomes, polymeric nanoparticles, dendrimers, and nanoemulsions—that allow precise control over drug release kinetics. These systems improve the stability and bioavailability of natural products, many of which have poor solubility or rapid metabolism. Controlled release also enables sustained drug levels in target tissues, reducing dosing frequency and enhancing patient compliance. Key advances include stimuli-responsive nanoparticles that release their cargo in response to pH, temperature, or enzymatic activity, enabling site-specific drug delivery. (67) Surface modifications with targeting ligands further enhance accumulation in diseased tissues. However, challenges remain in scaling up production, ensuring reproducibility, and fully understanding the interactions between nanoparticles and biological systems. Safety and long-term toxicity profiles must be carefully evaluated before clinical translation. Regulatory hurdles and high development costs also limit widespread adoption. (68,95) Overall, controlled release nanomedicine holds great promise for improving the delivery and efficacy of natural compounds, but continued research is needed to overcome technical and regulatory barriers. (68)

**9. Issues:**

Natural product-based nanomedicine represents an innovative approach to drug delivery, combining the therapeutic benefits of natural compounds with advanced nanotechnology to improve treatment outcomes. (69) However, despite significant progress, numerous challenges and issues remain that hinder its widespread adoption and clinical success. Natural compounds often possess complex molecular structures that can be difficult to characterize fully. Additionally, their composition may vary due to differences in plant species, growth conditions, extraction methods, and purification processes. Such variability can lead to inconsistent drug formulations, making it challenging to standardize nanoparticle-based medicines containing these compounds. (70) This inconsistency can affect the reproducibility of results and the predictability of therapeutic effects. Many natural compounds are chemically unstable and prone to degradation under environmental stresses such as heat, light, humidity, and oxygen exposure. During the manufacturing process of nanoparticles, these compounds may lose potency due to exposure to solvents, temperature changes, or mechanical forces. Ensuring long-term stability of both the natural product and the nanoparticle carrier is critical to maintaining efficacy. The challenge is to formulate nanoparticles that protect the active compounds during storage and release them in a controlled manner once administered. (71)

Producing nanoparticles consistently on a laboratory scale is feasible; however, scaling up production to industrial levels presents significant hurdles. Nanoparticle synthesis requires strict control over parameters such as particle size, shape, surface chemistry, and drug loading efficiency. (72) Any variation can affect drug release profiles, bioavailability, and safety. Moreover, manufacturing processes must be cost-effective to make treatments accessible. Developing scalable, reproducible, and economically viable production methods remains a key obstacle.

Understanding how nanoparticles behave within the body is essential for safe and effective treatments. However, the pharmacokinetics (absorption, distribution, metabolism, and excretion) of natural product-loaded nanoparticles are complex and influenced by many factors. (73) Nanoparticles may interact with proteins and cells in the bloodstream, be recognized and cleared by the immune system, or accumulate in non-target tissues. Predicting and controlling these interactions to ensure that the drug reaches the desired site in therapeutic concentrations is challenging and requires detailed in vivo studies. (74) While nanoparticles can enhance drug delivery, they may also introduce new safety concerns. (75) Some nanomaterials used as carriers could elicit immune responses, cause inflammation, or accumulate in organs, leading to toxicity. Additionally, natural compounds themselves may have toxic effects, which could be altered by nanoparticle encapsulation. Comprehensive toxicity testing, including long-term and chronic exposure studies, is necessary to ensure that nanomedicines are safe for human use. Regulatory frameworks for nanomedicines, especially those based on natural products, are still developing. Regulatory agencies require extensive evidence of safety, efficacy, and manufacturing quality before approval. However, standardized guidelines specific to nanoparticle-based natural compounds are lacking, causing uncertainties and delays in the approval process. (94) Harmonizing international regulatory standards and creating clear pathways will be vital to facilitate clinical translation. (76)

Achieving precise targeting of nanoparticles to specific tissues or cells remains difficult. Biological barriers such as the immune system, blood flow dynamics, and tissue architecture can prevent nanoparticles from reaching their targets efficiently. Moreover, controlling the timing and rate of drug release from nanoparticles is complex but crucial for maximizing therapeutic benefit and minimizing side effects. Advances in stimuli-responsive nanoparticles and surface modifications offer potential solutions, but practical application is still limited. (77)

The high cost of developing, manufacturing, and testing nanoparticle-based natural product therapies may limit their accessibility, particularly in low-resource settings. (78) Ensuring that these innovative treatments are affordable and available to diverse populations is an important consideration for future development. Navigating intellectual property rights, patents, and licensing agreements related to both natural products and nanotechnology can be complicated. These issues may affect investment and collaboration opportunities, influencing the pace of commercialization. (79) Despite these challenges, ongoing research is making strides in improving nanoparticle design, stability, targeting, and multifunctionality. Techniques like microfluidic synthesis enable better control over nanoparticle characteristics at scale. Combining natural compounds with adjuvants or other drugs can enhance therapeutic outcomes. Additionally, advances in understanding nanoparticle-biological system interactions are guiding safer and more effective formulations. (80) Multidisciplinary collaboration across chemistry, biology, material science, medicine, and regulatory fields is essential to

overcome existing barriers. With continued innovation and rigorous evaluation, natural product-based nanomedicine holds immense promise for delivering safer, more effective therapies for a wide range of diseases.

## CONCLUSION

The integration of nanotechnology with natural product research is transforming the future of therapeutic development by offering innovative solutions to overcome the intrinsic limitations of natural compounds. Natural products have long been recognized for their diverse pharmacological activities, including anti-inflammatory, anticancer, antioxidant, and antimicrobial properties. (1,81) However, many of these compounds face challenges such as poor water solubility, low bioavailability, rapid degradation, and limited target specificity, which have hindered their clinical application. Nanopharmaceuticals provide a powerful platform to address these challenges by encapsulating natural compounds within nanoscale carriers. These nanocarriers protect the active molecules from premature degradation, improving their chemical stability and enhancing systemic circulation time. (82,83,84,85,86) Through controlled and sustained release mechanisms, nanoparticles maintain therapeutic drug concentrations over extended periods, which reduces dosing frequency and enhances patient compliance. (87)

Additionally, nanoparticles can be engineered to specifically target diseased tissues or cells by surface modification with ligands such as antibodies, peptides, or small molecules. This targeted delivery reduces off-target effects and systemic toxicity, thereby improving the safety profile of natural product-based therapies. Targeting capabilities are especially valuable in treating complex diseases like cancer, neurological disorders, and chronic inflammatory conditions, where precision is critical for effective treatment. Another significant advantage is the ability of nanoparticles to traverse biological barriers that normally restrict drug delivery, such as the blood-brain barrier. This capability opens new possibilities for delivering natural compounds to sites previously considered difficult to reach. Furthermore, multifunctional nanoparticles can combine therapeutic and diagnostic functions, leading to the promising field of theranostics, which allows clinicians to monitor treatment effects in real time and adjust therapy accordingly. (88)

Despite these exciting advances, challenges remain in translating nanopharmaceuticals from the laboratory to the clinic. The complex nature of natural product extracts, which often contain multiple bioactive constituents, creates difficulties in standardization and quality control. Manufacturing processes must be optimized to produce nanoparticles with consistent size, shape, and drug loading while maintaining the biological activity of the compounds. Ensuring scalability and cost-effectiveness in production is essential for widespread clinical adoption. (89)

Safety concerns also require thorough investigation. Nanoparticles may interact with biological systems in unpredictable ways, potentially causing immune reactions or accumulation in non-target organs. Comprehensive toxicological evaluations and long-term safety studies are critical to ensure patient safety. (90) Additionally, regulatory guidelines specific to nanomedicines incorporating natural products are still evolving, necessitating clear frameworks to facilitate approval and commercialization. Interdisciplinary collaboration is key to overcoming these hurdles. Chemists, material scientists, biologists, pharmacologists, and clinicians must work together to deepen understanding of nanoparticle behavior in biological environments, optimize drug formulations, and design clinical trials that address unique aspects of nanopharmaceuticals. (91)

Looking ahead, advances in nanomaterial design, such as stimuli-responsive and smart nanoparticles, will further enhance the precision and efficacy of natural product delivery. Personalized medicine approaches that tailor nanoparticle formulations to individual patient profiles hold promise for improving therapeutic outcomes and minimizing adverse effects. In conclusion, the convergence of nanotechnology and natural product research heralds a new era in drug development. (92) Nanopharmaceuticals offer transformative potential by improving drug delivery, enhancing pharmacokinetics, enabling targeted therapy, and reducing toxicity. While challenges remain, continued research and innovation will unlock the full therapeutic potential of natural compounds, leading to safer, more effective, and more personalized treatments that can significantly impact global health. (93,103)

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