Nano-Enabled Delivery of Phytoconstituents: Overcoming Bioavailability Barriers in Herbal Drugs — An Advanced Review

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Abstract: Phytochemicals separated from medicinal herbs have a broad range of pharmacological activities like anti-inflammatory, antioxidant, anticancer, and antimicrobial activities. However, their application in clinical settings is greatly limited due to poor bioavailability that results from factors such as low solubility in water, poor permeability, instability, and significant first-pass metabolism. Based on nanotechnology, drug delivery systems emerged as a revolutionary solution to address these challenges. This review provides a wide and critical overview on the use of nano-enabled delivery systems to phytochemicals, such as polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions and novel hybrid systems. It discusses the mechanisms of bioavailability enhancement, recent advances (2019–2026), therapeutic applications, and translation challenges. The review also covers regulatory issues and future opportunities for the clinical use of.

Keywords: *Phytoconstituents, Nanotechnology, Bioavailability, Herbal Drugs, Nanocarriers, Drug Delivery*.

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I. INTRODUCTION

Herbal drugs continue to serve as a backbone of various health care systems around the world especially in underdeveloped nations. Various phytoconstituents including alkaloids, flavonoids, terpenoids, and phenolic compounds constitute the biological activity of such drugs. However, due to poor pharmacokinetics properties, they continue to struggle when used in a clinical setting.[(1)]

Bioavailability constitutes an essential factor in terms of drug effectiveness and is defined as the proportion of an orally ingested drug absorbed into systemic circulation. Several phytoconstituents demonstrate a very low bioavailability rate which does not exceed 10%.

➢ *Nanotechnology Offers an Innovative Approach in the Following Areas:*

- Solubility and dissolution
- Degradation
- Permeability and targeting

II. BIOAVAILABILITY BARRIERS IN HERBAL DRUGS

➢ *Physicochemical Barriers*

- Poor water solubility
- High molecular weight
- Lipophilicity imbalance

➢ *Biological Barriers*

- Intestinal epithelial barrier
- Efflux transporters
- Enzymatic degradation

➢ *Pharmacokinetic Barriers*

- First-pass metabolism
- Rapid clearance
- Low plasma retention

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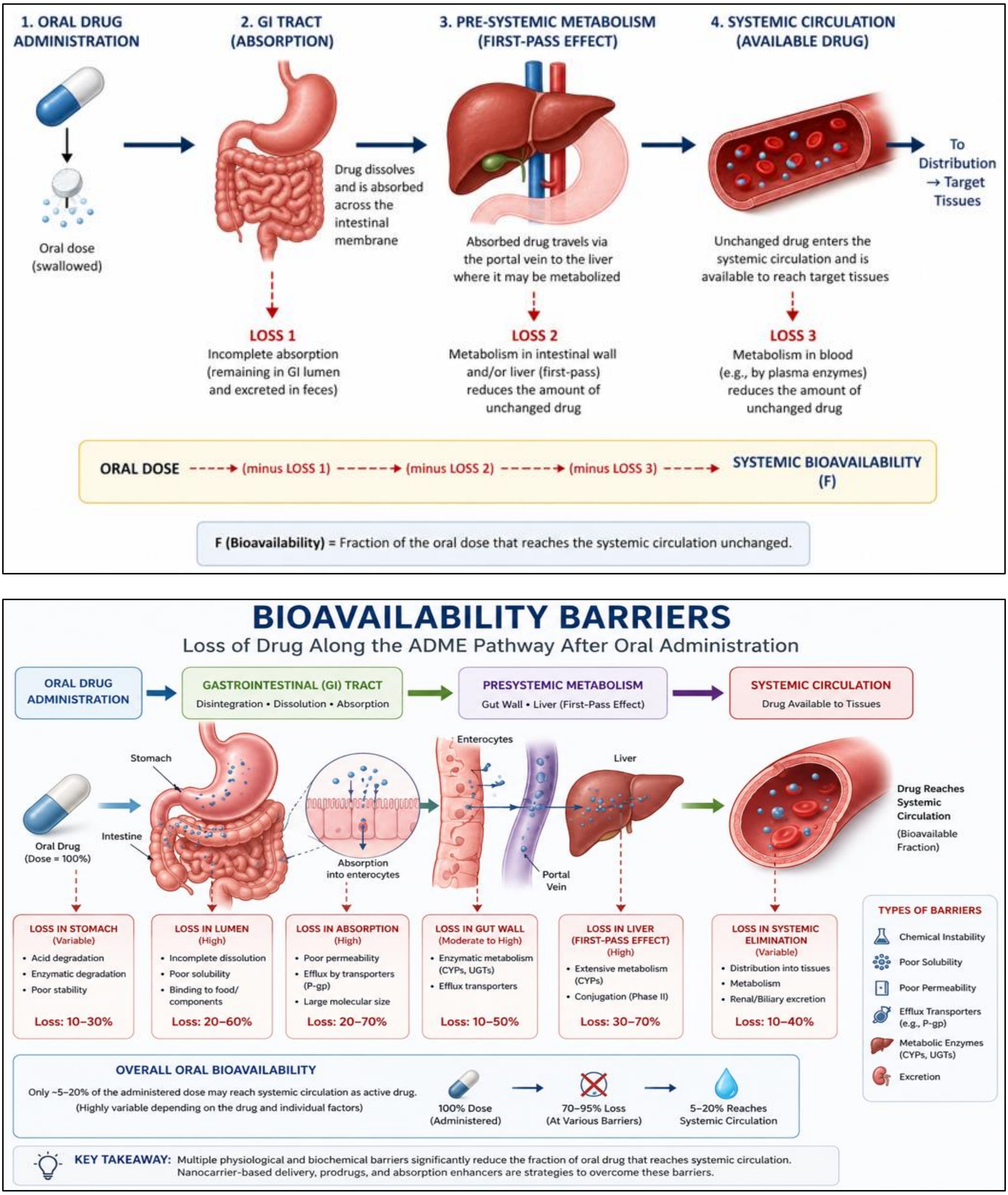

Fig 1 Bioavailability Barriers

III. CLASSIFICATION OF NANO DRUG DELIVERY SYSTEMS

Nano drug delivery systems based on nanocarriers can be classified according to their chemistry, physical form, and function. They are used in order to improve the bioavailability, stability, targetability, and controlled drug release of poorly water-soluble phytoconstituents and traditional medicines [27]

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A. Polymeric Nanoparticles

➢ *Introduction*

Polymeric nanoparticles are widely explored nanocarrier systems in advanced drug delivery due to their biodegradability, biocompatibility, and versatility. These solid colloidal particles range from 10–1000 nm in size and are designed to enhance drug stability, bioavailability, and targeted delivery. [23]

➢ *Classification*

Based on structural organization, polymeric nanoparticles are broadly classified into two types:

- Nanospheres: Matrix systems in which the drug is uniformly dispersed throughout the polymer network.
- Nanocapsules: Core–shell systems where the drug is enclosed within a central cavity surrounded by a polymeric membrane.

➢ *Polymers Used*

A wide range of polymers are utilized in the formulation of polymeric nanoparticles:

- Synthetic polymers: Poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL)
- Natural polymers: Chitosan, alginate, gelatin

The selection of polymer plays a crucial role in determining the physicochemical properties, degradation rate, and drug release behavior [24].

➢ *Key Properties*

Polymeric nanoparticles exhibit several important characteristics:

- Controlled and sustained drug release through polymer degradation
- Protection of drugs from enzymatic and environmental degradation
- Surface modification for targeted delivery via ligand attachment

➢ *Drug Release Mechanism*

Drug release from polymeric nanoparticles occurs through multiple mechanisms, including diffusion, polymer erosion, and swelling followed by drug release. These mechanisms can be tailored based on the type of polymer and formulation strategy.

➢ *Applications*

Due to their advantageous properties, polymeric nanoparticles have been extensively applied in various therapeutic areas, including:

- Delivery of anticancer drugs
- Gene delivery systems
- Enhancement of bioavailability of herbal bioactives such as curcumin and quercetin

Overall, polymeric nanoparticles represent a promising and efficient platform for the development of advanced drug delivery systems in modern therapeutics.[44]

B. Liposomes

➢ *Introduction*

Liposomes are spherical vesicular drug delivery systems composed of phospholipid bilayers, structurally similar to biological cell membranes. Due to this resemblance, liposomes are highly biocompatible and serve as efficient carriers for a wide range of therapeutic agents, improving drug stability, bioavailability, and targeted delivery. [22]

➢ *Structure*

Liposomes possess a unique structure that enables the encapsulation of both hydrophilic and lipophilic drugs:

- Aqueous Core: The inner compartment is hydrophilic (water-friendly), allowing encapsulation of water-soluble drugs.
- Phospholipid Bilayer: The outer lipid membrane is lipophilic (fat-friendly), suitable for incorporating lipid-soluble drugs.

This dual nature makes liposomes versatile carriers in drug delivery systems.

➢ *Types*

Liposomes are classified based on their size and number of bilayers:

- Small Unilamellar Vesicles (SUVs): Small-sized liposomes with a single phospholipid bilayer.
- Large Unilamellar Vesicles (LUVs): Larger liposomes with a single bilayer.
- Multilamellar Vesicles (MLVs): Liposomes consisting of multiple concentric bilayers.

➢ *Advantages*

Liposomes offer several benefits in pharmaceutical applications:

- High biocompatibility and biodegradability with minimal toxicity
- Ability to encapsulate both hydrophilic and lipophilic drugs simultaneously
- Protection of drugs from degradation
- Reduced side effects and improved therapeutic efficacy

➢ *Mechanism of Action*

Liposomes deliver drugs to target sites through various mechanisms:

- Fusion with cell membranes, leading to direct drug release into cells
- Uptake by cells via endocytosis
- Controlled and localized release of encapsulated drugs

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➢ *Applications*

Liposomes have been extensively utilized in modern therapeutics, including:

- Cancer therapy: Liposomal formulations of drugs such as doxorubicin enhance efficacy and reduce toxicity
- Vaccine delivery: Widely used as carriers in vaccine formulations
- Topical and transdermal delivery: Effective in skin and transdermal drug delivery systems [2, 6,18]

C. Solid Lipid Nanoparticles (SLNs)

➢ *Introduction*

Solid lipid nanoparticles (SLNs) are submicron-sized lipid-based nanocarriers typically ranging from 50 to 1000 nm. They are composed of solid lipids stabilized by surfactants and are designed to combine the advantages of traditional lipid systems with improved stability and controlled drug delivery. [3,15.17,43]

➢ *Composition*

SLNs are formulated using the following components:

- Solid lipids: Triglycerides, fatty acids, waxes
- Surfactants: Tween, Poloxamer

These components play a crucial role in stabilizing the nanoparticle system and determining its performance.

➢ *Key Features*

SLNs possess several characteristic properties:

- Solid matrix that remains stable at room and body temperature
- High physical stability compared to other lipid-based systems
- Ability to provide controlled and sustained drug release

➢ *Advantages*

SLNs offer multiple benefits in drug delivery:

- Protection of drugs from chemical and physical degradation during storage
- Avoidance of organic solvents in preparation (in many methods)
- Feasibility for large-scale production

➢ *Limitations*

Despite their advantages, SLNs have certain drawbacks:

- Limited drug loading capacity
- Risk of drug expulsion during storage due to lipid crystallization

➢ *Applications*

SLNs are widely applied in:

- Topical and dermal drug delivery systems
- Cosmetic formulations
- Controlled release preparations

D. Nanostructured Lipid Carriers (NLCs)

➢ *Introduction*

Nanostructured lipid carriers (NLCs) are the second-generation lipid nanoparticles developed to overcome the limitations associated with SLNs. They provide improved drug loading capacity, enhanced stability, and better control over drug release.[10,17,21,41]

➢ *Composition*

NLCs are composed of:

- Solid lipids + Liquid lipids (oils)

This combination creates a less ordered lipid matrix compared to SLNs.

➢ *Structural Types*

NLCs exhibit different structural arrangements:

- Imperfect (incompletely crystalline) structure
- Amorphous structure
- Multiple oil compartment structure

➢ *Advantages Over SLNs*

NLCs demonstrate several improvements:

- Higher drug loading capacity
- Reduced drug leakage during storage
- Enhanced physicochemical stability[24,25]

➢ *Benefits*

Key benefits of NLCs include:

- Improved bioavailability of poorly soluble drugs
- Controlled and sustained drug release
- Efficient delivery of lipophilic drugs

➢ *Applications*

NLCs are extensively used in:

- Targeted drug delivery, including brain targeting
- Cosmetic and dermatological formulations
- Delivery of natural and herbal bioactives

Overall, SLNs and NLCs represent important lipid-based nanocarrier systems, with NLCs offering significant advancements over SLNs in terms of drug loading, stability, and therapeutic efficiency.[4.8.25]

E. Nanoemulsions

➢ *Introduction*

Nanoemulsions are advanced colloidal dispersion systems consisting of oil and water phases stabilized by surfactants, with droplet sizes typically ranging from 20–200 nm. They are either thermodynamically or kinetically stable

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and are widely used to enhance the solubility and bioavailability of poorly soluble drugs.[11,19,44]

➢ *Classification*

Based on composition, nanoemulsions are categorized into:

- Oil-in-Water (O/W): Oil droplets dispersed in an aqueous phase
- Water-in-Oil (W/O): Water droplets dispersed in an oil phase
- Bicontinuous systems: Interconnected oil and water phases [3,12,24]

➢ *Composition*

Nanoemulsions are composed of:

- Oil phase
- Aqueous phase
- Surfactants and co-surfactants

These components help reduce interfacial tension and stabilize the system.

➢ *Key Characteristics*

Nanoemulsions exhibit several unique properties:

- Large surface area leading to enhanced drug absorption
- Transparent or translucent appearance
- Improved solubility of lipophilic and poorly water-soluble drugs

➢ *Mechanism of Action*

Nanoemulsions enhance drug delivery through:

- Improved permeation across biological membranes due to small droplet size
- Rapid drug absorption and distribution [6,16, 29]

➢ *Advantages*

- Simple and cost-effective preparation methods
- Enhanced bioavailability of drugs
- Suitable for multiple routes of administration (oral, topical, parenteral)

➢ *Applications*

Nanoemulsions are widely utilized in:

- Delivery of essential oils
- Administration of natural and herbal drugs
- Antimicrobial and therapeutic formulations

F. Recent Nano Drug Delivery Systems

➢ *Introduction*

Recent advancements in nanotechnology have led to the development of highly specialized and multifunctional nanocarriers with improved targeting efficiency, drug loading capacity, and therapeutic outcomes.[39]

➢ *Dendrimers*

- *Overview*

Dendrimers are highly branched, tree-like macromolecules with a well-defined structure and high surface functionality, making them suitable for precise drug delivery applications.[35]

- *Key Characteristics*

✓ High density of surface functional groups
✓ Ability to encapsulate or conjugate multiple drug molecules
✓ Uniform and well-defined molecular weight

- *Advantages*

✓ Targeted and site-specific drug delivery
✓ Suitable for gene and nucleic acid delivery
✓ Controlled drug release

- *Applications*

✓ Tumor and cancer therapy
✓ Diagnostic imaging and nuclear medicine

➢ *Nanogels*

- *Overview*

Nanogels are nanoscale hydrogel particles (20–200 nm) capable of retaining large amounts of water, offering a unique platform for drug delivery.[34]

- *Key Characteristics*

✓ High drug loading capacity
✓ Stimuli-responsive behavior (pH, temperature, enzymes)
✓ Soft, elastic, and flexible structure

- *Advantages*

✓ Excellent biocompatibility
✓ Controlled and targeted drug release

- *Applications*

✓ Delivery of proteins and peptides
✓ Transdermal drug delivery
✓ Anti-inflammatory therapies

➢ *Hybrid Nanocarriers*

- *Overview*

Hybrid nanocarriers combine two or more types of nanocarrier systems to overcome individual limitations and enhance overall performance.[41]

- *Types*

✓ Lipid–polymer hybrid systems

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- ✓ Inorganic–organic hybrid nanocarriers

- *Advantages*

- ✓ Improved stability and structural integrity
- ✓ Enhanced drug delivery efficiency
- ✓ Capability for combined therapeutic and diagnostic functions

- *Applications*

- ✓ Theranostics (simultaneous diagnosis and therapy)
- ✓ Advanced targeted drug delivery systems

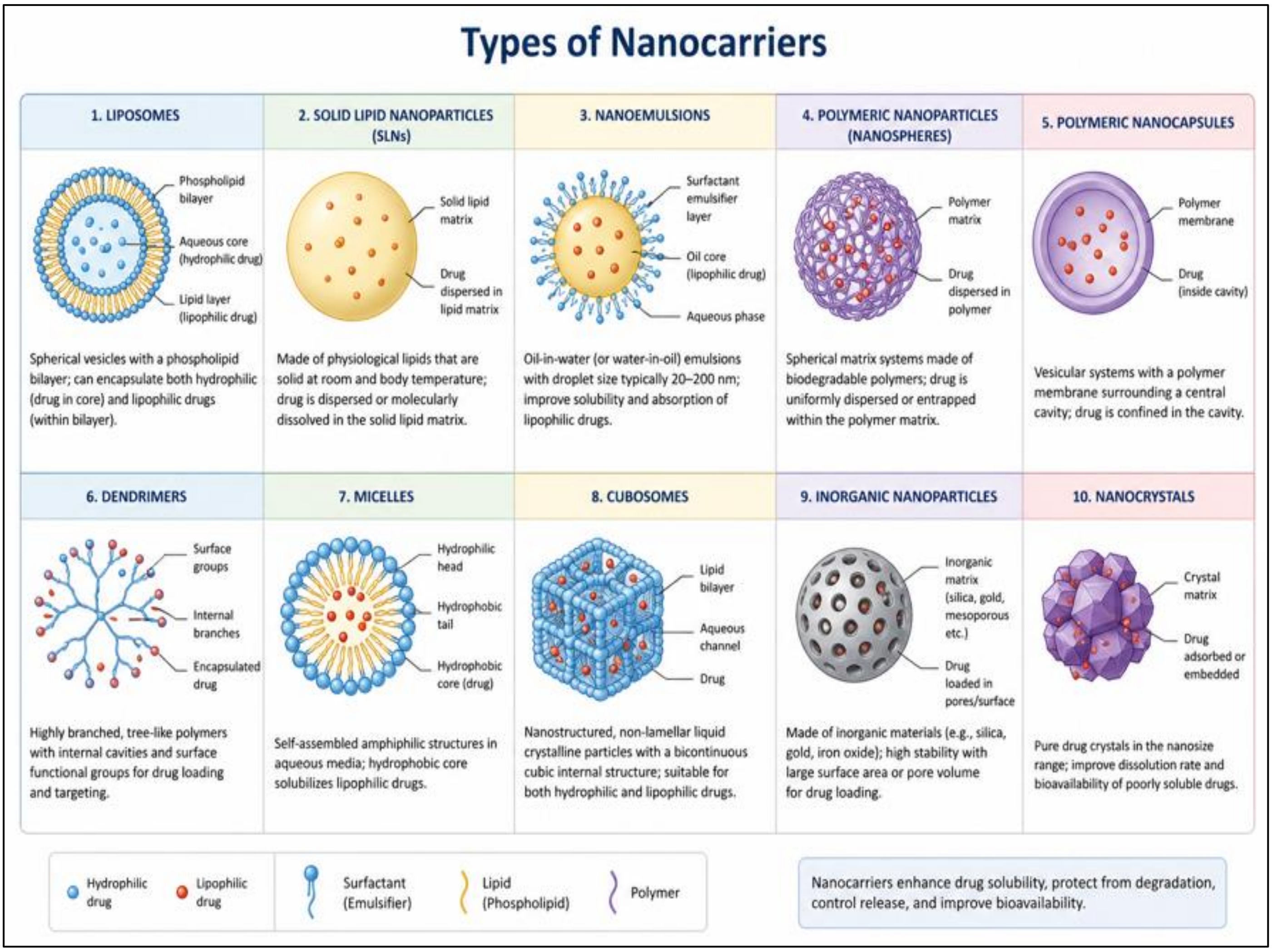

Fig 2 Types of Nanocarriers

- ➢ *Mechanisms of Bioavailability Enhancement*

Table 1 Mechanisms of Bioavailability Enhancement

Mechanism	Description	Outcome
Particle Size Reduction	Increased surface area	Faster dissolution
Encapsulation	Protection from degradation	Increased stability
Surface Modification	Targeted delivery	Reduced toxicity
Lymphatic Uptake	Bypass liver metabolism	Improved bioavailability

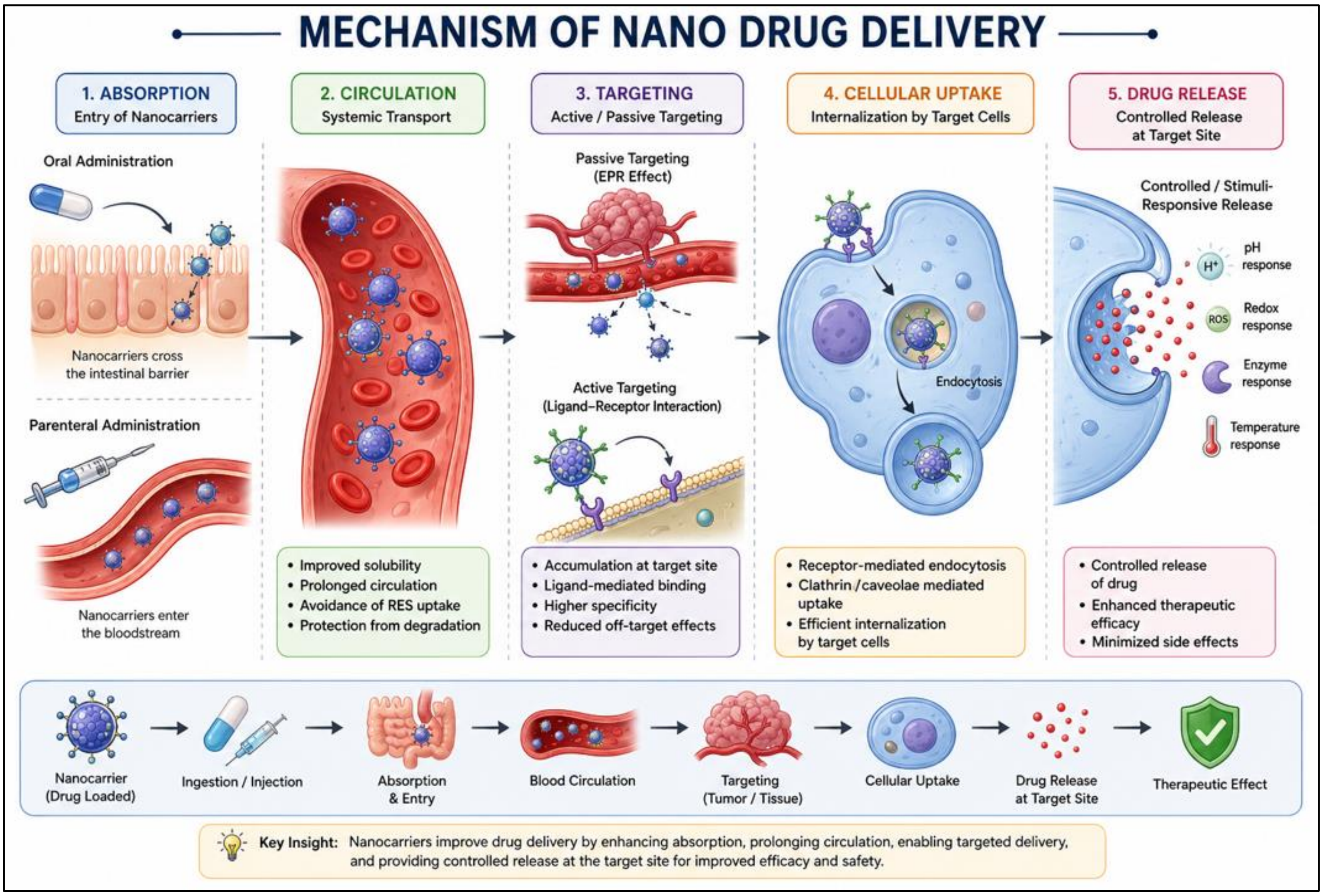

Fig 3 Mechanism of Nano Drug Delivery

➢ *Advanced Comparison of Nano Systems*

Tabe 2 Advanced Comparison of Nano Systems

System	Size Range	Drug Type	Advantages	Limitations	Clinical Status
Polymeric NP	10–500 nm	Hydrophobic	Controlled release	Cost, toxicity	Preclinical
Liposomes	50–1000 nm	Both	Biocompatible	Leakage issues	Approved (some drugs)
SLNs	50–300 nm	Lipophilic	Stability	Drug expulsion	Preclinical
NLCs	100–500 nm	Lipophilic	High loading	Complex prep	Emerging
Nanoemulsions	20–200 nm	Lipophilic	High absorption	Instability	Clinical trials

IV. RECENT ADVANCES

➢ *Curcumin Nano-Formulations*

Curcumin, a poorly water-soluble phytoconstituent, has shown significant improvement in its therapeutic performance when formulated into nano-based delivery systems. Nano-formulations such as polymeric nanoparticles, liposomes, and nanoemulsions have demonstrated more than 20-fold enhancement in solubility, leading to improved bioavailability. These systems also exhibit enhanced anticancer efficacy by facilitating better cellular uptake, sustained release, and targeted delivery to tumor tissues.[36]

➢ *Quercetin Nanoparticles*

Quercetin nanoparticles have gained attention due to their ability to overcome limitations associated with poor solubility and rapid metabolism. Nanoencapsulation improves its antioxidant potential by enhancing stability and protecting it from degradation. Additionally, these formulations lead to higher plasma concentration and prolonged circulation time, thereby increasing overall therapeutic effectiveness.[37]

➢ *Berberine Nanocarriers*

Berberine, known for its antidiabetic properties, suffers from low bioavailability due to poor intestinal absorption. Nanocarrier-based delivery systems such as solid lipid nanoparticles and polymeric nanoparticles have been developed to address these challenges. These systems enhance intestinal permeability, improve absorption, and significantly boost its antidiabetic activity by maintaining optimal drug levels in the systemic circulation.[38]

➢ *Green Nanotechnology*

Green nanotechnology represents an emerging and sustainable approach in nanoparticle synthesis, utilizing plant

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extracts and natural biomolecules as reducing and stabilizing agents. This plant-mediated synthesis method is eco-friendly, cost-effective, and minimizes the use of toxic chemicals. Furthermore, nanoparticles produced through green methods often exhibit improved biocompatibility and reduced toxicity, making them highly suitable for pharmaceutical and biomedical applications.

Overall, recent advances in nano-formulations of phytoconstituents and the adoption of green nanotechnology approaches are significantly contributing to the development of safer, more effective, and sustainable drug delivery systems. [33]

Table 3 Recent Studies Summary

Author (Year)	Phytoconstituent	Nano System	Key Outcome
Sharma (2021)	Curcumin	Polymeric NP	↑ Bioavailability
Patel (2022)	Quercetin	Liposome	↑ Antioxidant
Khan (2023)	Berberine	SLN	↑ Antidiabetic effect
Singh (2024)	Resveratrol	Nanoemulsion	↑ Absorption

V. THERAPEUTIC APPLICATIONS OF NANO-ENABLED PHYTOCONSTITUENT DELIVERY

Nano-enabled delivery systems have significantly enhanced the therapeutic potential of phytoconstituents by improving their solubility, stability, permeability, and targeting efficiency. These systems overcome major limitations associated with herbal drugs such as poor bioavailability, rapid metabolism, and low systemic retention.[40]

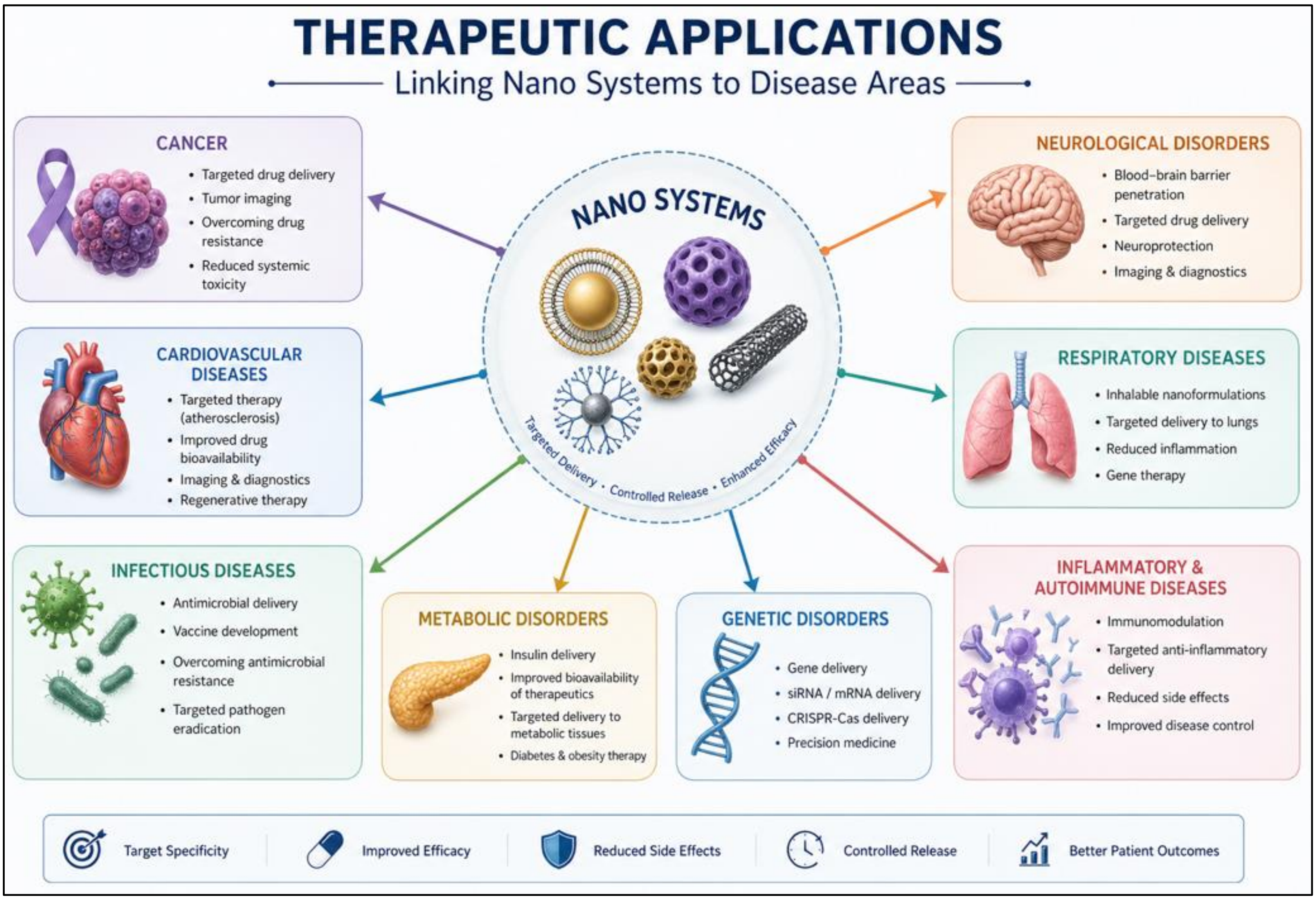

Fig 4 Therapeutic Applications of Nano-Enabled Phytoconstituents

A. *Anticancer Applications*

Phytochemicals such as curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) exhibit potent anticancer activity but suffer from poor bioavailability.[27,30]

➢ *Nano-Enabled Advantages:*

- Enhanced tumor targeting via EPR effect
- Increased cellular uptake
- Reduced systemic toxicity

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➢ *Examples:*

- Curcumin-loaded nanoparticles for breast and colon cancer
- Resveratrol nanoemulsions for prostate cancer

B. Anti-Inflammatory and Antioxidant Activity [(26)]

Herbal drugs like Curcuma longa (turmeric) and Glycyrrhiza glabra (mulethi) show strong anti-inflammatory properties.

➢ *Mechanism:*

- Inhibition of inflammatory mediators (TNF-α, IL-6)
- Scavenging of reactive oxygen species (ROS)

➢ *Nano Benefits:*

- Sustained release
- Enhanced tissue penetration

Table 4 Nano-Formulated Phytoconstituents for Anti-Inflammatory Activity

Phytoconstituent	**Nano-formulation**	**Therapeutic Effect**	**Phyto-constituent**
Curcumin	Polymeric nanoparticles	Anti-inflammatory	Curcumin
Quercetin	Liposomes	Antioxidant	Quercetin
Boswellic acid	SLNs	Anti-arthritic	Boswellic acid

C. Antimicrobial Applications [(31)]

Phytoconstituents exhibit broad-spectrum antimicrobial activity but are limited by poor penetration and stability.

➢ *Nano-Enabled Improvements:*

- Enhanced membrane permeability
- Increased bioavailability
- Controlled drug release

➢ *Applications:*

- Essential oil nano-emulsions for bacterial infections
- Silver nanoparticle-herbal conjugates

D. CNS Disorders (Neuroprotective Applications) [(32)]

The blood-brain barrier (BBB) restricts drug entry into the brain.

➢ *Nano-Based Strategies:*

- Surface-modified nanoparticles
- Lipophilic nano-carriers

➢ *Examples:*

- Curcumin nanoparticles for Alzheimer's disease
- Ginkgo biloba nano-formulations for cognitive enhancement

E. Cardiovascular Applications[(29)]

Phytoconstituents like flavonoids and polyphenols are beneficial in cardiovascular diseases.

➢ *Nano Advantages:*

- Improved bioavailability
- Targeted delivery to vascular tissues

➢ *Therapeutic Roles:*

- Anti-hypertensive
- Anti-atherosclerotic

F. Antidiabetic Applications [(27)]

Natural compounds such as berberine and gymnemic acid show antidiabetic effects but suffer from poor absorption.

➢ *Nano-Enabled Effects:*

- Improved glucose regulation
- Enhanced pancreatic targeting

Table 5 Nano-Delivery Systems in Herbal Antidiabetic Therapy

Herbal Drug	**Nano System**	**Benefit**
Berberine	Nanoparticles	Improved absorption
Gymnema extract	Nanoemulsion	Enhanced bioavailability
Amla extract	Liposomes	Antioxidant effect

G. Gene Delivery and Immunomodulation [(24)]

Nano-enabled phytoconstituents are being explored in:

- Gene therapy
- Vaccine delivery
- Immune modulation

➢ *Advantages:*

- Target-specific delivery
- Reduced degradation

H. Wound Healing and Skin Disorders [(28)]

Herbal nanocarriers are widely used in dermatology.

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➢ *Applications:*

- Aloe vera nano-gels
- Neem-based nano-formulations

➢ *Benefits:*

- Faster wound healing
- Enhanced antimicrobial action

I. Hepatoprotective Applications [(25)]

Phytoconstituents such as silymarin and andrographolide are used for liver protection.

➢ *Nano Advantages:*

- Improved liver targeting
- Reduced metabolism

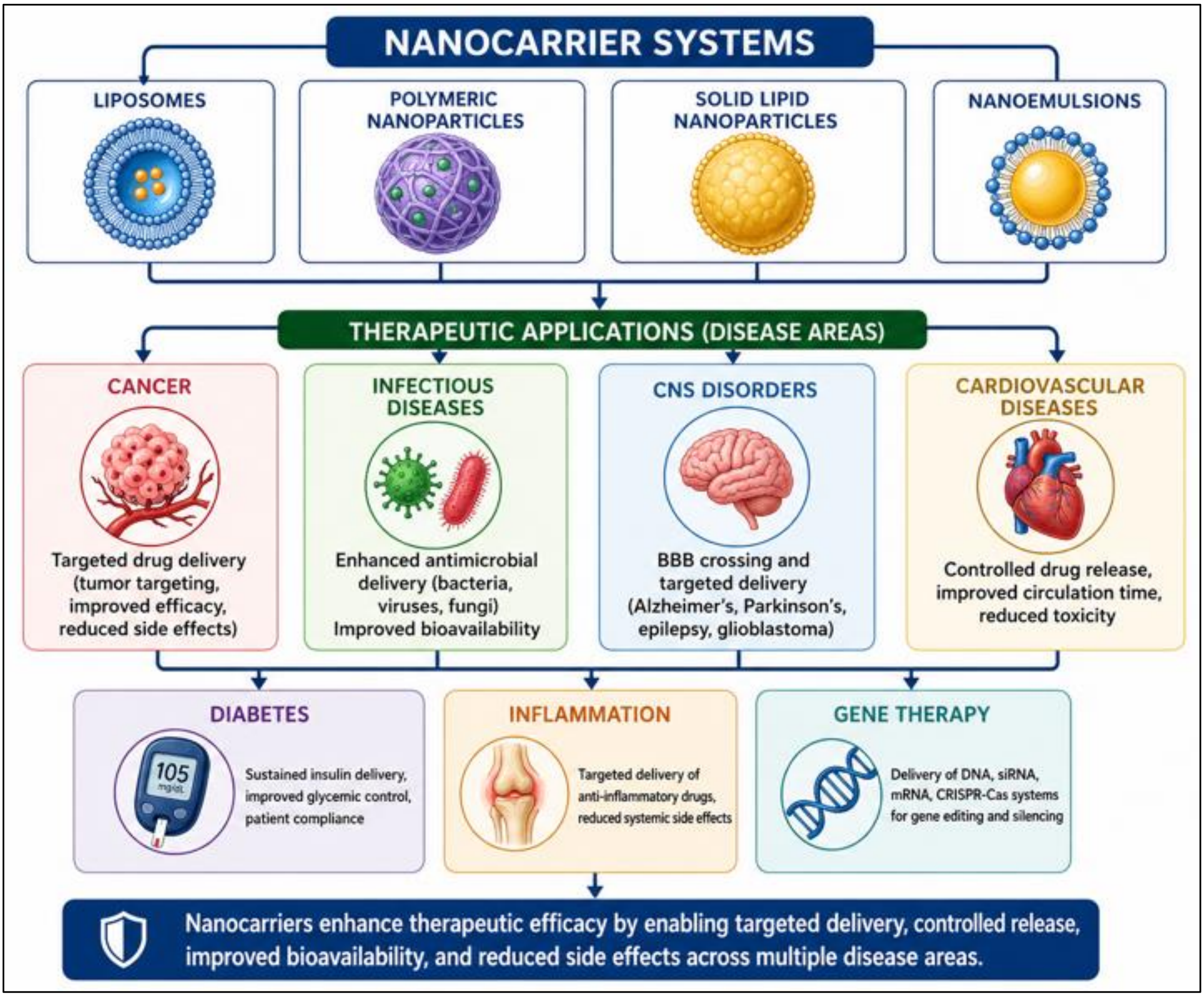

Fig 5 Therapeutic Applications

VI. EXPANDED CRITICAL DISCUSSION

The use of nanotechnology to deliver drugs helps to overcome the pharmacokinetics limitations of the phytoconstituents to some extent. Nevertheless, many studies are carried out within preclinical models only. The problem of the transition from lab scale studies to clinical practice faces several obstacles.

Firstly, the issue of scaling down poses difficulties. There exist many nano-formulations that cannot be used in industry because they require costly processes. Secondly, there are not enough regulations to guide the production of nano-formulated herbal medicines.

In addition, standardization is another limitation since different methods of preparation may give different outcomes. Another problem is the underestimation of toxicity and the absence of information about long-term effects.

Nevertheless, it is worth mentioning that nano-technological methods could be combined with novel

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technologies like artificial intelligence. Furthermore, personalized nano-medicine is a promising way.

VII. LIMITATIONS AND PROBLEMS

- Need for clinical trials
- Inconsistency in regulatory frameworks
- Expensive to manufacture
- Inconsistent stability
- Safety problems

VIII. FUTURE PROSPECTS

➢ *In the Future, there will be:*

- Nano-carrier technology (sensitive to pH and stimulus)
- Use of artificial intelligence in designing formulations
- Custom-made nano-herbal drugs
- Combining with precision medication

IX. CONCLUSION

The application of nanotechnology in the delivery of phytoconstituents is one of the most outstanding innovations in the modern pharmaceutical industry because it enables overcoming key problems associated with herbs that include poor solubility, instability, metabolism, and inadequate bioavailability. With the help of the use of nanocarriers such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanogels, it becomes possible to ensure controlled and targeted effect from these drugs.

With the help of their superior pharmacokinetic and pharmacodynamic properties, phytoconstituents can become extremely effective with reduced side effects and systemic toxicity. In addition to that, it becomes possible to develop innovative pharmaceutical products for complex diseases such as cancer, heart-related ailments, degenerative disorders, and infections. The ability to apply ligand-targeted and stimuli-responsive nanodelivery approaches creates a bright prospect for developing personalized medicines. Nevertheless, some issues related to scaling of the technology, regulatory compliance, and economic and safety factors should be considered.

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