# Advancing Anti-Inflammatory Therapy Through Naringin-Loaded Liposomes: Formulation Strategies, Characterization, and Therapeutic Potential

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***ABSTRACT***

Numerous acute and chronic diseases, such as rheumatoid arthritis, osteoarthritis, pulmonary fibrosis, neurological disorders, inflammatory bowel disease, and inflammatory skin ailments, are caused by inflammation, a complicated biological reaction. Naringin—a naturally occurring flavanone glycoside that is mostly found in citrus fruits—has gained a lot of interest due to its strong anti-inflammatory, antioxidant, antiarthritic, and immunomodulatory qualities. Naringin reduces oxidative stress, suppresses NF-κB signaling pathways, and inhibits pro-inflammatory cytokines, among other processes that contribute to its therapeutic effects. Due to its poor water solubility, low oral bioavailability, substantial gastrointestinal metabolism, rapid systemic clearance, and instability under physiological conditions, its clinical applicability remains limited despite these encouraging pharmacological actions. Nanotechnology-based drug delivery methods, with liposomes among the most promising carriers, have been thoroughly studied to address these issues. Liposomes are biocompatible phospholipid vesicles that can improve the solubility of drugs, prevent the degradation of encapsulated chemicals, extend the duration of circulation, and distribute drugs in a controlled and precise manner. This review comprehensively discusses the physicochemical properties of naringin and the limitations associated with the conventional delivery of naringin, which restrict its therapeutic efficacy. Special emphasis is placed on naringin-loaded liposomal formulations as promising nanocarriers for anti-inflammatory drug delivery, including their formulation approaches, methods of preparation, and characterization techniques. Furthermore, the review highlights the co-administration of naringin with other bioactive compounds as a combinational therapeutic strategy to enhance anti-inflammatory and other regenerative outcomes.

**Keywords:** Naringin; Liposomes; Anti-inflammatory drug delivery; Nanocarriers; Co-encapsulation; Combination therapy.

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## 1. INTRODUCTION

Inflammation, which primarily appears as redness, swelling, heat, discomfort, immune cell infiltration, and dysfunction, is a defensive reaction to exposure to the environment, infection, tissue damage, and autoimmune induction1. On the other hand, inflammatory disease results from severe and unchecked persistent inflammation, which is a pathological process involving local or systemic tissue. Excessive, aberrant, and persistent immunological responses in immune cells and inflammatory responses in stromal cells are the causes of inflammatory illnesses, which have similar physiologic and pathological characteristics. Therefore, a viable approach to treating inflammatory illnesses is to prevent the emergence of aberrant immune responses[2].

Through TNF-α receptor signaling, peripherally induced inflammation can raise the systemic inflammation alarm of adult neural stem cells (NSCs) and drive inflammation by temporarily activating TNF-α-mediated primer NSCs. Treating inflammation-related illnesses requires precise control of homeostasis in the inflammatory process. The anti-inflammatory qualities of naringin have long been acknowledged. Natural anti-inflammatory

antioxidants like naringin actively support the body's immunological response and preserve the integrity of the immune barrier. There are two types of inflammation: acute and chronic. Immediate injuries cause acute inflammation, which draws inflammatory cells to the injury site and starts the healing process. On the reverse contrary, long-term tissue damage and conditions like rheumatoid arthritis result from chronic inflammation, which continues even in the absence of external dangers. By stimulating the AMPK/SIRT1 pathway, it can increase autophagy flux and shield human nuclear myelocytes from oxidative damage, inflammation, and loss of cellular homeostasis caused by TNF-α. It's important to remember that oxidative stress and inflammation are two-way processes. Thus, reducing oxidative stress is another useful strategy for managing inflammatory illnesses.

## 2. NARINGIN

Citrus fruits, grapes, and Chinese herbal medicine all naturally contain naringin, a flavonoid. The flavanone naringenin and the disaccharide neohesperidose combine to generate this flavanone glycoside, which is primarily derived from yellowish dihydro flavonoids that are isolated from the dried peel of grapefruit and Rutaceae plants. Four processes are involved in the extraction, identification, isolation, and purification of naringin from plants or fruits.

The most prevalent methods for determining naringin are high-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UHPLC) using a mass spectrometer (MS) or photodiode array (PAD) detector. Studies have demonstrated that naringin has an important role in promoting anti-inflammatory[3], anti-apoptotic[4], anti-tumor[5], anti-ulcer[6], oxidative stress[7], antiviral+, and skeletal muscle fiber remodeling[9,10].

Naringin's powerful anti-inflammatory properties have therapeutic effects in the prevention and treatment of cardiovascular disease and metabolic syndrome, as well as renal and neuroprotective effects, and the ability to treat and relieve a wide range of inflammatory diseases in various body organs and airway inflammation.[11]

An immunological reaction and persistent stimulation of the brain's glial cells (astrocytes and microglia) are the main causes of neuroinflammation. In the pathophysiology of neurodegenerative diseases (NDDs), it frequently occurs. Alzheimer's disease (AD), Parkinson's disease (PD), brain injury, and cerebral ischaemia are the most common neurodegenerative disorders. Neurodegeneration has a complex pathology and few effective treatments. As a result, naringin, derived from medicinal plants or fruits, has the potential to treat a wide range of neuroinflammatory conditions by targeting several signaling pathways. [12, 13]

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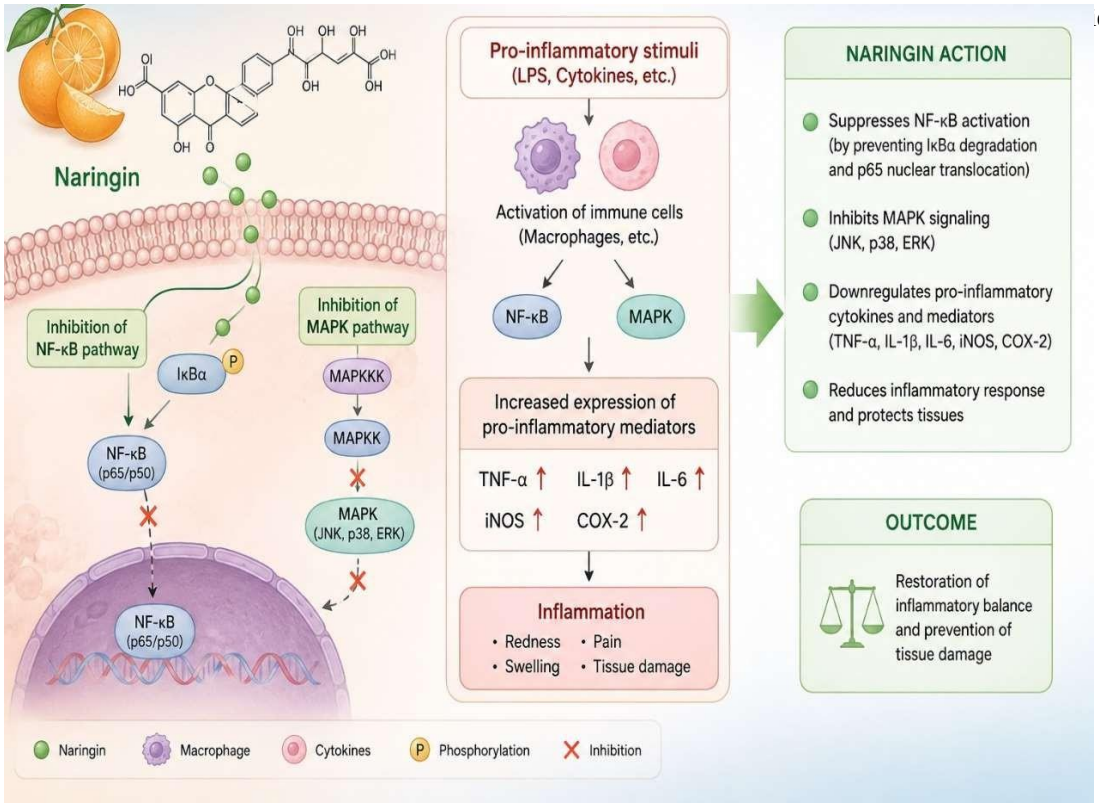
Naringin
Inhibition of NF-κB pathway
IκBα
P
NF-κB (p65/p50)
Inhibition of MAPK pathway
MAPKKK
MAPKK
MAPK (JNK, p38, ERK)
NF-κB (p65/p50)
Pro-inflammatory stimuli (LPS, Cytokines, etc.)
Activation of immune cells (Macrophages, etc.)
NF-κB
MAPK
Increased expression of pro-inflammatory mediators
TNF-α ↑ IL-1β ↑ IL-6 ↑
iNOS ↑ COX-2 ↑
Inflammation
• Redness • Pain
• Swelling • Tissue damage
NARINGIN ACTION
Suppresses NF-κB activation (by preventing IκBα degradation and p65 nuclear translocation)
Inhibits MAPK signaling (JNK, p38, ERK)
Downregulates pro-inflammatory cytokines and mediators (TNF-α, IL-1β, IL-6, iNOS, COX-2)
Reduces inflammatory response and protects tissues
OUTCOME
Restoration of inflammatory balance and prevention of tissue damage
Naringin
Macrophage
Cytokines
P Phosphorylation
Inhibition

**Figure 1: Naringin's mechanism of action as anti-inflammatory agent**

Source and Chemical Structure

Naringin is a flavanone glycoside chemically known as 4′,5,7-trihydroxyflavanone-7-rhamnoglucoside.

It is mainly isolated from:

- Grapefruit (*Citrus paradisi*)
- Orange (*Citrus sinensis*)
- Pomelo (*Citrus grandis*)
- Lemon (*Citrus limon*)

Naringin consists of:

- Aglycone: Naringenin
- Sugar moiety: Neohesperidose

Pharmacological Activities

Naringin exhibits a broad spectrum of biological activities, including:

- Anti-inflammatory activity
- Antioxidant activity
- Antiarthritic activity
- Hepatoprotective activity
- Cardioprotective activity
- Neuroprotective activity
- Anticancer activity
- Osteogenic and bone-protective effects

Among these properties, its anti-inflammatory effect has garnered significant attention due to its capacity to concurrently control several inflammatory mediators.[14]

### 2.1 Chemical Composition of Naringin

Naringin, a flavonoid, is mostly found in grapefruits and other citrus fruits. Chemically, it is a glycoside made up of the disaccharide neohesperidose and the flavone naringenin. Naringin's chemical structure consists of two phenolic rings, a heterocyclic pyran ring, and a flavonoid backbone. The chemical formula is C27H32O14, and the molecular weight per mole is 580.54 g. Naringin's bitter taste and a variety of biological benefits, including as antioxidant, anti-inflammatory, anti-cancer, and cardioprotective properties, have piqued the interest of pharmaceutical and nutraceutical researchers.[15]

### 2.2 Bioavailability and Pharmacokinetic Properties of Naringin

NRG is slightly soluble in water (1 mg/mL at 40°C). Due to the hydrophilic sugar residues in its structure, NRG dissolves more easily in polar solvents (methanol > ethanol > ethyl acetate) than in nonpolar solvents. Rising temperatures in certain ranges increase the likelihood of NRG solubility in different solvents.

However, NRG is classified as a class IV agent by the Biopharmaceutical Classification of Drugs (BCS), meaning that it has substantial oral administration constraints. Because of its massive hydrophobic ring shape, NRG has a limited bioavailability due to its low permeability and lack of solubility.[17]

NRG metabolism is closely linked to the degree of conjugation with sugar moieties and the corresponding removal by gut bacterial species. Furthermore, β-glycosidase in the stomach enzymatically cleaves NRG because it is unstable at acidic pH.

NRG will ultimately make it to the colon because it is also impervious to enzymatic assaults in the stomach and small intestine.

Oral absorption of NRG from citrus products revealed that NRG is frequently exposed to enzymes generated by the gut flora and is poorly absorbed from the gastrointestinal system in its natural form. Using the enzymes β-glucosidases, the process starts with the removal of rhamnose and then glucose.[18]

### 2.3 Biological Activities of Naringin

NRG's pharmacological and biological effects have been extensively studied. The shared chemical structure of natural flavonoids and the presence of sugar moieties and hydroxyl groups attached to both aromatic rings—structures that provide particular physicochemical and physiological properties, enabling them to perform a variety of functions and distinguish themselves from other compounds—are responsible for most of NRG's health benefits. Recent research suggests that NRG may have therapeutic advantages by altering the expression of particular proteins and enzymes.

Despite its potential benefits in the prevention and treatment of a variety of diseases, NRG has yet to be licensed for clinical use as a single therapy or in combination with other bioactive substances. This is primarily due to flavonoids' high in vivo metabolism, which restricts their therapeutic efficiency.

Furthermore, when given orally, NRG's weak solubility and dissolution rate result in a low bioavailability (about 8.8%). Because NRG is poorly soluble in water, there is a limiting step in the organism's absorption, lowering its therapeutic efficacy.

The oral route is commonly used in large NRG

research; however, the digestive tract does not absorb it in the same manner. In comparison, the GIT's absorption of NRG is often slow and variable.

NRG can potentially break down during blood circulation when given intravenously (IV). In the bloodstream, this structure is usually unstable and easily oxidises in the serum and liver, where β-glucosidases break it down.[20]

The aforementioned article states that NRG quickly interacts with bovine serum albumin under physiological settings that define its pharmacokinetic profile. This interaction encourages excretion, which in turn affects NRG's bioavailability.

To increase the bioavailability and bioactivity of biologically active substances for therapeutic applications, a number of approaches are frequently put forth. These tactics include, among other things, chemical structural alterations of a therapeutic candidate, the use of suitable bioenhancers, inhibition of intestinal cell transporters, and developments in drug delivery methods from nanotechnology, pharmaceutical technology, and colloidal systems.

The development of micro- and nanoformulations is one of the most effective research routes for overcoming the physicochemical and biologic limits of drugs used to treat pathologies and diseases. A number of micro- and nanotechnology-based drug delivery technologies have improved NRG's bioavailability and pharmacokinetics, thereby protecting it from deterioration and chance interactions over long periods of circulation.[20]

Anti-Inflammatory Mechanisms of Naringin

Naringin suppresses inflammation through several molecular pathways:

**2.3.1 Inhibition of Pro-Inflammatory Cytokines**

Naringin reduces the production of:

- Tumor necrosis factor-alpha (TNF-α)
- Interleukin-1β (IL-1β)
- Interleukin-6 (IL-6)
- Interferon-gamma (IFN-γ)

These cytokines play critical roles in the progression of chronic inflammatory disorders.

**2.3.2 Suppression of NF-κB Signaling**

One important transcription factor controlling the production of inflammatory genes is NF-κB. Naringin reduces the generation of cytokines and the recruitment of inflammatory cells by inhibiting NF-κB activation.

**2.3.3 Antioxidant Activity**

Naringin increases endogenous antioxidant enzymes like these and scavenges reactive oxygen species (ROS).

- Superoxide dismutase (SOD)
- Catalase (CAT)
- Glutathione (GSH)

Reduction of oxidative stress contributes significantly to its anti-inflammatory effects.[20]

## 3. CHALLENGES ASSOCIATED WITH NARINGIN DELIVERY AND THE NEED FOR ADVANCED DRUG DELIVERY SYSTEMS

NRG has not yet been approved for clinical usage as a stand-alone medication or in conjunction with other bioactive compounds, despite its potential advantages in the prevention and treatment of numerous diseases. This is mostly because the rapid in vivo metabolism of flavonoids limits their medicinal efficacy.[21]

Furthermore, when taken orally, NRG has a limited bioavailability (around 8.8%) due to its low solubility and dissolution rate. Because NRG is poorly soluble in water, there is a limiting step in its absorption in the body, which reduces its therapeutic efficiency.

Additionally, this particular medication breaks down in an acidic pH environment and is readily metabolised in the intestinal region by the intestinal microflora's natural enzyme β-glucosidase.[21]

Significant NRG exploration often takes place mostly orally; nevertheless, the digestive tract does not absorb NRG in the same way. In contrast, the GIT's absorption of NRG is typically quite sluggish and unpredictable.

Furthermore, the bioavailability and clinical effectiveness of flavonoids like NRG are significantly influenced by the microorganisms found in the stomach. Currently, a number of initiatives are focused on getting over some of NRGs' drawbacks so they can be used in clinical settings. Attempts have been attempted in vitro to enhance the bioavailability and absorption of flavonoids by altering their rates of solubility and dissolution as well as preventing their breakdown by gut microorganisms, most notably by encasing them in nanoparticles or microparticles.

NRG can potentially break down during blood circulation when given intravenously (IV). In the bloodstream, this structure is usually unstable and easily oxidises in the serum and liver, where β-glucosidases break it down.[22]

According to the aforementioned publication, NRG reacts swiftly with bovine serum albumin in physiological circumstances that characterise its pharmacokinetic profile. This interaction promotes excretion, which affects NRG's bioavailability.

A variety of strategies are routinely used to improve the bioavailability and bioactivity of biologically active compounds for medicinal

purposes. These strategies include, among other things, chemical structural changes to a therapeutic candidate, the use of appropriate bioenhancers, the blockage of intestinal cell transporters, and advances in drug delivery methods from nanotechnology, pharmaceutical technology, and colloids.

The development of micro- and nanoformulations is one of the most effective research routes for overcoming the physicochemical and biological limits of drugs used to treat pathologies and diseases. A range of micro- and nanotechnology-based drug delivery technologies have improved NRG's bioavailability and pharmacokinetics, thereby protecting it from deterioration and chance interactions over long periods of circulation.

Once these systems are modified appropriately and elements are precisely targeted to increase accumulation at particular places, they may display a sustained release profile. Conjugating NRG to an appropriate micro- or nanotransporter can therefore increase its bioavailability.[23]

Liposomes are one of the most promising nanocarrier methods for enhancing naringin delivery. Naringin is shielded from acidic breakdown and enzymatic metabolism by liposomes, which are phospholipid vesicles that can encapsulate both hydrophilic and lipophilic substances. Liposomal encapsulation prolongs systemic circulation and decreases premature clearance while improving medication solubility, stability, membrane permeability, and bioavailability. Additionally, liposomes can promote preferential accumulation at inflammatory tissues and offer regulated medication release. Liposomes are thought to be an efficient method for getting beyond naringin's physicochemical and pharmacokinetic restrictions and enhancing its anti-inflammatory effectiveness because of their biocompatibility, biodegradability, and targeting capacity.[24]

## 4. LIPOSOMES FOR NARINGIN DELIVERY

Small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), multilamellar vesicles (MLV), and multivesicular vesicles (MVV) are the four categories into which liposomes are divided according to the size and quantity of bilayers. A monophospholipid bilayer is found in a unilamellar structure, whereas liposomes have a multilamellar structure like an onion. A multilamellar structure with concentric phospholipid spheres is produced when several unilamellar vesicles form inside bigger liposomes[25]. For hydrophilic substances, the effectiveness of liposome encapsulation falls with the number of bilayers but rises with liposome size. The size of the vesicles mostly controls the half-life of liposomes in circulation. The size and number of bilayers determine how much medication is included. For liposome-based medication delivery, vesicles with a size range of 50 to 150 nm are optimal. The mechanisms by which liposomes interact with the cell membrane include phagocytosis, absorption into the membrane, local fusion (adhesion), and selective (modified by receptor-mediated) or nonspecific endocytosis. Liposome-cell interactions are influenced by a variety of factors, such as composition, liposome diameters, surface charge, targeting ligand on the liposome surface, and the biological environment.[26]

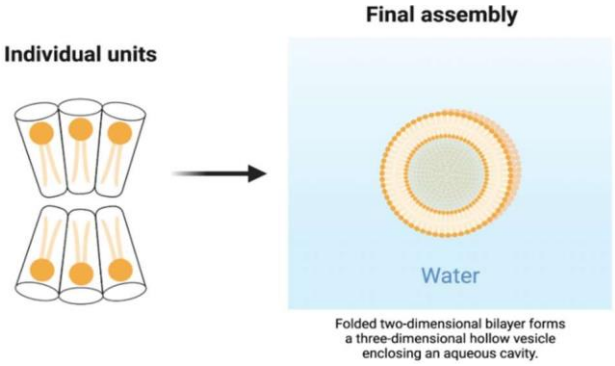


**Figure 2: Structure of Liposome**

Composition of Liposomes

Liposomes are spherical or multilayered spherical vesicles formed by diacyl-chain phospholipids head of the phospholipid bilayer membrane (lipid bilayers) self-assembling in aqueous solutions. The hydrophobic tail and hydrophilic

combine to form an amphiphilic structure. Liposomes can be made from synthetic or natural phospholipids.[27]

### 4.1 Role of lipophilic and hydrophilic groups

**in Liposomes**

Liposome composition has a substantial impact on particle size, stiffness, fluidity, stability, and electric charge. Liposomes derived from naturally occurring unsaturated phosphatidylcholine, such as soybean or egg phosphatidylcholine, have low stability and high permeability. Liposomes containing saturated phospholipids, such as dipalmitoyl phosphatidylcholine, created stiff and almost impermeable bilayer structures.[28,29]

Hydrophilic groups in lipids can be positive, negative, or zwitterionic. The charge of the hydrophilic group provides stability due to electrostatic repulsion. The hydrophobic group in lipids changes according to the length of the acyl chain, its symmetry, and saturation.

The lipids that used in liposomes preparation may be classified as:

**4.1.1 Natural Lipids**

Natural phospholipids are the most commonly employed lipids in liposome synthesis because they are similar to the components of biological cell membranes. These phospholipids are composed of a polar head group containing phosphate and a glycerol backbone linked to two fatty acid chains. Phospholipids are classified as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), phosphatidylglycerol (PG), and phosphatidic acid (PA) based on the kind of polar head group. Egg yolks and soybeans contain lecithin, which is a natural phospholipid. Palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid are among the phospholipids found in soybeans, whereas egg-derived phospholipids primarily contain palmitic acid, stearic acid, oleic acid, linoleic acid, and arachidonic acid. Natural phospholipids are less stable in storage and formulation than synthetic phospholipids because they include a higher percentage of unsaturated fatty acids, making them more susceptible to oxidation and degradation.[29]

**4.1.2 Synthetic Lipids**

Natural phospholipids are chemically modified to create synthetic phospholipids. These changes enable exact control over the content and structure of the lipid molecules, improving stability, repeatability, and purity. Saturated fatty acids like stearic and palmitic acid, which increase membrane stiffness and lessen vulnerability to oxidative degradation, are found in the majority of synthetic phospholipids. Synthetic lipids are widely used in sophisticated liposomal compositions that need reliable performance and extended shelf life because of their well-defined properties.[29]

**4.1.3 Steroids**

Hydrophobic lipids with a four-ring molecular structure are known as steroids. The most often utilised ingredient in liposome compositions is cholesterol. To increase the stability and rigidity of the membrane, cholesterol is added to the phospholipid bilayer, usually at amounts less than 30% of the total lipid content. Cholesterol improves the structural integrity of liposomes during storage and administration, lowers membrane permeability, and lessens drug leakage. Other sterols, like β-sitosterol, have also been studied in addition to cholesterol. These sterols can affect particle size and surface charge, decrease membrane fluidity, and enhance liposome physicochemical stability in general. As a result, adding the right steroid components is essential to maximizing the effectiveness of liposomal drug delivery systems.[29]

**4.2 Method of Preparation of liposomes**

**4.2.1 Thin-Film Hydration (TFH) Method (Bangham Method)**

The Bangham procedure, commonly known as Thin-Film Hydration (TFH), is one of the most prevalent liposome preparation processes. This method produces a thin lipid film by dissolving lipids in an organic solvent then evaporating the solvent. Following that, the film is constantly swirled while being hydrated with an aqueous buffer at a temperature above the lipid phase transition temperature.

Multilamellar vesicles (MLVs) are usually the result of the lipid layers swelling and spontaneously forming liposomes during hydration. The TFH method is frequently used in laboratory-scale liposome production because of its simplicity and convenience of use. Nevertheless, the resulting liposomes are frequently inconsistent in size, necessitating additional size reduction using sonication or extrusion.[30]

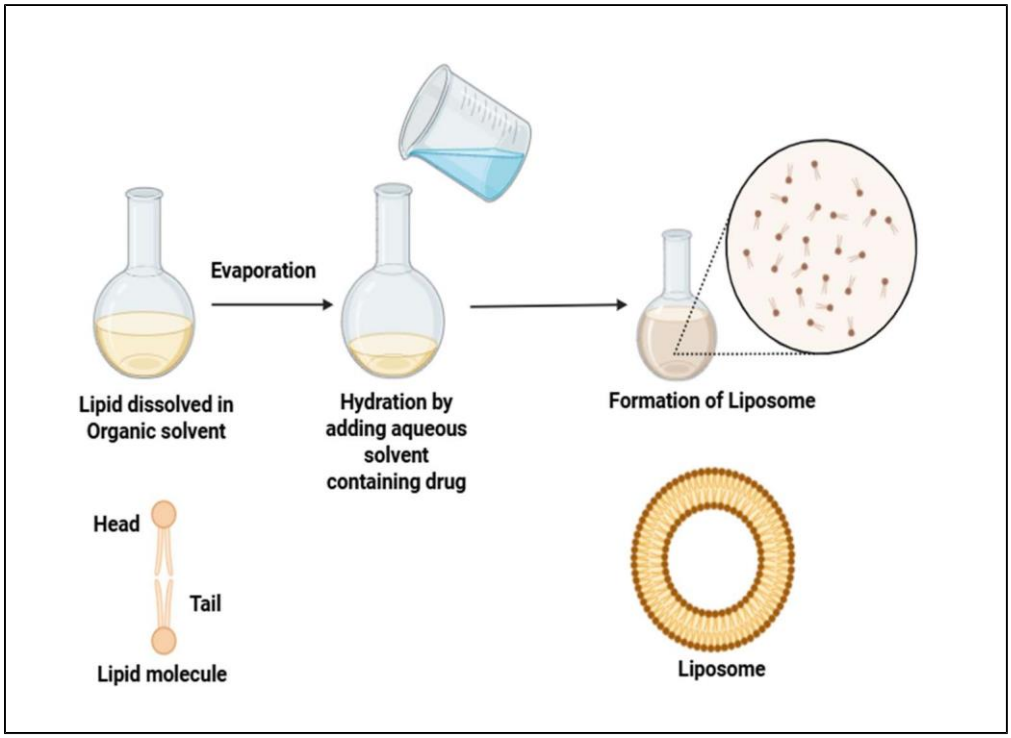


**Figure 3: Liposome preparation by Thin-film Hydration method**

#### 4.2.2 Detergent Removal (Depletion) Method

Unilamellar liposomes are typically generated utilizing the detergent removal method. This approach produces mixed lipid-detergent micelles by first solubilising phospholipids with detergents such sodium cholate, Triton X-100, sodium deoxycholate, or alkyl glycosides. As the detergent is gradually removed, these micelles become more lipid-rich and spontaneously reorganize into liposomes. Dilution, dialysis, gel chromatography, centrifugation, and adsorption onto hydrophobic resin beads are all ways for eliminating detergents. Because dialysis produces liposomes with good size uniformity and reproducibility, it is widely used.[30]

For the integration of membrane proteins into liposomes, this technique is especially helpful. Nevertheless, it could lead to low liposome concentrations, poor hydrophobic drug entrapment effectiveness, and the final formulation containing leftover detergent.

#### 4.2.3 Ethanol Injection Method

Phospholipids are dissolved in ethanol and swiftly injected into an aqueous phase, such as buffer or distilled water, using the ethanol injection technique. When lipids are diluted, they self-assemble into liposomes, most of which are large unilamellar vesicles (LUVs) or small unilamellar vesicles (SUVs). The ethanol residue is removed using evaporation or dialysis.[31]

**Advantages:**

- Simple and reproducible method
- Uses relatively safe solvent (ethanol)
- Easy to scale up for industrial production

**Limitations:**

- Difficult complete removal of residual ethanol
- Produces relatively dilute liposome suspensions
- Possible instability of sensitive biomolecules in the presence of ethanol

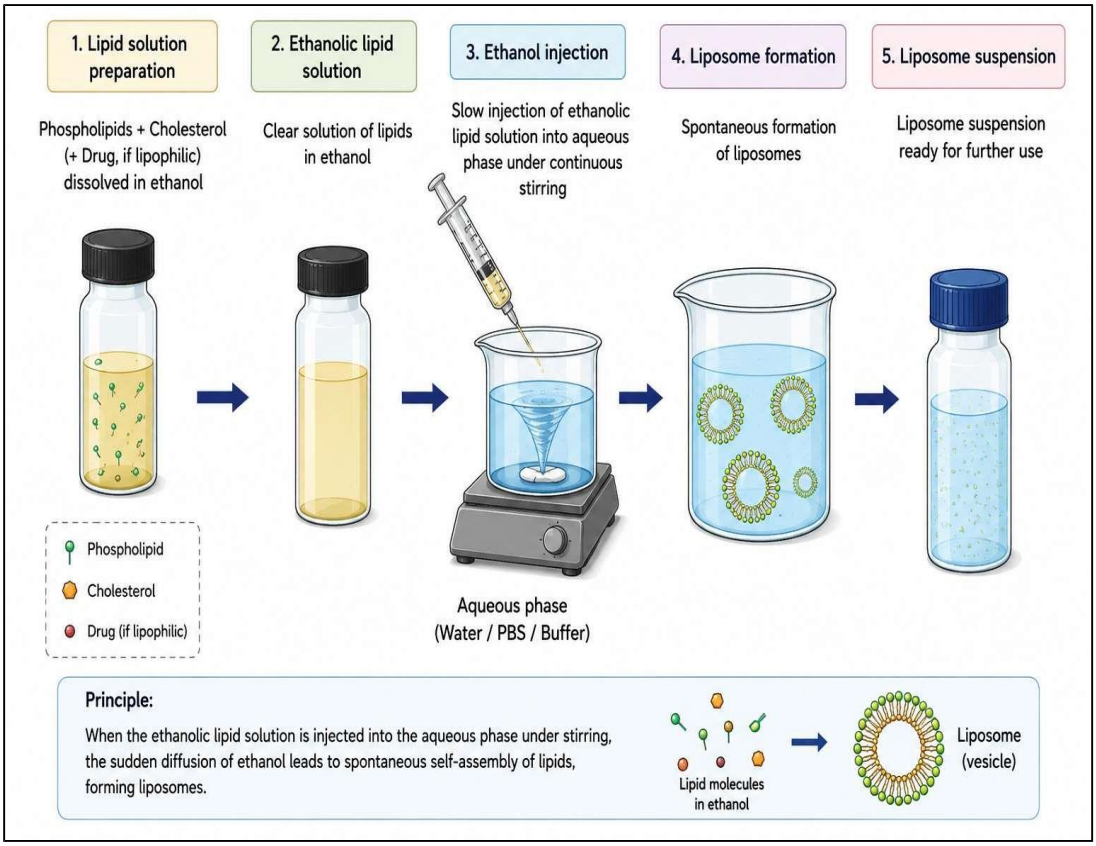


**Figure 4: Liposome preparation by Ethanol Injection method**

### 4.2.4 Ether Injection Method

Lipids dissolved in ether are gradually injected into a heated aqueous phase using the ether injection method. Liposomes are created as the ether evaporates, typically resulting in unilamellar vesicles. After that, the solvent is extracted at lower pressure. [31]

**Advantages:**

- Better solvent removal than ethanol injection
- Produces concentrated liposomal dispersions
- High drug entrapment efficiency

**Limitations:**

- Broad particle size distribution
- Exposure of drugs to organic solvents and elevated temperatures
- Potential reduction in drug stability

### 4.2.5 Reverse-Phase Evaporation Method

The reverse-phase evaporation method produces a water-in-oil emulsion by dissolving lipids in an organic solvent and then mixing them with an aqueous phase. Large unilamellar vesicles (LUVs) occur when the emulsion collapses due to the gradual evaporation of the organic solvent under reduced pressure. [31]

**Advantages:**

- High encapsulation efficiency, especially for hydrophilic drugs
- Suitable for preparing large unilamellar vesicles

**Limitations:**

- Use of organic solvents
- Possible degradation of sensitive compounds during processing
- Requires complete removal of residual solvent

### 4.2.6 Downsizing and Post-Formation Processing

In order to achieve uniform particle size, the required lamellarity, and enhanced stability, post-formation processing is a crucial stage in the manufacture of liposomes. Sonication, extrusion, and high-pressure homogenization are the most widely utilized downsizing methods. [32]

### 4.2.7 Sonication Method

Sonication creates smaller liposomes by reducing

the size of multilamellar vesicles (MLVs) using ultrasonic sound. It can be done using a bath sonicator or a probe sonicator. This simple and widely used approach can be used to create small unilamellar vesicles (SUVs) in the laboratory.[32]

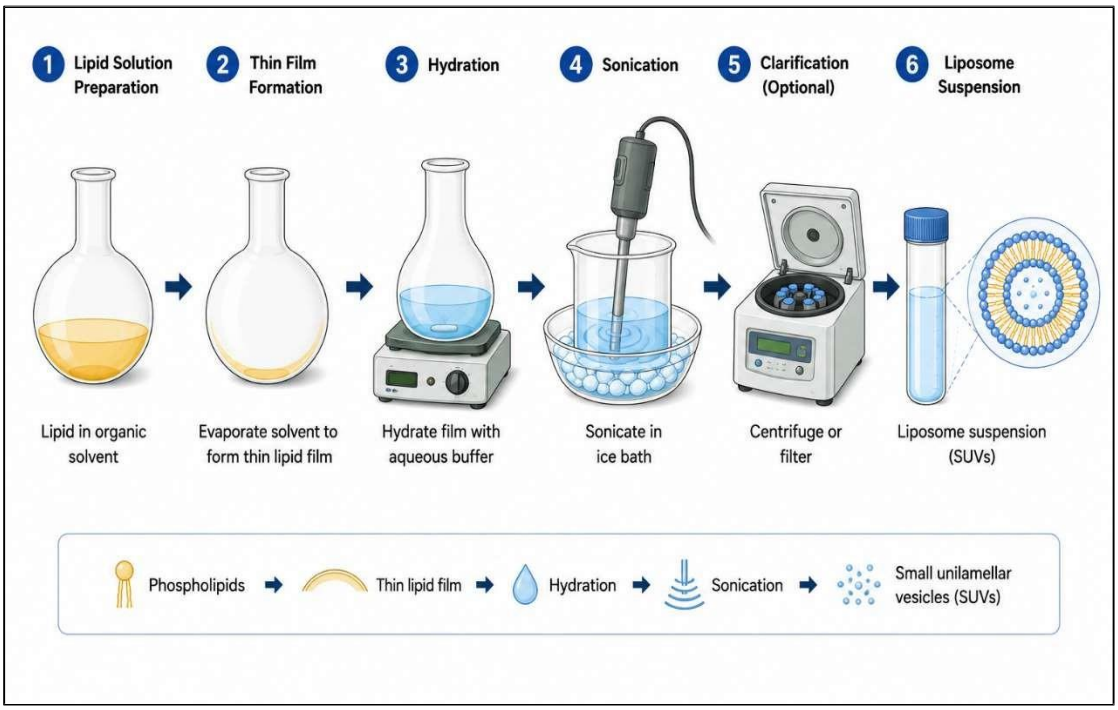


**Figure 5: Liposome preparation by Sonication method**

**Advantages:**

- Simple and rapid process
- Effective size reduction
- Suitable for small-scale production

**Limitations:**

- Possible degradation of lipids and encapsulated drugs
- Risk of metal contamination from probe tips
- Produces liposomes with broad size distribution

### 4.2.8 Extrusion Method

Liposomes are pushed through polycarbonate membranes with predetermined pore diameters using the extrusion process. Liposomes with a restricted size dispersion and consistent size are produced by repeated extrusion. [33]

**Advantages:**

- High reproducibility
- Produces homogeneous liposomes
- Good control over particle size

**Limitations:**

- Product loss during processing
- Less suitable for large-scale production

### 4.2.9 High-Pressure Homogenization Method

This technique entails applying high pressure while pushing liposomal suspensions via a small opening. Vesicle size is decreased by the interaction of shear forces, cavitation, and turbulence. [34]

**Advantages:**

- Suitable for large-scale production
- Efficient particle size reduction

**Limitations:**

- High operating pressures required
- Possible contamination from equipment
- Particle size distribution may remain broad

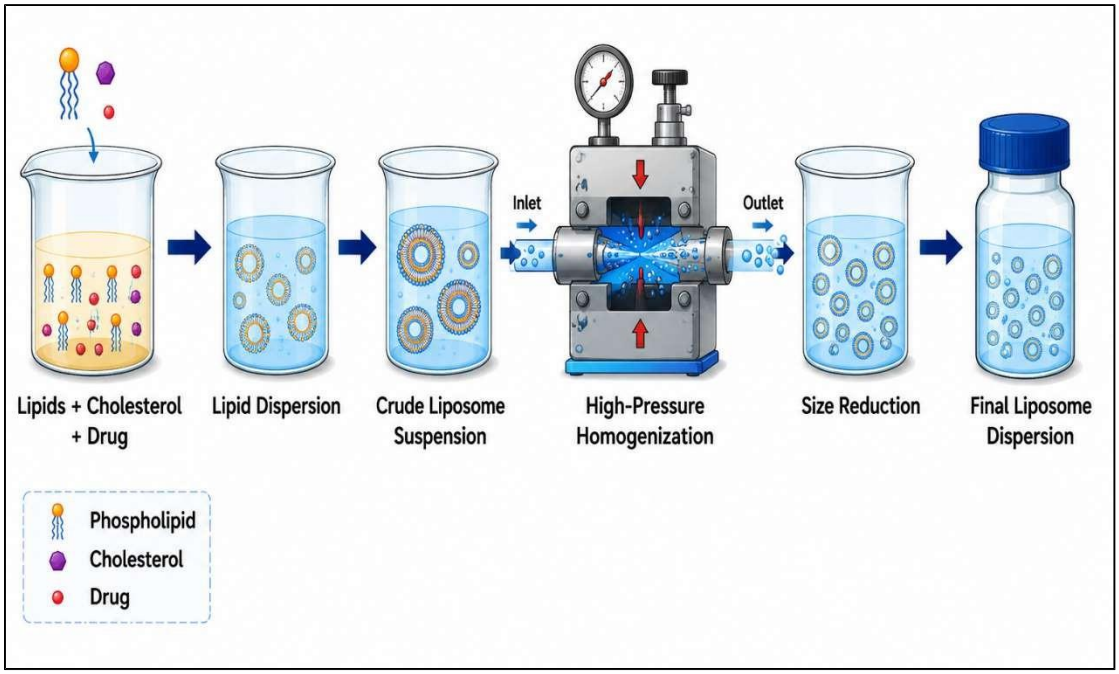


**Figure 6: Figure 5: Liposome preparation by Sonication method**

**4.2.10 Freeze-Drying (Lyophilisation) Method**

One post-processing method for extending the stability and shelf life of liposomal compositions is freeze-drying. This technique involves freezing the liposome suspension and then applying a vacuum to extract the frozen water by sublimation. Remaining moisture is eliminated by a second drying stage. [35]

**Advantages:**

- Improves long-term stability
- Prevents drug degradation and leakage
- Facilitates storage and transportation

**Limitations:**

- Time-consuming process
- Requires specialized equipment
- Improper drying may affect liposome structure

**4.3 Post-Formation Processing of Liposomes**

**4.3.1 Purification of Liposomal Nanoformulations**

Unencapsulated drugs, free molecules, and other contaminants are still present in the external medium after liposome synthesis and need to be eliminated in order to provide a pure and efficient formulation. Ultrafiltration, ultracentrifugation, dialysis, and chromatographic techniques like size-exclusion and ion-exchange chromatography are examples of common purification procedures. These methods can lower the ultimate liposome yield and be time-consuming despite their effectiveness. [35]

The elimination of leftover organic solvents, which are frequently utilized in the manufacture of liposomes and include ethanol, methanol, chloroform, and ether, is another crucial part of purification. The stability and safety of liposomes may be impacted by residual solvents; thus, their levels should be kept to a minimum and closely watched. Additionally, lipid oxidation must be prevented in liposomal compositions, especially when unsaturated phospholipids are utilized. By shielding formulations from light, keeping them under inert gases like nitrogen or argon, and adding antioxidants like butylated hydroxytoluene (BHT) or α-tocopherol, oxidation can be minimized. [35]

**4.3.2 Sterilization of Liposomes**

Liposomes need to be sterile and microbe-free because they are often given parenterally. Numerous sterilization techniques have been investigated, such as heat treatment, chemical sterilization, gamma irradiation, ultraviolet irradiation, steam sterilization (autoclaving), and membrane filtering.

However, liposomes are extremely sensitive systems, and a variety of sterilization techniques may cause structural changes, lipid oxidation, hydrolysis, vesicle aggregation, or drug leakage. One of the most popular methods for small liposomes is membrane filtering using a 0.22 μm filter, however it is not appropriate for larger vesicles. Another successful tactic is aseptic manufacture under carefully regulated sterile

settings, but it is costly and technically challenging. Supercritical carbon dioxide (SC-$CO_2$) technology has become a viable substitute for simultaneous sterilisation and liposome manufacturing in more recent times.[36]

#### 4.3.3 Microfluidic Lab-on-Chip Technology

Recent developments in microfluidics have made it possible to create lab-on-a-chip systems that produce liposomes. These devices combine drug loading, purification, characterisation, and liposome synthesis into one platform. Microfluidic systems lower production costs and reagent use while offering fine control over liposome size, lamellarity, and encapsulation efficiency. Additionally, tangential flow filtering in conjunction with continuous-flow microfluidic devices can effectively eliminate residual solvents and non-encapsulated substances in a little processing time. These technologies are appealing for upcoming industrial-scale production of liposomal formulations because they provide enhanced repeatability, scalability, and process integration. [36]

### 4.4 Physical Characterization

#### 4.4.1 Particle Size and its distribution

Electron microscopy is the most reliable method for evaluating liposome size since it allows for the observation of individual liposomes and offers exact information on the profile of the liposome population across the whole size range. Unfortunately, it takes a long time and requires equipment that isn't always available. On the other hand, the laser light scattering (quasi-elastic laser light scattering) method is rapid and simple to apply, but it only assesses an average property of the liposomes' bulk. [37]

#### 4.4.2 Microscopic methods

Large vesicles made from single chain amphiphiles have been examined for gross size and distribution using light microscopy. The players can use a fluorescence microscope to inspect the liposomes if they have fluorescent hydrophilic probes. This method's ability to fully capture the preparation's size distribution is limited by the light microscope's resolution. However, the bottom end of the size distribution can be estimated by negative stain electron microscopy.

Negative stain electron microscopy is not appropriate for determining the size distribution of big vesicles (5um) since it is impossible to measure the diameter of the original particle due to vesicle distortion during specimen preparation. The spreading of the vesicles on the carbon-coated grid is a technical challenge in getting effective negative staining of liposomes. [37]

#### 4.4.3 Gel Permeation

SUVs and radial MLVs were separated using exclusion chromatography on large pure gels. Large vesicles with a diameter of 1-3 um, however, typically stay on the top of the column and are unable to penetrate the gel. A quick and easy method for estimating the size distribution of a liposome preparation is a thin layer chromatography device that uses agarose beads. Unlike the more traditional column chromatography, it was not stated whether this process was susceptible to a physical obstruction of the agarose gel's pores. [38]

#### 4.4.4 Surface Charge

The surface charge of MLVs is measured using free flow electrophoresis. A method has been devised that uses electrophoresis on a cellulose acetate plate in a sodium borate buffer pH 8.8 to differentiate extruded vesicles based on their surface charge. Electrophoresis is performed on a flatbed device at 4 degrees Celsius for 30 minutes at 18V/cm after the lipid samples (5 moles) are deposited to the plate. The molybdenum blue reagent is used to see the phospholipids once the plate has been dried.

This approach allows liposomes up to 0.2 um in diameter to migrate, and it can detect as little as 2 mole% of charge lipids in a liposome player. This sensitive assay should be useful for tracking the fusion of two populations of vesicles with differing charges and for analyzing the charge heterogeneity in liposome production. [38]

#### 4.4.5 Percent capture (entrapment)

Measuring the amount of material trapped in liposomes is crucial before studying how this material behaves in physical and biological systems because the effects seen in experiments are typically dose-related. One may presume that the amount of material left is 100% entrapped after unincorporated material has been removed using separation techniques, however the preparation may alter over storage. A method for separating free of entrapped material is required for long-term stability testing and for creating novel liposome formulations or production techniques. [39]

#### 4.4.6 Mini Column Centrifugation method

This approach involves filling a 1 mL syringe barrel without a plunger with hydrated gel (Sephadex G-50) and plugging it with a Whatman GF/B filter pad. In a centrifuge tube, this barrel is at rest. To get rid of extra saline solution from the gel, this tube is spun for three minutes at 2000 rpm. Eluted saline is taken out of the collection tube once the gel column has dried and separated from the breathing side during centrifugation. The column is spinning at 2000 RPM for three minutes while a dropwise application of liposome suspension (0.2 ml undiluted) is made to the top

of the gel bed. After that, the Eliot is taken out and put aside for testing. [39]

#### 4.4.7 Entrapped Volume

Measurements of the total amount of solute entrapped in liposomes can often be used to determine the entrapped volume of a population of liposomes (inuL/mg phospholipid), provided that no solute has leaked out of the liposomes after separation from unentrapped material and that the concentration of solute in the aqueous medium inside liposomes is the same as that in the initial solution. However, this assumption is often false. For instance, during the drying down step to eliminate organic solvent in two-phase preparation procedures, water may be lost from the interior compartment. [39]

#### 4.4.8 Lamellarity

Freeze electron microscopy and 31P-NMR can be used to determine the average number of bilayers in a liposome. The latter method records the signals both before and after broadening agents, like manganese ions, are added. These agents interact with the outer leaflet of the outermost bilayers. Therefore, a 50% decrease in the NMR signal indicates that the liposome preparation is unilamellar, and a 25% decrease in the initial NMR signal's intensity indicates that the liposome contains two players. [39]

#### 4.4.9 Drug Release

A properly calibrated in vitro diffusion cell can be used to investigate the process of drug release from liposomes. Liposome-based formulations can benefit from in vitro experiments that forecast the drug's pharmacokinetics and bioavailability before doing costly and time-consuming in vivo research. An alternative assay was utilised to examine the drug's bioavailability, measuring intracellular drug release induced by liposome disintegration in the presence of the mouse-liver lysosome list. The pharmacokinetic performance of liposomal formulations was anticipated utilising dilution-induced drug release in the buffer and plasma.[39]

Chemical Characterization of Liposomes (Short Note)

**a) Quantitative Determination of Phospholipids**

The presence of residual solvents in dried lipids makes it challenging to detect phospholipids directly. As a result, phosphate content is typically measured to indirectly infer phospholipid levels.

- **Bartlett Assay**

Inorganic phosphate is produced through the hydrolysis of phospholipid phosphorus. Phosphomolybdic acid is created when ammonium molybdate and inorganic phosphate combine. Amino-naphthyl-sulfonic acid reduces this to a blue complex. Spectrophotometric measurements of the absorbance are made, and the results are compared to standards.

**Advantage:** Highly sensitive.

**Limitation:** Easily affected by inorganic phosphate contamination, reducing reproducibility.

- **Stewart Assay**

In an organic solvent, phospholipids and ammonium ferrothiocyanate combine to produce a complex. Spectrophotometry is used to measure the complex.

**Advantage:** Inorganic phosphate does not interfere with the assay.

**b) Phospholipid Oxidation**

A free-radical chain reaction oxidises phospholipids, particularly polyunsaturated fatty acids.

**Methods used to evaluate oxidation:**

i. UV Absorbance Method
ii. Thiobarbituric Acid (TBA) Method
iii. Iodometric Method
iv. Gas-Liquid Chromatography (GLC)

**c) Cholesterol Analysis**

- **Qualitative Analysis**

Performed using capillary column gas chromatography with flexible fused silica columns.

- **Quantitative Analysis**

A purple complex is created when cholesterol combines with sulphuric acid, ethyl acetate, and ferric perchlorate. At 610 nm, absorbance is measured. used to estimate cholesterol levels between 0 and 8 µg. [40]

## 5. THERAPEUTIC APPLICATIONS OF NARINGIN-LOADED LIPOSOMAL DELIVERY SYSTEMS

Liposomes are among the most extensively investigated nanocarrier systems for drug delivery owing to their excellent biocompatibility, biodegradability, and ability to encapsulate hydrophilic, hydrophobic, and amphiphilic therapeutic agents. These vesicular structures, which can vary in size from nanometres to several micrometres, are made up of phospholipid bilayers encircling an aqueous core. Oral, intravenous, topical, ophthalmic, pulmonary, and transdermal delivery of liposomes have all been accomplished with success. They are excellent carriers for natural substances like naringin (NRG) because of their capacity to enhance medication solubility, stability, bioavailability, and targeted administration.

### 5.1 Ultra deformable Liposomes for Skin Inflammatory Disorders

Ultradeformable liposomes intended for topical

therapy of inflammatory skin conditions were among the first successful uses of NRG-loaded liposomes. The phospholipids and surfactants that make up these vesicles function as edge activators, boosting membrane flexibility and making it easier to pass through the skin barrier. The developed formulation exhibited a particle size of approximately 100 nm, high encapsulation efficiency (about 88%), and a negative zeta potential indicating good stability. In vitro studies using mouse dermal fibroblast cells demonstrated excellent biocompatibility. Furthermore, in vivo anti-inflammatory studies revealed that the formulation significantly reduced skin inflammation and showed greater efficacy than conventional betamethasone cream. These findings suggest that ultradeformable liposomes can effectively enhance the topical delivery and therapeutic activity of naringin.[41]

**5.2 PEGylated Liposomes for Rheumatoid Arthritis Therapy**

The chronic inflammatory illness known as rheumatoid arthritis (RA) is typified by increasing tissue damage and joint inflammation. PEGylated liposomes co-loaded with naringin and bioactive isothiocyanates such phenethyl isothiocyanate (PEITC) and sulforaphane (SFN) have been created to increase therapeutic efficacy. By adding polyethylene glycol (PEG) to the liposomal surface, the ELVIS (Extravasation through Leaky Vasculature and Inflammatory Cell-Mediated Sequestration) effect extended systemic circulation and encouraged accumulation at inflammatory sites. These liposomes had a strong negative surface charge, a narrow size distribution, with particle sizes ranging from 140 to 166 nm.

The formulations markedly decreased oedema, pro-inflammatory cytokines, oxidative stress indicators, rheumatoid factor, and C-reactive protein levels in animal models of acute and chronic inflammation. Anti-inflammatory cytokine levels rose concurrently. Because of their sustained release characteristic, which offers extended drug availability at the site of inflammation, NRG-PEITC liposomes showed the best therapeutic efficacy among the evaluated formulations. [41]

**5.3 Naringin-Loaded Liposomes for Pulmonary Fibrosis**

Excessive collagen deposition and compromised lung function are the hallmarks of pulmonary fibrosis, a progressive respiratory condition. Phosphatidylcholine-based liposomes that imitate pulmonary surfactant were created for naringin inhalation administration in order to enhance lung targeting. These liposomes had good encapsulation efficiency, nanoscale size, and outstanding aerodynamic characteristics that made them ideal for aerosol delivery. Their surfactant-like action promoted deep lung deposition and decreased alveolar surface tension. While in vivo research employing bleomycin-induced lung fibrosis models revealed notable decreases in inflammatory cell infiltration, oxidative stress, and collagen buildup, in vitro studies showed effective airway patency. [42]

Histopathological examination further confirmed improved lung architecture and reduced tissue damage. These findings indicate that inhalable NRG-loaded liposomes may serve as an effective therapeutic strategy for pulmonary fibrosis and other chronic respiratory diseases.

Peptide-Modified Liposomes for Bone Regeneration

The development of targeted liposomal systems for regenerative medicine applications has been the focus of recent developments. To increase naringin's osteogenic potential, liposomes modified with TAT (Transactivator of Transcription) and RGD (Arginine-Glycine-Aspartate) peptides have been studied. RGD peptides selectively bind integrin receptors involved in cell adhesion and differentiation, whereas TAT peptides promote intracellular uptake. The resultant liposomes had sustained drug-release properties and an average particle size of about 160 nm. Research on human dental pulp stem cells showed improved mineralization, increased expression of osteogenic genes, increased alkaline phosphatase activity, and increased cell proliferation. According to these results, peptide-modified NRG-loaded liposomes could be useful platforms for regenerative medicine and bone tissue engineering. [4]

**5.4 Emerging Liposomal Systems for Naringin Delivery**

Next-generation liposomal systems such ethosomes, transfersomes, proliposomes, and phytosomes have been developed as a result of advances in nanotechnology. These carriers have extremely malleable and flexible membranes that allow for improved penetration through biological barriers, especially the skin. These systems have shown better naringin topical and transdermal distribution, which increases drug retention, improves therapeutic efficacy, and lowers systemic side effects. For upcoming pharmaceutical applications, their distinctive structural characteristics make them appealing substitutes for traditional liposomes. [42]

**6. POTENTIAL CO-THERAPEUTIC AGENTS WITH NARINGIN**

Curcumin and Naringin as potent bioactive compounds

Curcumin is a 1,7-bis 4-hydroxy-3-

methoxyphenyl 1,6 heptadiene-3,5-dione. It is a polymeric phenol compound with several targets; it acts on the body's biological level and aids in the treatment of various illnesses. Curcumin (CUR) is utilised extensively in the food industry, cosmetics, and medical treatments. It is a polyphenol that comes from turmeric and is frequently referred to as the "golden spice." Co-amorphization with naringin (NRG) can improve CUR's poor oral bioavailability and low solubility of less than 1 µg/ml.[43]

### 6.1 Naringin (NAR), sulforaphane (SFN), and phenethyl isothiocyanate (PEITC)

Naringin (NAR), sulforaphane (SFN), and phenethyl isothiocyanate (PEITC) have considerable anti-inflammatory properties but have low solubility and bioavailability. To address these limitations, liposomal formulations of NAR+SFN and NAR+PEITC were created and tested in acute and chronic inflammatory models. The formulations demonstrated great encapsulation efficiency, nanosized particle dispersion (140-166 nm), good stability, and long-term drug release. In a Freund's full adjuvant-induced arthritis model, NAR+PEITC liposomes dramatically reduced paw oedema and arthritic scores compared to free drug combinations. The liposomal formulations also improved haematological and biochemical markers, inhibited inflammatory cytokines, and decreased joint injury, cartilage breakdown, and inflammatory cell infiltration. These data show that liposomal co-delivery of NAR with SFN or PEITC improves anti-inflammatory and antiarthritic efficacy, indicating their potential for arthritis therapy.[44]

### 6.2 Naringin and naringenin for combination therapy in the treatment of Inflammation

The study demonstrated that citrus flavonoids, particularly naringin (NG) and naringenin (Nar), have strong anti-inflammatory and regenerative properties for intervertebral disc degeneration. Treatment with these flavonoids increased discogenic marker expression, indicating that nucleus pulposus (NP) cells were repaired and regenerated. Gene expression study demonstrated regulation of genes involved in inflammation and regeneration, while molecular docking investigations confirmed robust interactions with major inflammatory targets. These findings indicate that naringin and naringenin may be effective therapeutic agents for enhancing intervertebral disc health and controlling lumbar diseases.[45]

### 6.3 Naringin and naringenin as anticancer agents and adjuvants in cancer combination therapy

Although many cancer rates are under control in Western countries, several cancers, such as lung, breast, and colorectal cancer, are on the rise in many low- and middle-income countries due to increased risk factors caused by development and societal issues. Furthermore, endogenous factors such as inherited mutations, steroid hormones, insulin and insulin-like growth factor systems, inflammation, oxidative stress, and exogenous factors (such as tobacco, alcohol, infectious agents, and radiation) are thought to impair cell function and contribute to carcinogenesis. Some of the approaches used to treat cancer include chemotherapy, surgery, radiation therapy, hormone therapy, and targeted therapies.

However, numerous short- and long-term side effects can have a significant impact on patient prognosis dependent on treatment-related clinical criteria. Recently, a growing number of research have been done to uncover novel therapeutic agents from natural products, with a particular focus on plant-derived bioactive chemicals. Naringin (NG) and its aglycone, naringenin (NGE), are plentiful in citrus fruits such as grapefruits and oranges. Their anti-carcinogenic properties have been demonstrated to function through a variety of cell signal transduction pathways. Recently, many pharmacological techniques based on combination therapy including NG and NGE with current anti-cancer medicines have demonstrated enormous synergistic results when compared to monotherapy. Furthermore, NG and NGE have been shown to overcome multidrug resistance, which is caused by many cancer defence mechanisms and is one of the most significant barriers to therapeutic treatment.[46]

### 6.4 Naringin with Quercetin and Rutin on Cervical Cancer as combinational therapy

Cervical cancer is currently the second leading cause of cancer in women worldwide. Most current research focuses on anticancer medicinal plants and bioactive chemicals derived from natural flavonoids such as quercetin (Q), naringin (N), and rutin (R). The compounds' anticancer potential was studied using assays involving apoptosis, ROS detection, rhodamine 123 staining, AO/EtBr staining, scratch testing, real-time methods, and Western blot techniques in protein-mediated autophagy pathways. Based on the MTT assay results and the combination index, appropriate RQ and RQN combinations were chosen. Experiments demonstrated a considerable increase in Beclin1 protein levels and a matching decrease in P62, indicating increased autophagic flux in HeLa cells treated with flavonoid combinations.

Assays for apoptosis revealed that the overall number of apoptotic cells rose in a time-

dependent manner. The percentages of apoptotic cells enriched with the RQN combination were 16.07%, 65.02%, and 8.91% at 24, 48, and 72 hours, respectively. The combination of RQ resulted in the following percentages of apoptotic cells at the same time points: 31.04%, 32.36%, and 11.46%. Thus, these findings indicate that flavonoid combinations may cause cervical cancer cell death via an autophagy-mediated mechanism and apoptosis. These flavonoid combinations are prospective therapeutic methods for cervical cancer.[47]

**6.5 Boswellia serrata with Naringin as combinational therapy for anti-inflammatory effect**

Boswellia serrata Roxb., a member of the Burseraceae family, is a branching tree native to India, the Middle East, and North Africa that flourishes in arid and desert conditions. Its resin, also known as frankincense, olibanum, or kundur (Unani medicine), has been extracted for ages by incising the tree bark during dry seasons, and its oleo gum resin is used in traditional Arab, Ayurvedic, and Chinese medicine. Extensive research has shown that B. serrata has significant therapeutic promise, particularly in modulating inflammation and combating microbial infections. Its pharmacological effects are mostly due to the inhibition of 5-lipoxygenase, an enzyme involved in leukotriene production, resulting in reduced inflammation. Furthermore, boswellic acids have shown potential antimicrobial activity against a wide range of multi-resistant bacterial strains and biofilm-forming microorganisms, allowing them to adhere to surfaces (such as medical devices or tissues) and evade immune responses and antibiotic treatment.

## 7. THERAPEUTIC SIGNIFICANCE AND FUTURE PERSPECTIVES

The research that is currently available unequivocally shows that liposomal encapsulation greatly increases naringin's therapeutic potential by enhancing its stability, bioavailability, controlled release, and tissue targeting. Numerous liposomal formulations have demonstrated encouraging results in the treatment of bone-related diseases, rheumatoid arthritis, pulmonary fibrosis, and inflammatory skin conditions.

To help NRG-loaded liposomal systems move from lab research to clinical practice, future research should concentrate on improving formulation parameters, assessing long-term safety, and carrying out clinical investigations. Targeting ligands and cutting-edge nanotechnology techniques could improve these formulations' efficacy and broaden their medicinal uses.

## CONCLUSION

Naringin is a bioactive flavonoid that has outstanding anti-inflammatory properties due to its capacity to regulate various inflammatory mediators, reduce oxidative stress, and modulate important cellular signalling pathways. However, its therapeutic efficacy is severely hampered by poor water solubility, low bioavailability, fast metabolism, and limited stability in physiological circumstances. These constraints have hampered its successful clinical translation, despite significant preclinical evidence of its pharmacological effects.

Liposome-based drug delivery systems are an excellent way to overcome these obstacles. Naringin can be preserved from chemical and enzymatic destruction by encapsulating it in phospholipid vesicles, which also improves its solubility, absorption, circulation time, controlled release, and targeted accumulation in inflamed tissues. Various liposomal formulations, such as ultradeformable liposomes, PEGylated liposomes, peptide-modified liposomes, and advanced deformable vesicular systems, have shown significant anti-inflammatory activity in a variety of disease models.

Studies on inflammatory skin conditions, rheumatoid arthritis, pulmonary fibrosis, and regenerative applications have repeatedly demonstrated that naringin-loaded liposomes outperform standard formulations. Furthermore, advances in liposome engineering, surface modification, and targeted delivery tactics continue to increase their therapeutic utility. Overall, naringin-loaded liposomal systems offer a promising nanotherapeutic platform for the treatment of inflammatory disorders. Future research should concentrate on large-scale manufacturing, long-term stability assessment, regulatory issues, and clinical evaluation to help these formulations make the successful transition from laboratory to clinical practice. With continued advances in nanomedicine, liposomal naringin administration may emerge as an effective and safe therapeutic method for the treatment of a wide spectrum of inflammatory conditions.

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