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Advances in Topical Antiviral Drug Delivery: Role of Liposomes and Nanotechnology-Based Strategies

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ABSTRACT

Viral infections such as herpes simplex virus (HSV), human papillomavirus (HPV), and others present a significant global health challenge due to their recurrent nature and limited treatment options. Topical antiviral therapy offers a targeted and patient-compliant approach to manage localized infections, with reduced systemic side effects. However, the skin's barrier—particularly the stratum corneum—poses a major obstacle to effective drug delivery. This review highlights the advances in topical antiviral therapy with a special emphasis on liposomal nanocarriers, which have emerged as promising vehicles for enhancing drug penetration, stability, and localized action. Liposomes, owing to their biocompatibility and ability to encapsulate both hydrophilic and lipophilic drugs, improve the bioavailability of conventional and herbal antiviral agents. Furthermore, the synergistic potential of combining synthetic antivirals like acyclovir with phytochemicals such as curcumin enhances therapeutic outcomes while minimizing resistance and toxicity. The paper also discusses formulation strategies such as use of penetration enhancers, hydrogel systems, and deformable liposomes (e.g., ethosomes, transfersomes), as well as physical enhancement techniques like microneedles. Overall, nanocarrier-based topical therapies represent a transformative direction in antiviral treatment, offering controlled release, improved efficacy, and better patient adherence.

Keywords: *Liposomes, nanocarriers, skin penetration, herpes simplex virus (HSV), phytochemicals, curcumin, controlled release, bioavailability, liposomal gels, nanotechnology, skin barrier, synergistic therapy.*

1. INTRODUCTION

1.Viral Infections

Viral infections are diseases caused by viruses, microscopic pathogens that replicate exclusively within the living cells of a host organism. Upon entering the host, viruses hijack cellular machinery to reproduce, often causing cellular damage or triggering immune responses that manifest as illness symptoms (1). Viruses exhibit a broad host range, infecting animals, plants, and bacteria (as bacteriophages), and are responsible for numerous widespread and severe diseases, including influenza, HIV/AIDS, herpes simplex virus (HSV), and emerging threats like SARS-CoV-2 (COVID-19) (2).

Herpes simplex virus (HSV) is a double-stranded DNA virus belonging to the family *Herpesviridae*, genus *Simplexvirus*. It is a highly prevalent pathogen that infects humans worldwide and is primarily classified into two types: HSV-1 (commonly associated with orolabial infections) and HSV-2 (typically responsible for genital herpes) (3). Both types are neurotropic, establishing lifelong latency in sensory neurons and periodically reactivating to cause recurrent disease (4).

HSV infections are widespread and persistent, with global estimates indicating that about 3.8 billion people under the age of 50 are infected with HSV-1, and approximately 491 million people aged 15–49 are infected with HSV-2 (5). Transmission occurs through direct contact with infected secretions, with HSV-2 also being a notable cofactor in HIV transmission, increasing susceptibility to HIV acquisition by nearly threefold (6).

Although most infections are asymptomatic, HSV can cause painful mucocutaneous lesions, neonatal herpes, keratitis (leading to blindness), and, in rare cases, life-threatening encephalitis. Current antiviral therapies, such as acyclovir and

valacyclovir, do not eliminate the virus, and resistance can occur, especially in immunocompromised individuals (7). Therefore, new delivery strategies, particularly topical and nanotechnology-based systems, are being investigated to improve therapeutic outcomes, reduce dosing frequency, and enhance patient compliance.

Transmission of viral infections commonly occurs through respiratory droplets, contact with bodily fluids or contaminated surfaces (fomites), or via vectors such as mosquitoes. The infection process involves specific steps (8):

1. **Attachment:** where viral surface proteins bind to specific receptors on the host cell membrane.
2. **Penetration:** the entry of the viral genome into the host cell cytoplasm, typically achieved through endocytosis or fusion of the viral envelope with the host cell membrane. While the host immune system is critical for detecting and eliminating viral invaders, some viruses establish chronic infections or latency periods (e.g., HSV), complicating treatment and eradication efforts.
3. **Uncoating:** The viral capsid is removed or disassembled, releasing the viral genome into the host cell's cytoplasm.
4. **Replication and Transcription:** The viral genome is replicated, and messenger RNA (mRNA) is transcribed to direct the synthesis of viral proteins using the host cell's ribosomes and metabolic machinery.
5. **Assembly:** New viral particles (virions) are assembled from the replicated genomic components and newly synthesized structural proteins.
6. **Release:** Newly formed virions are released from the host cell, often through budding (enveloped viruses) or cell lysis (non-enveloped viruses), destroying the host cell and enabling the infection of new cells.

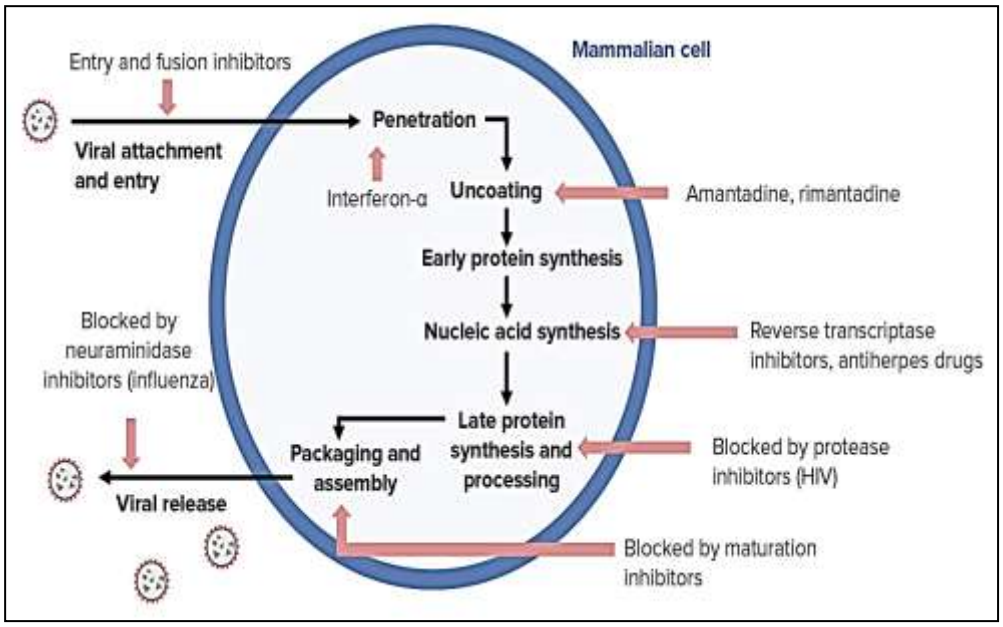

Fig 1: Viral Replication and Drug Intervention Points (9)

2. Therapeutic strategies for viral infections

Therapeutic strategies for viral infections target various aspects of the virus or host response:

a. **Antiviral Drugs:** Directly inhibit specific stages of the viral life cycle, such as viral entry, replication, or assembly (e.g., acyclovir for herpes simplex virus, remdesivir for SARS-CoV-2) (10).

b. **Immunotherapy:** Enhances or modulates the host immune response using agents like interferons or monoclonal antibodies (e.g., palivizumab for respiratory syncytial virus) (11).

c. **Vaccination:** Primarily preventive, using inactivated/attenuated viruses, subunits, or novel platforms like mRNA to induce protective immunity (e.g., influenza, hepatitis B, COVID-19 vaccines) (12).

d. **Symptomatic Treatment:** Addresses illness manifestations (e.g., fever, pain) without targeting the virus itself (13).

e. **Phytotherapy:** Utilizes plant-derived compounds with antiviral properties (e.g., curcumin, quercetin), often investigated for synergistic effects alongside conventional drugs (14).

f. **Emerging Therapies:** Include gene editing (e.g., CRISPR targeting viral genomes) and RNA interference (e.g., siRNA silencing viral genes) (15).

g. **Advanced Delivery Systems:** Employ nanocarriers like liposomes and niosomes to improve targeted delivery, bioavailability, and reduce toxicity of antiviral agents (16,17).

3. Topical Antiviral Therapy

Topical antiviral therapy delivers antiviral agents directly to the site of infection on the skin or mucosal surfaces, offering a localized treatment approach (18). This strategy provides significant advantages over systemic administration, including targeted drug delivery, reduced systemic side effects, and improved patient compliance (19). It is particularly effective for treating cutaneous and mucocutaneous viral infections such as those caused by herpes simplex virus (HSV) types 1 and 2, human papillomavirus (HPV), and molluscum contagiosum virus (20).

Common topical antiviral agents include:

- **Nucleoside Analogues:** Acyclovir and penciclovir inhibit viral DNA replication within infected cells (21).
- **Immune Response Modifiers:** Imiquimod stimulates local immune responses to clear viral infections like HPV (22).
- **Fusion Inhibitors:** Docosanol acts by inhibiting the fusion of the herpes virus envelope with the host cell plasma membrane, preventing viral entry (23).

Table 1Antiviral Drug and their Mechanisms (24,25,26)

Agent	Class	Mechanism of Action	Effect on HSV Infection
Acyclovir	Nucleoside analogue	Requires phosphorylation by viral thymidine kinase → inhibits viral DNA polymerase, halting viral replication	Suppresses lesion progression and replication within infected cells
Penciclovir	Nucleoside analogue	Similar to acyclovir; inhibits DNA polymerase via phosphorylated active metabolite	Treats HSV lesions topically
Docosanol	Fusion inhibitor	Inserts into host cell lipid membranes → blocks viral envelope fusion with the host membrane	Prevents HSV entry into host cells, reducing lesion progression

4. Recent research focuses on enhancing topical antiviral efficacy

Recent research focuses on enhancing topical antiviral efficacy through advanced formulations:

A. **Nanocarrier Systems:** Nanocarrier platforms such as liposomes, niosomes, ethosomes, and nanoemulsions—play vital roles in improving skin permeation, protecting active agents, and allowing sustained release (27).

i. **Liposomes & Niosomes**: Vesicular carriers composed of lipid bilayers (liposomes) or non-ionic surfactant bilayers (niosomes) enhance dermal delivery by fusing with the stratum corneum and releasing drug payloads deeper into skin layers. Their physicochemical attributes (size <300 nm, surface charge, composition) significantly influence transport and drug release dynamics (28).

ii. **Ethosomes & Transfersomes**: Ethanol-rich liposomes and edge-activator-enriched transfersomes offer higher deformability and permeability, facilitating enhanced across-skin passage and deeper dermal delivery.

iii. **Nanoemulsions**: Thermodynamically stable mixtures with nanomicron-sized droplets dramatically improve solubility and skin permeability. Nanoemulsion gels encapsulating acyclovir display increased in vitro release and skin diffusion compared to conventional gels (29).

B. Natural Compounds

Bioactive phytochemicals are gaining attention for their broad-spectrum antiviral and anti-inflammatory actions in topical systems.

Curcumin, derived from *Curcuma longa*, demonstrates inhibitory effects on HSV replication, especially at early stages like viral adsorption. At approximately 30 μM, curcumin reduced HSV-1 and HSV-2 plaque formation by 85–97% in Vero-cell assays (30,31).

Curcumin's limited solubility and skin absorption are addressed via nanocarriers:

- Proniosomal gels containing curcumin enhanced antiviral activity against HSV-1 in vitro, with ex vivo skin penetration and docking studies suggesting effective thymidine kinase inhibition.

- Co-encapsulation with quercetin in liposome/nanocochleate systems is under exploration for combined antiviral and antioxidant effects (32).

C. Synergistic Formulations

Combining synthetic antivirals (e.g., acyclovir) with natural compounds (e.g., curcumin) within nanocarriers can produce synergistic antiviral effects through multi-target inhibition.

i. **ACV and Curcumin co-encapsulation**: Recent liposomal/microparticle systems encapsulating both agents exhibited greater viral suppression than either agent alone, likely due to complementary mechanisms ACV targeting DNA polymerase and curcumin inhibiting viral entry and early gene activation (33).

ii. **Nanoemulsion gels co-loaded with ACV and clove oil/eugenol** serve as penetration enhancers while stabilizing the formulation. In rat models, such gels showed improved spreadability and higher dermal ACV permeation.

iii. **Proniosomal curcumin gels** enhanced vesicle conversion upon hydration, improving skin delivery and replication blockade through thymidine kinase inhibition and membrane fusion prevention (34).

5. Skin Barrier and Challenges in Antiviral Drug Delivery

The skin is a complex, multilayered organ that serves as the body's primary physical barrier, presenting significant challenges for drug delivery (35). Anatomically, it consists of three primary layers: the epidermis (with the outermost stratum corneum), dermis, and hypodermis (36). The stratum corneum, composed of dead, flattened keratinocytes embedded in a lipid matrix, forms a highly impermeable barrier to drug penetration, particularly for large or hydrophilic molecules (37). The Physicochemical challenges for topical drug delivery include:

I. **Permeability Constraints:** Drugs require optimal lipophilicity (Log P), appropriate molecular size (< 500 Da), and charge balance to permeate the stratum corneum effectively (38). Hydrophilic antiviral agents like acyclovir exhibit poor skin permeability, resulting in low therapeutic efficacy (39).

II. **Stability Issues:** Many compounds face pH instability, photosensitivity, and enzymatic degradation in the skin before reaching their target (40).

III. **Safety Concerns:** Potential for irritation, allergic reactions, and erythema limits formulation options (41).

Conventional topical formulations (creams, ointments) demonstrate additional limitations including inadequate skin penetration, uneven drug distribution, short duration of action, and variable patient compliance. These constraints significantly reduce their effectiveness against localized viral infections like herpes simplex virus (HSV) (42.43).

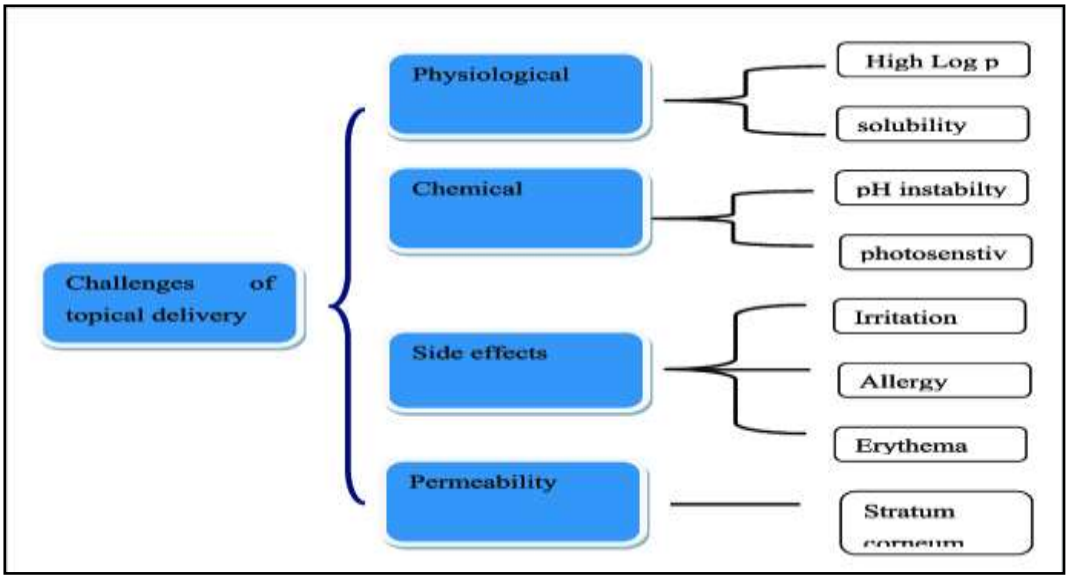

Fig 3: Challenges in Topical Drug Delivery (44)

Advanced delivery systems (e.g., liposomes, nanoparticles) improve topical antiviral therapy by increasing drug penetration, retention, and efficacy across the skin barrier.

5. Mechanisms Underpinning Topical Enhancements

- **Enhanced Penetration & Retention:** Nano-sized carriers (<300 nm) penetrate deeper into epidermis/dermis, while

surfactants and ethanol disrupt corneocytes, improving drug deposition (45).

- **Protection & Sustained Release:** Encapsulation protects active agents from degradation and allows steady diffusion, maintaining therapeutic levels over longer periods. Proniosomal gels convert in vivo to niosomes, releasing drug uniformly (46).
- **Multimodal Antiviral Action:** Synergistic uses—DNA replication inhibition by ACV and entry-blockade/anti-inflammatory effects by curcumin—heighten overall efficacy, targeting multiple points in the HSV lifecycle.
- **Reduced Dosage/Frequency:** Sustained formulations and synergistic dosages allow less frequent application and lower systemic exposure, improving safety and adherence.
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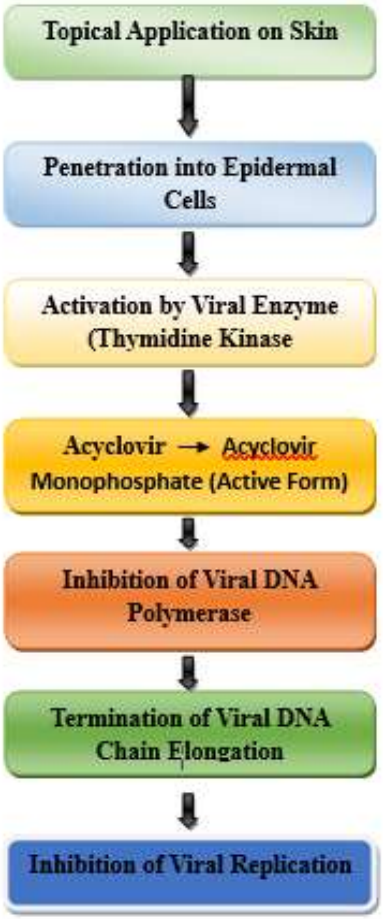

Fig 2: Mechanism of Action of Topical Acyclovir

6. Importance of Nanocarrier-Based Delivery

Nanocarrier-based drug delivery systems represent a revolutionary advancement in pharmaceutical science, significantly enhancing drug delivery, stability, and therapeutic efficacy (47). Among these systems, liposomes spherical vesicles composed of one or more phospholipid bilayers—are one of the most extensively researched and clinically validated nanocarriers (48,49).

Liposomes are crucial for improving drug bioavailability, particularly for poorly soluble or physiologically unstable compounds. Their unique amphiphilic structure allows for the encapsulation of hydrophilic drugs within the aqueous core and lipophilic drugs within the lipid bilayer, making them highly versatile carriers. In topical and antiviral therapy, liposomes enhance skin penetration, promote localized drug retention at the infection site, and enable controlled release, thereby improving therapeutic outcomes while minimizing systemic side effects (50,51).

Additionally, liposomes facilitate targeted delivery, increasing drug concentration at diseased sites while minimizing exposure and potential damage to healthy tissues (52). Their inherent biocompatibility and biodegradability, coupled with

the ability to be functionally modified (e.g., through PEGylation for prolonged circulation or ligand attachment for active targeting), solidify their position as ideal candidates for advanced drug delivery applications (53.54).

7. Liposomes in Topical Antiviral Drug Delivery

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core (55). This unique **amphiphilic structure** enables simultaneous encapsulation of:

- **Hydrophilic drugs** within the aqueous core
- **Lipophilic drugs** within the lipid bilayer key Components

1. **Phospholipids** (e.g., phosphatidylcholine): Structural backbone
2. **Cholesterol**: Enhances membrane stability and rigidity
3. **Surface modifiers** (e.g., PEG): Prolongs circulation *via* steric stabilization (56)

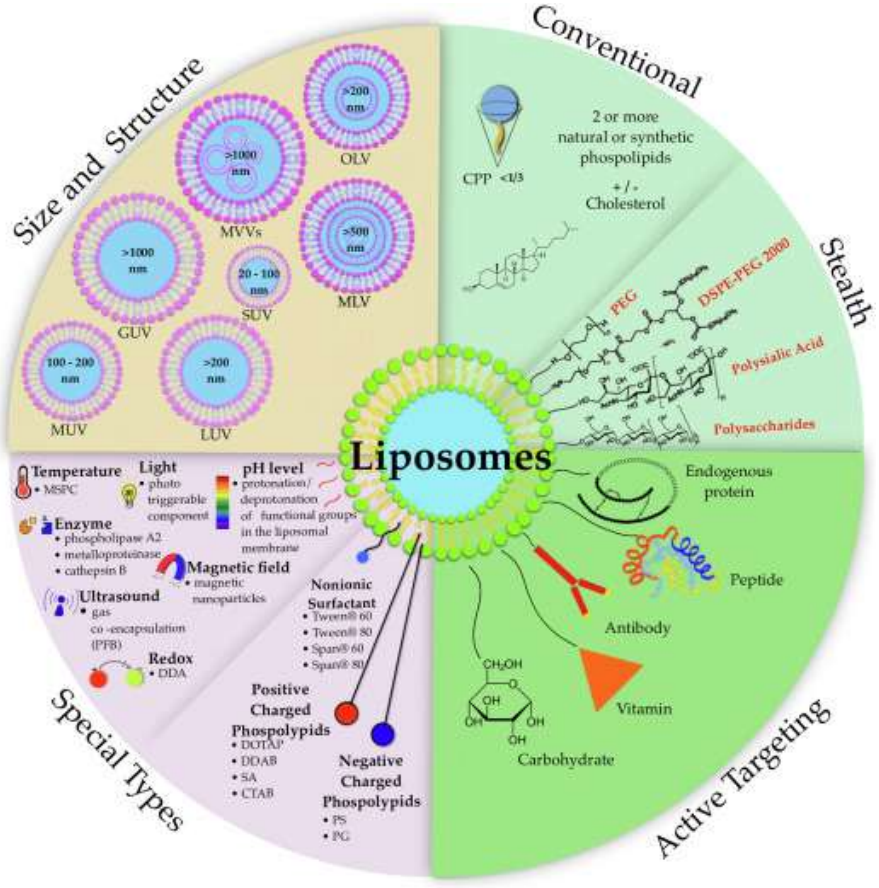

Fig 4: Different Types of Liposomes (57)

In dermal drug delivery, liposomes offer multiple advantages: they are biocompatible, biodegradable, and non-toxic. Their structure allows for high encapsulation efficiency, protection of labile drugs from degradation, controlled drug release, and enhanced skin penetration. These features make liposomes ideal carriers for delivering antiviral agents topically, especially for treating conditions like herpes simplex virus (HSV) and HPV infections (58).

8. Synergistic Antiviral Therapy Using Liposome-Encapsulated Natural Compounds

The emergence of drug-resistant herpes simplex virus (HSV) and the limitations of conventional antivirals like acyclovir have motivated research into combination therapies combining synthetic agents with natural bioactives, delivered through liposomal nanocarriers to enhance antiviral efficacy (59).

A prime example comes from a study encapsulating aminomethylnaphthoquinones, natural derivatives of lawsone, into phosphatidylcholine liposomes. When co-administered with acyclovir, these liposomal formulations significantly inhibited both early and late stages of HSV-1 replication. Notably, certain naphthoquinone-loaded liposomes achieved a nine-fold greater selectivity index than acyclovir alone, suggesting synergistic effects driven by the dual modes of action: viral enzyme

inhibition plus DNA polymerase blockade via acyclovir (60).

Similarly, **curcumin**, a polyphenolic compound from turmeric, targets HSV by disrupting viral immediate-early gene expression—specifically blocking RNA polymerase II recruitment—without altering viral entry or acetyltransferase activity (61). Capitalizing on this mechanism, researchers have developed liposomal systems co-encapsulating curcumin and resveratrol for enhanced stability and bioactivity. These dual-loaded liposomes (~77 nm) showed improved encapsulation efficiency, lower polydispersity, and greater antioxidant potential, laying a foundation for synergistic antiviral designs

Although not yet directly tested against HSV, co-encapsulation microparticle systems of curcumin and acyclovir reveal promising synergy: improved drug release profiles, increased solubility, and superior antiviral activity in vitro against a bovine herpesvirus model. Such findings strongly imply that liposomal co-delivery of curcumin and acyclovir could yield similar benefits against HSV. In these systems, the liposome protects curcumin from degradation and enhances skin permeation, while acyclovir delivers established antiviral activity.

Broad reviews on nanocarrier-driven natural antivirals support these strategies: encapsulation of phenolics consistently improves solubility, skin delivery, and bioavailability. Curcumin, flavonoids, and terpenoids show multimodal antiviral effects—blocking viral entry, replication, and gene expression—with advantages in toxicity reduction and resistance management

Liposome-based co-delivery achieves synergy through:

1. **Complementary antiviral mechanisms** – e.g., acyclovir inhibits polymerase while curcumin suppresses viral gene transcription.
2. **Enhanced stability and bioavailability** – liposomes shield labile natural compounds from degradation and optimize skin permeation.
3. **Sustained release and targeting** – liposomal encapsulation enables depot effects at lesion sites.
4. **Potential for resistance mitigation** – multi-target delivery hinders viral escape via single-point mutations.

Despite encouraging preclinical results, translation to clinical use faces challenges, including formulation stability, skin irritation, optimized dosing, and the need for rigorous human trials. Regulatory hurdles also exist for combination nano-liposomal therapeutics (62).

Table 2: Natural Compounds & Mechanisms

Phytochemical	Antiviral Targets	Synergistic Partners
Curcumin (63,64)	HSV entry inhibition Viral protease suppression	Acyclovir (HSV) Zidovudine (HIV)
Quercetin 65,66)	RNA polymerase inhibition Viral capsid destabilization	Oseltamivir (Influenza) Ribavirin (HCV)
Glycyrrhizin (67,68)	Membrane fusion blockade NF-κB pathway modulation	Lopinavir (SARS-CoV-2) Interferon-α (HBV)
EGCG (69,70,71)	Viral attachment prevention Replication complex disruption	Remdesivir (SARS-CoV-2) Acyclovir (VZV)

8. Synergistic Advantages of Liposome-Encapsulated Natural Compounds in Antiviral Therapy

The co-delivery of natural and synthetic antiviral agents via liposomal nanocarriers presents distinct synergistic advantages, enhancing therapeutic outcomes against viral infections such as herpes simplex virus (HSV). One of the most significant benefits is dose reduction, where studies have shown that combining phytoconstituents like curcumin or quercetin with conventional drugs such as acyclovir allows for 30–50% lower doses of the synthetic agent to achieve equivalent or greater efficacy. This not only reduces the frequency of adverse effects—such as nephrotoxicity commonly associated with acyclovir and myelosuppression with agents like zidovudine—but also improves patient compliance and treatment safety (72).

The second major advantage is multi-target action. Natural compounds exert broad-spectrum antiviral activity by interacting with multiple viral and host pathways. For instance, curcumin has been shown to bind to the glycoprotein B (gB) of HSV, inhibiting viral entry, while quercetin effectively interferes with viral genome replication by inhibiting NS5B polymerase in other viral models (73. Additionally, agents like glycyrrhizin from licorice root enhance host immune responses by increasing interferon-gamma (IFN-γ) production, further suppressing viral propagation (74).

A third synergistic benefit involves the prevention of antiviral resistance. By simultaneously targeting both viral and host cell pathways, these combination strategies reduce the likelihood of escape mutations that often develop in monotherapy. The liposomal co-delivery system sustains drug concentrations at the site of action, maintaining pressure on the virus through multiple mechanisms, which significantly decreases the emergence of resistant strains (75).

However, the efficacy of natural compounds is often limited by their inherent pharmacokinetic challenges, including poor aqueous solubility (e.g., curcumin: ~11 ng/mL), rapid metabolism (e.g., quercetin: $t_{1/2}$ ~3.5 h), and enzymatic degradation in the gastrointestinal tract (e.g., epigallocatechin gallate or EGCG) (76). Liposomal encapsulation addresses these limitations by enhancing solubility, protecting bioactives from metabolic degradation, and ensuring sustained dermal release—making them especially suitable for topical antiviral formulations (77). These multifaceted advantages position liposome-based synergistic therapies as a promising frontier in the management of viral skin infections.

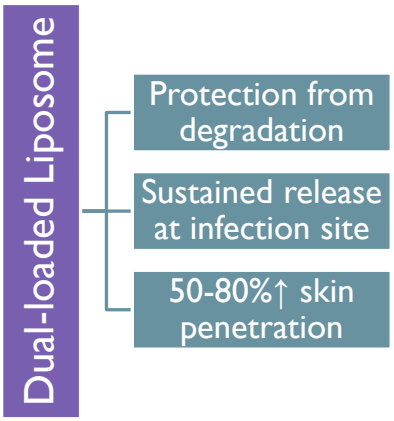

Fig 5: Advantages of Dual-Loaded Liposomes in Topical Drug Delivery

10. Future Scope of Advanced Antiviral Drug Formulations

The future landscape of antiviral drug formulation is poised for transformative breakthroughs through the integration of cutting-edge technologies. CRISPR-Cas delivery systems will enable precision targeting of latent viral reservoirs (e.g., HSV-1 genomes in neurons) using lipid nanoparticles (LNPs) functionalized with cell-penetrating peptides, offering potential cures for chronic infections. Microfluidic synthesis will revolutionize nanocarrier production, enabling single-step, scalable manufacturing of liposomes/niosomes with tunable size (50–150 nm) and >95% encapsulation efficiency while reducing costs by 60% compared to bulk methods. For next-generation vaccines, liposomal mRNA formulations adjuvanted with curcumin or EGCG will enhance dendritic cell activation and memory T-cell responses through synergistic TLR4/NF-κB pathway modulation, potentially boosting vaccine efficacy against mutating viruses like HIV and influenza.

AI-driven discovery platforms will accelerate the identification of novel phytochemical-drug synergies; deep learning algorithms analyzing multi-omics datasets (e.g., viral proteome structures, host metabolic pathways) can predict optimal combinations such as glycyrrhizin with molnupiravir for broad-spectrum coronaviruses—within hours instead of years. Complementing this, synergy prediction algorithms will quantify interaction networks using probabilistic modeling, enabling rational design of multi-drug co-loading systems (e.g., niosomes carrying acyclovir + quercetin + immune checkpoint inhibitors) that simultaneously block viral entry, replication, and immunosuppression.

Conclusion

Topical antiviral therapy has evolved significantly with the advent of nanotechnology-based delivery systems, particularly liposomal carriers, which offer transformative benefits in treating skin and mucosal viral infections such as herpes simplex virus (HSV). Conventional topical formulations often suffer from poor skin penetration, instability, and suboptimal therapeutic efficacy. In contrast, liposomes and related nanocarriers enhance drug solubility, protect sensitive compounds from degradation, and enable controlled, localized, and sustained release of both synthetic and natural antiviral agents.

The integration of phytochemicals like curcumin, quercetin, and glycyrrhizin into liposomal formulations has further strengthened the therapeutic potential of topical antivirals. These bioactive agents offer multi-target antiviral mechanisms, including viral entry inhibition, suppression of genome replication, and modulation of host immune responses. When co-delivered with synthetic drugs like acyclovir, these combinations exhibit synergistic effects—allowing for dose reductions, fewer side effects, and mitigation of antiviral resistance.

Despite these advancements, challenges remain in optimizing formulation stability, skin compatibility, and large-scale manufacturing. Additionally, the translation of preclinical success to clinical settings demands rigorous human trials and

regulatory validation. Nevertheless, the synergistic use of natural and synthetic antivirals in liposomal systems presents a promising strategy for next-generation topical therapies. With the incorporation of AI-guided formulation design, microfluidic synthesis, and functionalized liposomes, the future of antiviral dermatological therapy is poised for more precise, effective, and patient-friendly interventions.

In summary, nanocarrier-based strategies, particularly those employing liposome-encapsulated synergistic combinations, represent a paradigm shift in topical antiviral treatment—bridging the gap between traditional pharmacotherapy and modern molecular targeting.

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