ARTICLE

A Review of Advanced Use of Nanosponges in Herbal Drug Development for Antimicrobial Activity

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Abstract:

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ABSTRACT

The growing global burden of antimicrobial resistance (AMR) has created an urgent need for advanced therapeutic strategies. Among these, phytomedicine-based nanotechnology delivery systems have emerged as promising approaches for the effective delivery and targeted delivery of multifunctional bioactive compounds. This review provides a highly comprehensive evaluation of cyclodextrin-based nanosponge (NS) platforms and intricately integrated nanogel (NG) systems specifically engineered to encapsulate a remarkably potent tripartite antimicrobial blend: Karanj (Pongamia pinnata), Neem (Azadirachta indica), and Mint (Mentha spp.) oils. These powerful botanical oils offer a robust, multi-targeted approach to effectively combating dangerous pathogens through diverse mechanistic pathways, critically including profound cytoplasmic membrane disruption, essential biosynthesis inhibition, targeted enzyme suppression, and the complete eradication of protective biofilms. However, the practical clinical utility of these notoriously volatile essential oils is often severely limited by their intrinsically poor stability, exceptionally low aqueous solubility, and characteristically rapid degradation under harsh environmental conditions. Cyclodextrin-based nanosponges effectively emerge as an exceptionally effective strategy to decisively address these persistent limitations by enabling precise molecular encapsulation, which significantly enhances aqueous solubility, actively minimizes undesirable volatilization, reliably protects against oxidative degradation, and firmly ensures continuously sustained and controlled therapeutic release. Furthermore, the integration of these nanosponge-complexed oils into topical nanogels facilitates superior dermal penetration, improved bioavailability, and localized retention at the site of infection, thereby enhancing therapeutic efficacy and essential patient compliance. This comprehensive manuscript synthesizes current scientific literature on the molecular synergy of these three oils, evaluates critical formulation and characterization parameters, and highlights the challenges and valuable future perspectives necessary for successful clinical translation of nanosponge-based herbal therapeutics in antimicrobial applications worldwide.

Keywords: Nanosponges, Azadirachta indica, Pongamia pinnata, Antimicrobial Resistance, Herbal Drug Delivery, Cyclodextrin

How to cite this article: Dange PA, Kazi MA, Shaikh S., A Review of Advanced Use of Nanosponges in Herbal Drug Development for Antimicrobial Activity. Int J Drug Deliv Technol. 2026;16(77s): 787-797; DOI: 10.25258/ijddt.16.77s.96

1. INTRODUCTION

1.1. Rising Antimicrobial Resistance

Antimicrobial resistance (AMR) has become one of the most serious global public health challenges, with estimates suggesting it could be responsible for nearly 10 million deaths each year by 2050. AMR develops when microorganisms, including bacteria, viruses, fungi, and parasites, evolve mechanisms that render antimicrobial agents ineffective, allowing them to survive and continue multiplying within the host. The excessive and inappropriate use of antimicrobial drugs, especially antibiotics, remains the primary factor driving the rapid spread of resistance worldwide. To address this growing concern, international efforts have focused on monitoring antibiotic consumption and promoting responsible antimicrobial use through initiatives such as the Sustainable Development Goals (SDGs) and the One Health framework, which encourages collaborative action across the human, animal, and environmental health sectors. [1]

1.2. Role of Phytomedicines

In recent years, traditional knowledge of medicinal plants has gained renewed global importance, particularly with the emergence of novel diseases such as COVID-19. Plant-derived secondary metabolites, such as alkaloids, flavonoids, phenolic acids, and terpenoids, have gained considerable attention because of their broad range of pharmacological activities. Among their many therapeutic benefits, their ability to modulate immune responses and exhibit antiviral effects has been widely reported. The broad-spectrum antiviral efficacy of Chloroquine, a quinine analogue derived from the Cinchona tree, underscores the pharmaceutical relevance of plant-based compounds. Moreover, phytomedicines are generally associated with fewer adverse effects, contributing to the growing consumer demand for natural therapeutic products. [2]

1.3 Limitations of Traditional Herbal Oil Delivery

The therapeutic application of raw essential oils is constrained by several factors. Their poor dermal penetration and hydrophobic nature limit bioavailability, while variability in cultivation and processing leads to inconsistent quality and efficacy. Natural oils are highly susceptible to oxidative degradation, which limits their stability and shortens their shelf life. In addition, their direct use may be associated with undesirable effects, including skin irritation, allergic reactions, and increased sensitivity to sunlight

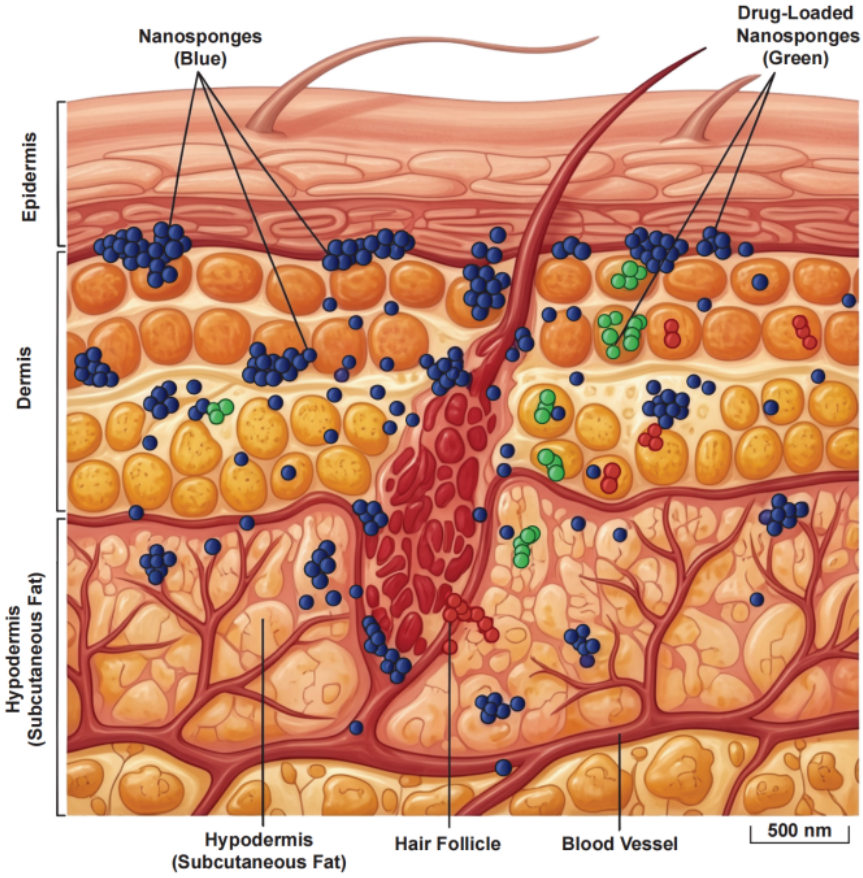
(photosensitivity). Additionally, they can interact with conventional medicines, be at risk of contamination due to inadequate quality control, and lack standardized usage guidelines. User discomfort due to odor, texture, or staining further reduces compliance. Importantly, many essential oils remain insufficiently validated through modern scientific methods, restricting their acceptance in evidence-based medicine. [3]

1.4 Nanosponges as an Advanced Herbal Delivery System

Nanosponges have emerged as an innovative drug delivery platform designed to address the shortcomings associated with conventional topical drug delivery systems. Their unique structure enhances drug stability, improves controlled release, and increases the overall effectiveness of topical formulations. Their highly porous, sponge-like architecture enables the entrapment of therapeutic agents within nanoscale cavities, thereby protecting drugs from degradation and facilitating controlled, sustained release for enhanced efficacy. Owing to their versatility, nanosponges can be administered through multiple routes and are capable of incorporating both hydrophilic and lipophilic compounds, broadening their therapeutic applicability. With pore sizes typically in the range of 1–2 nanometers, they can also sequester small molecules and toxins, making them valuable in detoxification and wound healing applications. The development of cyclodextrin-based nanosponges was initially reported by DeQuan Li and Min Ma. These nanosponges are synthesized by cross-linking cyclodextrin molecules with organic cross-linking agents, such as diisocyanates or carbamates, resulting in the formation of a three-dimensional polymeric network capable of encapsulating a wide range of therapeutic compounds. In this configuration, cyclodextrins serve as the structural units, while the cross-linking agents stabilize the matrix, resulting in a robust system with high molecular encapsulation capacity. This unique design underscores the pharmaceutical relevance of nanosponges as efficient carriers for precise drug delivery and therapeutic intervention [4].

1.5 Nanosponge–Nanogel (NS–NG) Hybrid Platform

This review presents an innovative, multi-step pharmaceutical approach in which Karanj seed oil, Neem seed oil, and Mint oil are taken in a fixed combination ratio and are encapsulated within nanosponge carriers, and then combined into a unified topical nanogel (NG) system. The main aim of this advanced formulation is to demonstrate antimicrobial synergy. By stabilizing the naturally unstable active constituents and enabling their sustained and simultaneous release through the nanosponge–nanogel (NS–NG) platform, the formulation is expected to produce a significantly stronger antimicrobial effect than any single oil or conventional blend. This strategy is designed to harness the distinct yet complementary mechanisms of the three herbal oils within one efficient, high-performance topical delivery system. The efficiency of nanosponge penetration over a conventional dosage form is shown in Figure 1.



Efficiency of nanosponge penetration over conventional dosage forms

2. DELIVERY OF NANOSPONGES FOR HERBAL DRUG

2.1. Structural Design

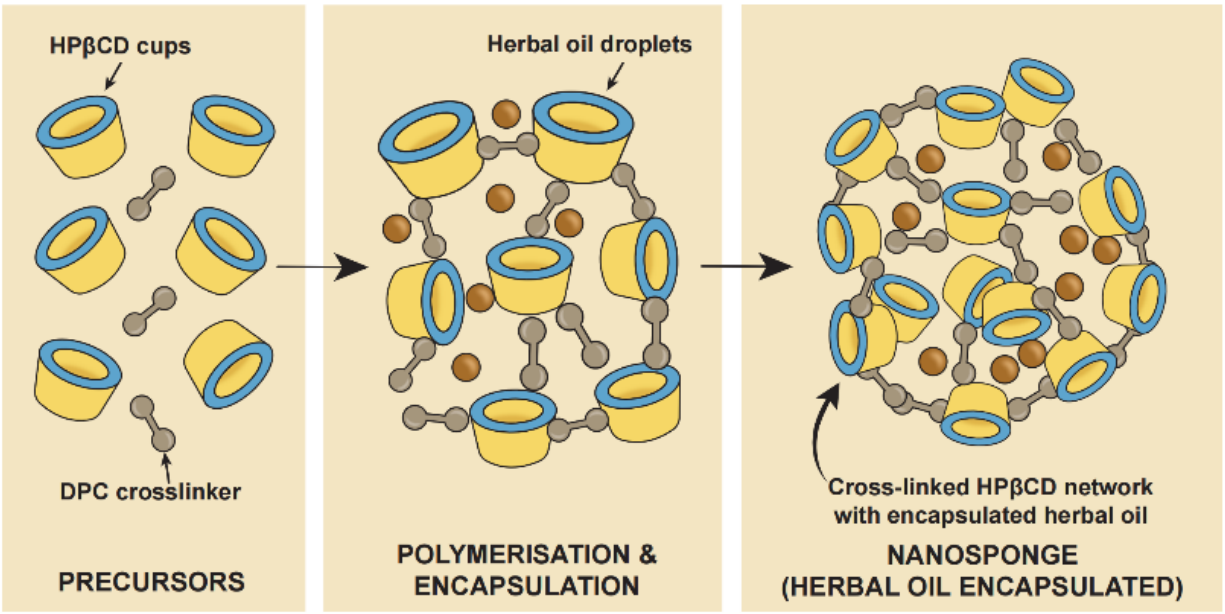
Polymers and copolymers:-

The choice of polymer or copolymer plays a critical role in nanosponge design, influencing cavity formation, pore size, and drug release kinetics. Selected polymers must be compatible with drug encapsulation and ligand binding to ensure stability and therapeutic efficacy. Common examples include methyl cyclodextrin, ethyl cellulose, and polyvinyl alcohol (PVA).

Cross-linking agents:-

The selection of cross-linking agents depends on the polymer type and the desired solubility profile of the nanosponge.

Appropriate agents can generate either water-soluble or insoluble structures, thereby tailoring the system for specific applications. Representative examples include epichlorohydrin, glutaraldehyde, diphenyl carbonate, dimethyl carbonate, isocyanates, pyromellitic anhydride, and dichloromethane. [5]. The chemical structure of β-cyclodextrin is shown in Figure 2.

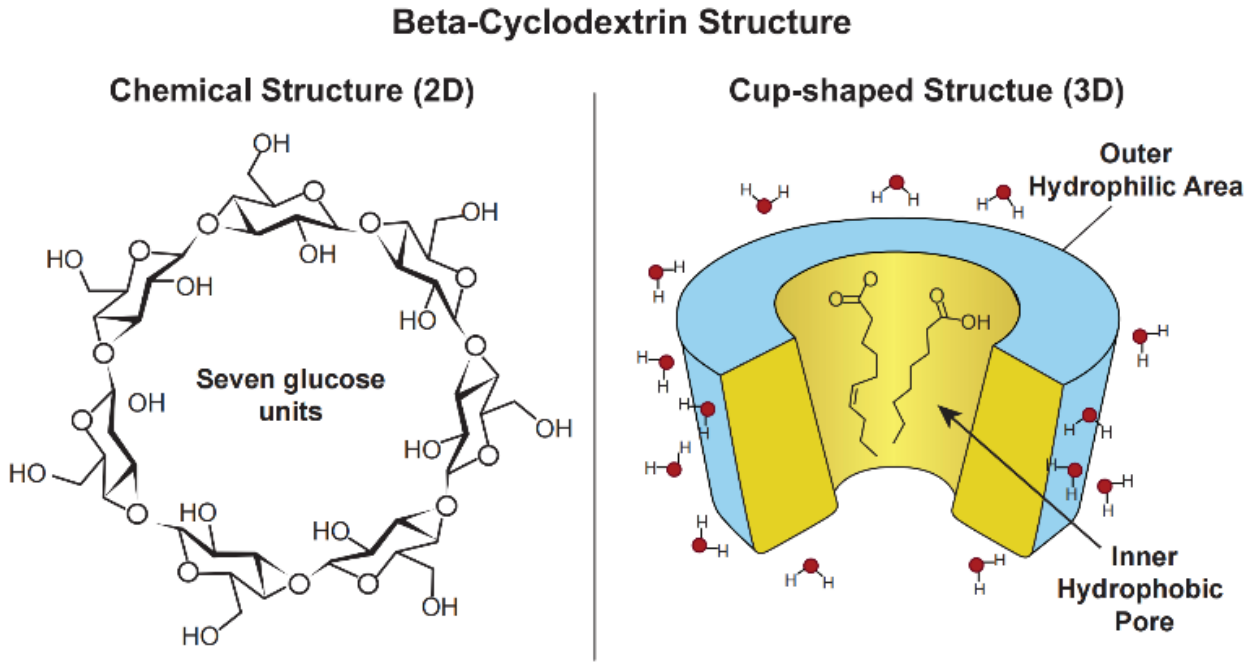


Chemical Structure of β-Cyclodextrin

2.2 Cyclodextrins: Structure and Role in Drug Delivery

Cyclodextrins (CDs) are naturally occurring cyclic oligosaccharides composed of α-D-glucopyranose units connected through α-(1→4)-glycosidic linkages. They are produced from starch by the enzymatic action of cyclodextrin glycosyltransferase and are classified into three major types based on the number of glucose units they contain: α-cyclodextrin (six units), β-cyclodextrin (seven units), and γ-cyclodextrin (eight units). Their unique molecular architecture forms a truncated cone-shaped structure with a hydrophobic inner cavity and a hydrophilic outer surface. The interior cavity, lined with C–H groups and glycosidic oxygen atoms, readily accommodates hydrophobic or poorly water-soluble molecules, whereas the hydroxyl groups present on the exterior enhance water solubility. Owing to this amphiphilic structure, cyclodextrins are capable of interacting with both lipophilic and hydrophilic compounds.

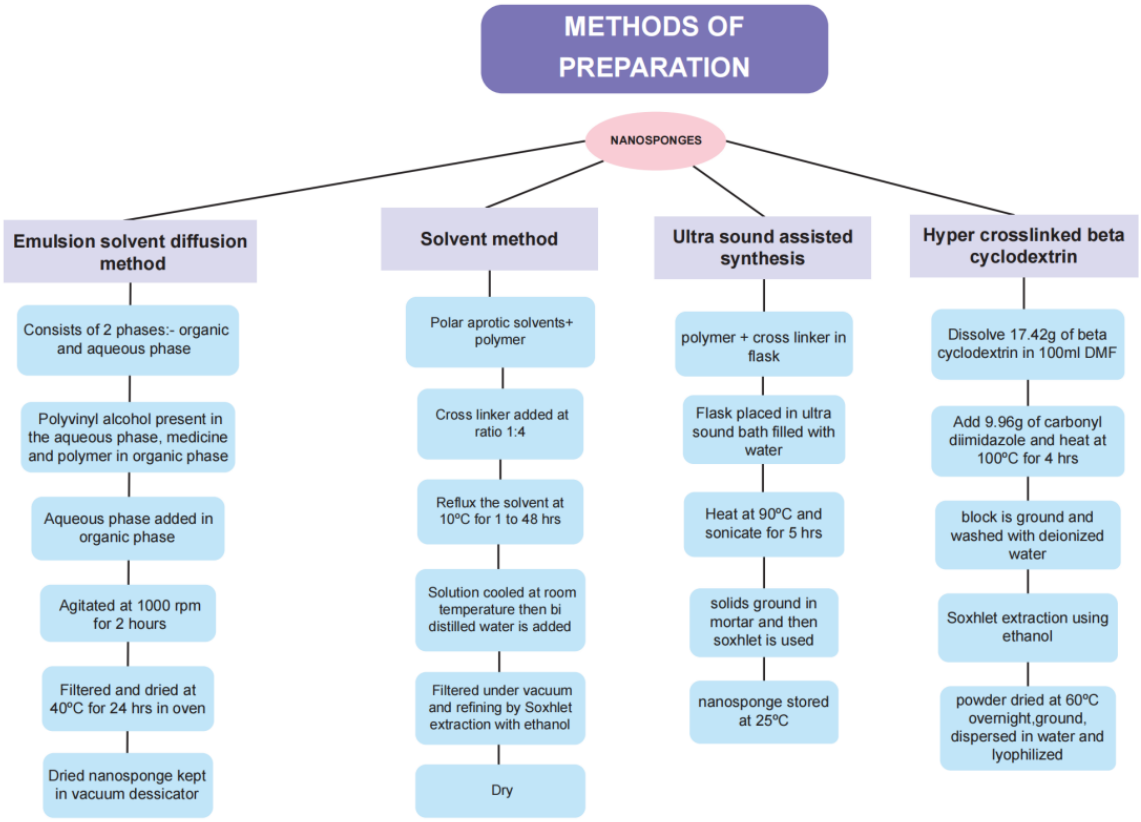
When drug molecules are entrapped within the cyclodextrin cavity, they form host–guest inclusion complexes that are stabilised by multiple noncovalent interactions, including hydrophobic interactions, hydrogen bonding, van der Waals forces, electrostatic attractions, dipole–dipole interactions, and dispersion forces. The formation of these inclusion complexes enhances the aqueous solubility, physicochemical stability, and bioavailability of encapsulated drugs. In addition, cyclodextrin-based complexes facilitate controlled and sustained drug release, making them highly valuable carriers in modern drug delivery systems. Consequently, CDs are widely employed as carriers in pharmaceutical formulations, improving therapeutic performance and expanding the applicability of drug delivery systems [6]. The synthesis of nanosponges using polymeric interactions is shown in Figure 3.



Nanosponge formation by polymeric interaction

2.3 Methods of preparation of Nanosponges

Figure 4 shows the different methods to synthesise the nanosponges.



Methods of Preparation of Nanosponges

2.4 Advantages of nanosponges

Nanosponges offer several distinct advantages that make them promising carriers in pharmaceutical formulations:

- **Reduces adverse effects:** By entrapping active pharmaceutical ingredients within their porous architecture, nanosponges minimise direct exposure of drug molecules to biological tissues. This mechanism significantly reduces irritation, toxicity, and other undesirable side effects.
- **Thermal and pH stability:** Nanosponges exhibit remarkable physicochemical stability, maintaining structural integrity at elevated temperatures (up to 300 °C) and across a broad pH spectrum (1–11). Such resilience ensures formulation robustness under diverse physiological and environmental conditions.
- Broad compatibility with drugs and delivery vehicles: The unique porous architecture of nanosponges enables the efficient encapsulation of both hydrophilic and lipophilic drug molecules. This versatility allows their incorporation into a variety of pharmaceutical solvents and dosage forms, making them suitable for diverse drug delivery applications.
- **Controlled and prolonged drug release:** The three-dimensional porous network of nanosponges supports the gradual and sustained release of encapsulated drugs, with therapeutic effects that may extend for up to 12 hours. This controlled release pattern helps reduce the frequency of administration while maintaining consistent drug levels and improving treatment outcomes.
- **Enhanced patient compliance:** By providing sustained drug delivery and lowering the incidence of dose-related adverse effects, nanosponge-based formulations reduce the need for frequent dosing, thereby improving patient adherence to therapy. Their non-irritant nature and ease of application further support patient acceptability.
- **Protection against first-pass metabolism:** Nanosponges safeguard drug molecules from enzymatic degradation and hepatic first-pass metabolism. This protective effect enhances bioavailability and optimizes therapeutic outcomes. [7]

3. PHYTOCHEMICAL PROFILES AND MECHANISMS OF ACTION

1.1 Karanj Seed Oil (Pongamia pinnata)

Pongamia pinnata (family: Leguminosae), commonly referred to as karanj, is a well-known non-edible oilseed plant widely used in traditional Indian systems of medicine, including Ayurveda and Siddha, for the treatment of various diseases. Its seed oil contains several bioactive phytoconstituents, with karanjin, a biologically active flavonoid, being one of the major therapeutic compounds. Phytochemical studies have identified multiple constituents in the seed oil, including sterols, sterol derivatives, a disaccharide, and eight fatty acids comprising both saturated and unsaturated forms.

Karanj seed oil possesses a wide range of pharmacological activities, such as antibacterial, antifungal, antiviral, anti-inflammatory, anti-ulcer, and anti-arthritic effects. Owing to these therapeutic properties, it has been traditionally and clinically used in the management of disorders including psoriasis, arthritis, and other inflammatory skin conditions. Its antimicrobial efficacy extends to both Gram-positive and Gram-negative bacteria, as well as pathogenic fungi, with complete inhibition of fungal growth observed particularly under vapor or fumigation application. [8] The mechanism of action of karanjin involves disruption of bacterial survival pathways by targeting cell membrane synthesis [9]. Specifically, it interferes with enzymes essential for fatty acid biosynthesis, forming stabilizing hydrogen bonds that compromise membrane and cell wall integrity [8,10]. By obstructing these fundamental metabolic and repair processes, Karanjin destabilizes bacterial cell structures, thereby enhancing susceptibility to agents that induce direct membrane damage.

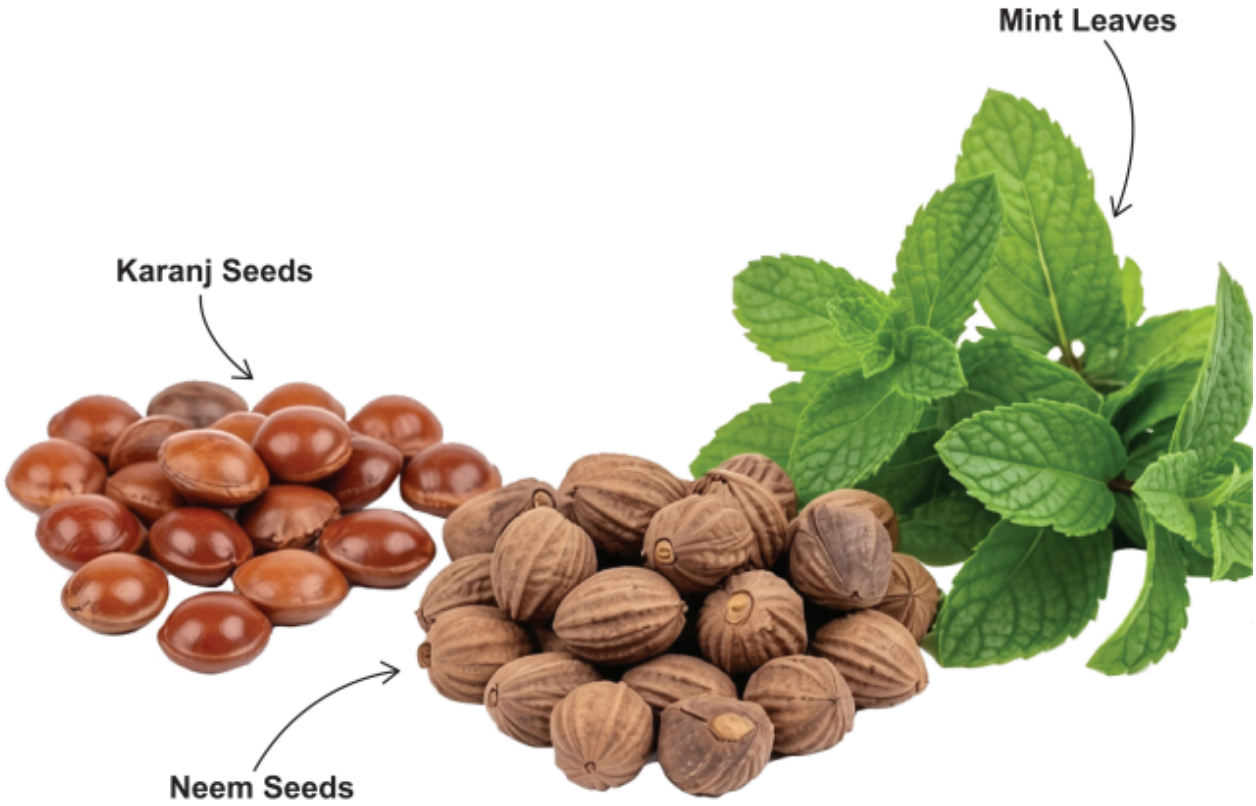
3.2 Neem Seed Oil (Azadirachta indica)

Azadirachta indica (*family: Meliaceae*), commonly known as neem, is a non-edible oilseed plant that has been extensively used in traditional systems of medicine, including Ayurveda, Unani, and Homoeopathy. The seeds contain nearly 45% oil, which is composed predominantly of oleic acid (approximately 50%) and linoleic acid (around 15%). Neem seed oil also contains several biologically active compounds, such as azadirachtin, nimbin, and nimbidin, which contribute to its medicinal value.

Extensive pharmacological studies have demonstrated that these bioactive constituents possess a wide range of therapeutic activities, including antibacterial, antifungal, anti-inflammatory, anti-arthritic, anti-ulcer, antimalarial, antipyretic, diuretic, hypoglycemic, and spermicidal properties, supporting the traditional use of neem in the treatment of various disorders. [11]. Mechanistically, neem exerts antimicrobial action through multiple complementary pathways. Its bioactive molecules disrupt membrane integrity, inhibit metabolic enzymes essential for energy production and DNA replication, suppress biofilm formation, and induce oxidative stress via reactive oxygen species generation. This multimodal activity enhances antimicrobial efficacy and positions neem as a critical anti-resistance agent, synergistically supporting the structural disruption mediated by karanjin and the lytic effects of mint [12,13].

1.3 Mint Oil (Mentha spp.)

Peppermint (Mentha piperita) oil is a globally cultivated medicinal herb widely recognized for its aromatic fragrance and industrial applications. It exhibits broad-spectrum antimicrobial activity and is enriched with bioactive constituents, including polyphenols (rosmarinic acid, eriocitrin, caffeic acid, cinnamic acid), flavonoids and glycosides (luteolin-7-O-rutinoside, narirutin, hesperidin, isorhoifolin), as well as volatile compounds such as menthone, isomenthone, menthofuran, limonene, cineole, carvone, pulegone, and menthyl acetate. These phytochemicals contribute to its anti-inflammatory, anti-allergic, and therapeutic properties. [14] The antimicrobial activity of peppermint oil is mainly attributed to its volatile and phenolic bioactive constituents. These compounds disrupt the integrity of microbial cell membranes by increasing membrane permeability, resulting in the leakage of essential intracellular components. This membrane damage ultimately leads to the death of both Gram-positive and Gram-negative bacterial cells. Incorporation of peppermint oil into nanosponges enhances its pharmacological potential by improving stability, enabling controlled and sustained release, and providing localized efficacy while maintaining broad-spectrum antimicrobial action. [15,16]. Figure 5 shows the image of dried seeds of *Pongamia pinnata* and *Azadirachta indica* and leaves of *Mentha piperita.*



Dried Seeds of Pongamia pinnata and Azadiracta indica and leaves of Mentha piperita

4. SYNERGISTIC ANTIMICROBIAL INTERACTIONS

4.1 Concept of Phytochemical Synergy

The concept of synergy, derived from the Greek term synergos, meaning "working together," describes the cooperative interactions among phytochemicals that enhance their collective biological activity. Rather than exerting merely additive effects, these compounds act in concert to produce a more pronounced impact than any single constituent could achieve independently. This phenomenon is particularly relevant as many phytochemicals display limited efficacy in isolation; however, when naturally combined within complex mixtures, their interactions can substantially amplify therapeutic effectiveness. The Mechanisms of Antimicrobial Action of the Triumvirate Phytoconstituents are given in Table 1.

4.2 Triple Mechanistic Synergy

Mechanisms of Antimicrobial Action of the Triumvirate Phytoconstituents(16)

Oil Source	Key Phytoconstituent Class	Representative Compound	Primary Mechanism of Action	Synergistic contribution
Karanj Seed Oil	Furanoflavonoids	Karanjin	Inhibits bacterial cell wall synthesis/fatty acid synthesis (Biosynthesis Blockade).	Weakens cellular structure, priming for lytic attack and complementing metabolic inhibition.
Neem Seed Oil	Limonoids (Tetranortriterpenoids)	Azadirachtin, Nimbidin	Multi-Target: Disrupts membrane, inhibits key enzymes (DNA Gyrase/ATPase), prevents biofilm formation.	Anti-resistance component; ensures broad-spectrum efficacy and long-term infection control.
Mint Oil	Monoterpenes (Volatile Oils)	Menthol, Carvacrol	Rapid Disruption of microbial lipid membranes, leading to cytoplasmic leakage (Lysis).	Provides rapid initial attack and sustained membrane destabilization when encapsulated.

5. FORMULATION STRATEGIES AND NANOGEL INTEGRATION

5.1 Preparation of Nanosponges

The preparation of nanosponges primarily depends on the judicious selection of materials and process parameters. β-Cyclodextrin is frequently employed as the polymer matrix due to its excellent biocompatibility and strong capacity to form inclusion complexes with lipophilic herbal oil constituents. Diphenyl carbonate (DPC) functions as a cross-linking agent during nanosponge synthesis, promoting the formation of a stable three-dimensional porous polymeric network. This interconnected structure efficiently encapsulates active pharmaceutical ingredients, thereby enhancing their stability and controlled release characteristics. To optimize nanosponge characteristics, experimental designs such as the Box–Behnken Design are utilized, enabling the production of formulations with minimal particle size and high drug-loading capacity. Such optimization is particularly critical for achieving maximum entrapment efficiency (EE%), especially in the case of volatile components like peppermint oil. For the development of a nanosponge-based nanoemulgel (NS-NEG) with enhanced synergistic antimicrobial activity, encapsulating a pre-mixed blend of Karanj seed oil, Neem seed oil, and peppermint (mint) oil in a ratio of 1:1:1 within the nanosponges is considered more effective than loading each oil individually. Co-encapsulation of the oil blend promotes the simultaneous delivery of the active

constituents, which may improve synergistic therapeutic effects, ensure uniform drug release, and simplify the overall formulation process. This approach ensures the preservation of the synergistic proportion, facilitates the simultaneous delivery of all three oils, enhances the protection of volatile constituents such as mint oil, and improves the overall inclusion efficiency of the system. [17, 18, 19, 20]. Key benefits of co-encapsulation of herbal oils over individual encapsulation are given in Table 2.

Key benefits of Co-encapsulation of Herbal oils over individual encapsulation

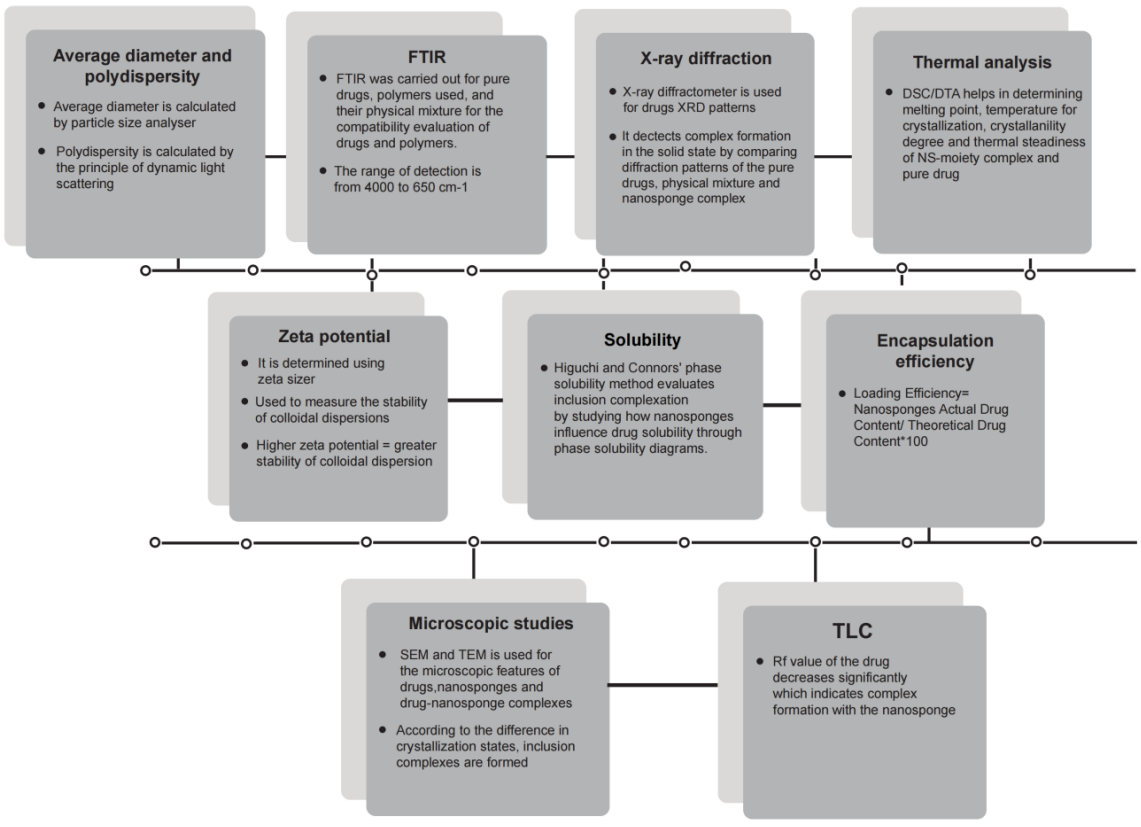
Feature	Individual Encapsulation	Combination (Co-encapsulation)
Synergy	Risk: Components may be released at different times, potentially reducing synergistic antimicrobial activity.	Optimal: Simultaneous release of all components ensures better synergistic action.
Formulation Complexity	High: Requires three separate loading and encapsulation processes.	Low: Requires a single loading process for the combined herbal oil blend.
Stability	Mint oil may evaporate or volatilize during its individual encapsulation process.	Heavy oils such as neem and karanj act as fixatives, helping to retain volatile mint oil.
Uniformity	Difficult to ensure equal distribution of separately encapsulated oils throughout the final gel.	Each nanosponge particle contains the complete oil combination, promoting more uniform distribution and dosing.

5.2 Incorporation into the Nanogel Matrix

For topical administration, nanosponge formulations are first prepared and characterized, followed by incorporation into a hydrophilic gel base to yield a topical nanogel (NG-T). Carbopol 934 or Carbopol 940 is frequently employed as the gelling agent owing to its high viscosity, excellent bioadhesive properties, and favorable skin compatibility. During the formulation process, Carbopol is allowed to hydrate overnight to ensure complete swelling of the polymer. Subsequently, the dried nanosponges are uniformly dispersed into the hydrated gel under continuous stirring to obtain a homogeneous matrix. The pH of the formulation is then adjusted to 4–6, a physiologically compatible range for topical application, using an appropriate neutralizing agent such as triethanolamine. This transformation of the nanosponge suspension into a nanogel converts a liquid and potentially irritating system into an elegant, high-viscosity dosage form with improved handling characteristics. Moreover, the nanogel exhibits shear-thinning behavior, which facilitates ease of spreading upon application, ensures uniform drug distribution across the skin surface, and enhances patient compliance. [21,22,28]

5.3 Physicochemical Characterisation

The characterization of nanosponges is given in Figure 6.



Characteristic Evaluation of Nanosponges

6. BIOPHARMACEUTICAL EVALUATION

6.1 In Vitro Drug Release

The drug-release behavior of the nanosponges (NSs) needs to be evaluated using a multi-compartment rotating cell setup. In this system, an aqueous dispersion of the NS–drug complex is placed in the donor compartment, while the receptor compartment is to be filled with phosphate buffer. A hydrophilic dialysis membrane is used to separate the two compartments. At predetermined time intervals, the receptor buffer should be completely withdrawn and replaced with fresh, unsaturated buffer to maintain sink conditions. The amount of drug released and the remaining drug content are then determined using an appropriate analytical method. [14]

6.2 Antimicrobial Activity and Synergy Assessment

The therapeutic effectiveness of the nanogel formulation (NG-T) should be thoroughly evaluated against a range of clinically important skin pathogens, including Gram-positive bacteria such as *Staphylococcus aureus* and Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*. Most importantly, the proposed synergistic interaction should be validated experimentally. This can be achieved using the checkerboard broth dilution assay, followed by calculation of the fractional inhibitory concentration index (FICI) to quantitatively determine the presence and extent of synergy among the three-component oil combination. The study should demonstrate that NG-T shows stronger antimicrobial activity than the free oil nanosponge formulations or the bulk oils alone. In addition, considering the well-known antibiofilm properties of Neem, the nanogel should be assessed for its ability to prevent or disrupt established bacterial biofilms, highlighting its potential use in managing stubborn and hard-to-treat infections. A comparative analysis of the antimicrobial synergy between the free oil blend (Neem, Karanja, and Mint) and the combined oil-encapsulated nanosponge nanoemulgel (NS-NEG) reveals a significant shift in both potency and pharmacological performance, as shown in Table 3. While the free oils possess inherent antimicrobial properties, the nanosponge system acts as a "force multiplier" that preserves and amplifies their synergistic potential. [12,13,23,24,25,31]

Comparative analysis of the synergism of free herbal oil blend vs. the synergism of Naosponge-encapsulated herbal oil blend.

Feature	Synergistic Free Oil Blend	Combined Oil NS-NEG
Antimicrobial Potency (MIC)	Higher MIC: Requires a greater amount of oil; components may degrade before reaching the target site.	Lower MIC: Potentially 2–10× greater potency due to encapsulation and protection of active molecules.
Release Kinetics	Burst release: High initial concentration followed by a rapid decline.	Sustained release: Controlled delivery over approximately 12–24 hours from the nanosponge reservoir.
Synergy Maintenance	Fragile: Individual oils may separate or penetrate the skin at different rates, potentially disrupting the intended synergistic ratio.	Stable: Oils are incorporated within each nanosponge particle in the optimized 2:2:1 ratio, helping maintain the synergistic composition.
Volatile Loss	High loss: Mint oil, particularly menthol, may be lost through evaporation.	Reduced loss: Mint oil is retained within the polymeric matrix, helping preserve its availability as a penetration enhancer.
Skin Penetration	Limited: Penetration may be restricted by the physicochemical properties and relatively high molecular weights of constituents such as azadirachtin and karanjin.	Enhanced: Nano-sized particles (200–500 nm) may facilitate deeper interaction with and penetration into the stratum corneum.
Sensory/Patient Comfort	Strong, unpleasant “garlic-like” odor; greasy texture; potentially higher risk of skin irritation.	Improved: Odor masking, a non-greasy and elegant feel, and potentially reduced irritation improve patient acceptability.

6.3 Skin Irritation and Safety

A significant advantage of incorporating essential oils into nanosponges is their ability to provide controlled and sustained release of the encapsulated constituents. This controlled delivery helps minimize the direct exposure of the skin to high concentrations of free essential oils, thereby reducing the likelihood of irritation and improving the overall safety and tolerability of the topical formulation. Safety is assessed through non-irritancy tests, such as in vivo skin irritation studies. A mean erythema score of 0.0 indicates the absence of redness or swelling, confirming that the formulated nanogel is safe and suitable for long-term topical use.

6.4 Ex Vivo Permeation and Retention

Ex vivo skin permeation studies using excised animal skin in Franz diffusion cells are carried out to measure drug flux and permeability. Since the treatment is intended for local antimicrobial action, the formulation is designed to retain the active components within the skin rather than allowing systemic absorption. Confocal Laser Scanning Microscopy (CLSM) is used to visually confirm penetration depth. CLSM results show that the nanosponge-based nanogel reaches deeper skin layers, forming a stable drug reservoir within the tissue. This confirms that the NS–NG system effectively delivers high local drug concentrations while reducing irritation through controlled release [21,26,27,28].

7. CONCLUSION

The incorporation of karanj, neem, and mint oils into nanosponge-nanogel (NS-NG) is a hybrid system that significantly represents an advancement in overcoming the limitations of traditional herbal therapies. Cyclodextrin-based nanosponges provide stability and allow sustained release for up to 12 to 24 hours, and improve dermal penetration for volatile and hydrophobic oils. This multi-component formulation provides triple mechanistic synergy: karanj helps to weaken bacterial cell walls, mint provides rapid lysis of the cell, and neem has broad-spectrum anti-resistance and anti-biofilm effects. Also, this formulation is useful to convert irritating essential oils into skin-friendly, high-performance topical dosage forms. Nanosponge-based drug delivery systems also help minimize treatment-related adverse effects while enhancing patient compliance through improved safety and sustained drug release.

8. FUTURE PERSPECTIVE

Conceptual and laboratory-scale efficacy of the NS-NG provides a promising platform. Future research must prioritize clinical translation and industrial scalability. For evaluating long-term stability and exploring scalable manufacturing processes that provide high entrapment efficacy for volatile components, systematic studies are very important. Beyond laboratory and tissue studies, human testing for this treatment is necessary, which provides confirmation that the formulation works better in treating difficult and drug-resistant skin infections. Incorporating nanogel into advanced wound-healing formulations provides a significant opportunity to address the global challenge of antimicrobial resistance through multifunctional, plant-based nanotechnology.

9. ETHICS APPROVAL

"Not applicable for this review article."

10. CONSENT FOR PUBLICATION

"Not applicable."

11. Availability of Data: No new datasets were generated or analyzed during the preparation of this study.

12. CONFLICT OF INTEREST

The authors declare that they have no competing interests or conflicts of interest.

13. FUNDING

The authors hereby declare that no financial support or funding was received while writing this manuscript.

14. Acknowledgement: The images were created using the generative AI tool Gemini Pro version to produce initial compositional variations and background elements. We provided original photographic assets and written prompts, selected the preferred outputs, and performed manual compositing and retouching to produce the final image. All final creative decisions and post-processing were made by the authors.

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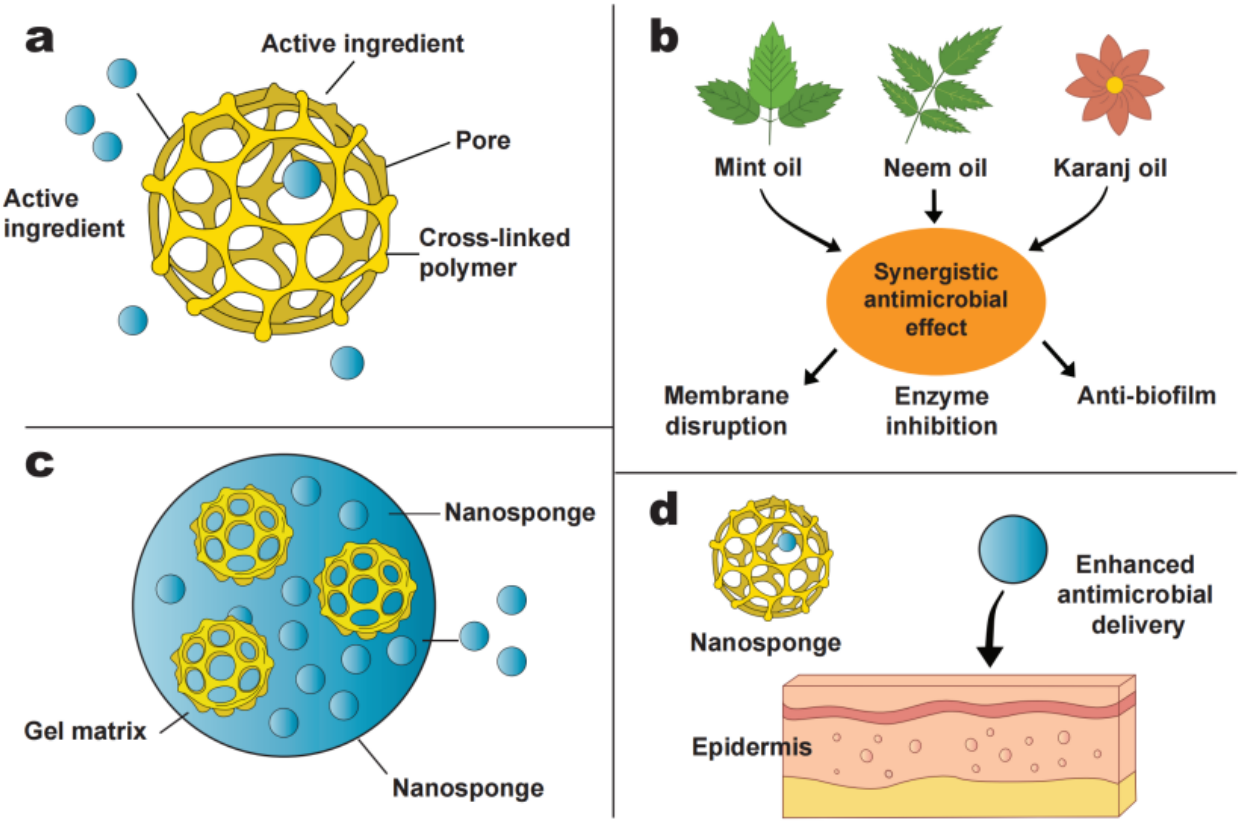

Conceptual illustration depicting: (a) nanosponge encapsulation and controlled release of volatile oils; (b) synergistic antimicrobial mechanisms of Karanj, Neem, and Mint oils; and (c) structural organization of the nanosponge–nanogel hybrid system. (d) Enhanced transdermal antimicrobial delivery of nanosponges.