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Review

Mentha Piperita Essential Oil in Nano-Hydrogel: An Effective Antifungal Strategy

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Abstract:
The utilization of essential oils, particularly Mentha piperita (peppermint) oil, in combating fungal infections has gained considerable attention due to their natural origin and potential efficacy. This abstract delves into the formulation of Mentha piperita essential oil within a nano-hydrogel matrix as a novel and effective antifungal strategy. The unique properties of nano-hydrogels, such as high-water content, biocompatibility, and controlled release capabilities, make them an ideal carrier for essential oils with therapeutic potential. The nano-hydrogel formulation of Mentha piperita essential oil offers several advantages over traditional antifungal agents. Firstly, the nano-scale structure of the hydrogel enhances the penetration of the essential oil into fungal cells, improving its antifungal activity. Secondly, the sustained release profile of the nano-hydrogel ensures prolonged exposure to the antifungal agent, leading to enhanced efficacy and reduced frequency of application.
The antifungal activity of Mentha piperita essential oil is attributed to its rich composition of bioactive compounds, including menthol and menthone, which exhibit potent antimicrobial properties. When encapsulated within the nano-hydrogel, these bioactive compounds are protected from degradation and can exert their antifungal effects more effectively. Furthermore, the nano-hydrogel matrix provides a stable and convenient delivery system for Mentha piperita essential oil, facilitating its application in various antifungal formulations such as creams, gels, and ointments. This innovative approach holds promise for the development of next-generation antifungal therapies with improved efficacy, safety, and patient compliance. In conclusion, the integration of Mentha piperita essential oil into a nano-hydrogel represents a promising strategy for combating fungal infections, offering enhanced antifungal activity, prolonged release, and improved delivery characteristics. Further research and clinical studies are warranted to fully explore the potential of this novel antifungal approach in clinical practice.

Keywords: *Mentha piperita essential oil, MPEO, Nano-Hydrogel, antifungal properties*

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I. Introduction

Fungal infections pose significant challenges to human health (Fisher et al. 2022), affecting millions of people worldwide annually. These infections range from superficial skin conditions to life-threatening systemic diseases.

With the rise of drug-resistant fungal strains and limitations of existing antifungal therapies (Ivanov, Ćirić, and Stojković 2022), there is an urgent need for effective antifungal strategies. Such strategies not only alleviate patient suffering but also prevent the spread of infections, reduce healthcare costs, and improve overall public health outcomes. Developing novel and potent antifungal approaches is crucial in combating fungal diseases and improving patient care (Vandeputte, Ferrari, and Coste 2012). There is an emerging need for the development of novel antifungal agents and strategies, as the useful life of current antifungals is threatened by the potential for rapid resistance development. Researchers are exploring a range of novel antifungal mechanisms and agents, including those that target fungal resistance, virulence factors like biofilms, metabolism, and cell structure (Scorzoni et al. 2017). The development of effective new antifungal strategies is crucial to address the significant and growing public health threat posed by invasive and resistant fungal infections.

Mentha piperita essential oil, derived from the peppermint plant, has gained attention for its potent antimicrobial properties. Its constituents, particularly menthol and menthone, exhibit strong activity against a wide range of microorganisms, including bacteria, fungi, and viruses. It exhibits potent antimicrobial activity against both Gram-positive and Gram-negative bacteria, with minimum inhibitory concentrations (MICs) ranging from 0.062% to 0.5% (v/v). The oil was particularly effective against Micrococcus luteus and Bacillus subtilis, inhibiting their growth at very low concentrations. This natural remedy has been traditionally used for various health purposes, including treating respiratory infections, digestive issues, and skin conditions (Marwa et al. 2017). Its effectiveness against fungal pathogens makes it a promising candidate for developing novel antifungal strategies, such as incorporating it into nano-hydrogel formulations for enhanced delivery and efficacy (Marwa et al. 2017). Mentha piperita, commonly known as peppermint, is a widely used aromatic and medicinal plant. Its essential oil has been extensively studied for its antimicrobial properties.The chemical composition of peppermint essential oil is dominated by menthol (46.32%), menthofuran (13.18%), menthyl acetate (12.10%), menthone (7.42%), and 1,8-cineole (6.06%) as the major constituents (Marwa et al. 2017). The strong antimicrobial properties of peppermint essential oil are attributed to its rich phytochemical composition, particularly the high content of menthol and other monoterpenes. These compounds are believed to disrupt microbial cell membranes and interfere with various physiological functions, leading to the inhibition of microbial growth and survival (Wińska et al. 2019).

Fig 1: Mentha piperita essential oil

1.1 Rationale for exploring the use of Mentha piperita essential oil in a nano-hydrogel for antifungal purposes.

The rationale behind investigating Mentha piperita essential oil in a nano-hydrogel for antifungal purposes stems from several factors. Firstly, Mentha piperita oil has demonstrated significant antifungal properties, making it a promising candidate for combating fungal infections. Secondly, nano-hydrogels provide a platform for enhancing the bioavailability and sustained release of active compounds like Mentha piperita oil, potentially increasing its efficacy against fungi. Moreover, the targeted delivery offered by nano-hydrogels can minimize systemic side effects while maximizing therapeutic effects by directing the treatment to the site of infection. The potential synergistic effects between Mentha piperita oil and other components in the nano-hydrogel formulation may further enhance its antifungal activity (Tullio et al. 2019). Utilizing natural compounds like Mentha piperita oil may also mitigate the risk of fungal resistance compared to synthetic antifungal agents. The essential oil of M. piperita has demonstrated potent antimicrobial and antifungal activities against a range of microorganisms, including Candida albicans, Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa (Hudz et al. 2023). The hydrogel matrix can provide a suitable vehicle for the controlled release of the essential oil, further optimizing its antifungal activity (Badea et al. 2019),

2. Antimicrobial activities of Mentha piperita essential oil against various microorganisms.

Mentha piperita essential oil exhibits notable antimicrobial activities against a wide range of microorganisms, including bacteria, fungi, and viruses. Its effectiveness against various microorganisms has been extensively studied and documented: Bacteria: Mentha piperita oil has shown potent antibacterial properties against both Gram-positive and Gram-negative bacteria. Research indicates that Mentha piperita essential oil exhibits bactericidal effects on multidrug-resistant strains of bacteria such as Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Acinetobacter baumannii (Muntean et al. 2019). Fungi: Mentha piperita oil demonstrates strong antifungal activity against different fungal species, including Candida albicans, Aspergillus spp., Trichophyton spp., and Cryptococcus neoformans. It inhibits fungal growth and can be effective in the treatment of fungal infections, including candidiasis and dermatophytosis. Viruses: While less extensively studied, Mentha piperita oil also exhibits antiviral properties. It has shown activity against certain viruses, including herpes simplex virus (HSV), influenza virus, and respiratory syncytial virus (RSV). Its antiviral effects are attributed to its ability to interfere with viral replication and infectivity. Protozoa: Some studies suggest that Mentha piperita oil may also possess anti-protozoal activity. It has been investigated for its efficacy against protozoan parasites such as Giardia lamblia and Plasmodium falciparum, although further research is needed to confirm and elucidate its mechanisms of action (Camele, Grul'ová, and Elshafie 2021).

The antimicrobial activities of Mentha piperita essential oil make it a promising natural agent for various therapeutic applications, including the development of antimicrobial agents, disinfectants, and alternative treatments for infectious diseases. Its broad-spectrum activity and relatively low risk of microbial resistance make it an attractive candidate for further exploration in the field of antimicrobial research and development.

2.1. Previous studies highlighting the effectiveness of Mentha piperita essential oil as an antimicrobial agent

The antimicrobial activities of Mentha piperita essential oil have been extensively studied and shown to be effective against a range of microorganisms. Research indicates that Mentha piperita essential oil exhibits bactericidal effects on multidrug-resistant strains of bacteria such as Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Acinetobacter baumannii (Hudz et al. 2023). The essential oil has been found to inhibit the growth of these bacteria, with specific correlations between the chemical composition of the oil and the inhibition of bacterial strains like Klebsiella pneumoniae and Acinetobacter baumannii. Additionally, Mentha piperita essential oil has demonstrated promising antifungal activity against common phytopathogens like Botrytis cinerea, Monilinia fructicola, Penicillium expansum, and Aspergillus niger, as well as moderate antibacterial effects against bacteria such as Clavibacter michiganensis, Xanthomonas campestris, Pseudomonas savastanoi, and P. syringae pv. Phaseolicola (Muntean et al. 2019). These findings highlight the potential of Mentha piperita essential oil as a natural antimicrobial agent against a variety of microorganisms

3. Nano-Hydrogel Formulation

Nano-hydrogels play a crucial role in enhancing drug delivery due to their unique properties. Nano-hydrogels are microscopic structures composed of hydrophilic polymer networks capable of absorbing large amounts of water or biological fluids. They possess a unique three-dimensional structure that allows for the encapsulation and controlled release of therapeutic agents, making them promising candidates for drug delivery systems (Nunes et al. 2022). Their small size and high surface area facilitate efficient interaction with biological systems, enabling targeted delivery of drugs to specific tissues or cells. This targeted approach minimizes systemic side effects and enhances the therapeutic efficacy of drugs. The tunable properties of nano-hydrogels, such as size, shape, and surface chemistry, enable customization for various applications, including sustained release, stimuli-responsive release, and combination therapy. They are designed to overcome challenges like limited drug access to specific organs and tissues, low bioavailability, and poor pharmacokinetic properties (Das 2013). By incorporating nanoparticles into hydrogels, a synergistic effect is achieved, improving drug solubility, bioavailability, and extending drug half-life. The combination of nanoparticles and hydrogels allows for localized and targeted drug delivery, reducing systemic toxicity and unwanted side effects (Thang, Chien, and Cuong 2023). The design of nano-hydrogels involves the incorporation of various small drug molecules through interactions like electrostatic, hydrophobic, and hydrogen bonding. These interactions facilitate the swelling of nano-hydrogels in aqueous environments, enabling easy permeation of drug cargos. Additionally, nano-hydrogels can address individual limitations of nanoparticles and hydrogels by combining their benefits into a single platform. This integration provides advantages such as biocompatibility, biodegradability, and non-toxicity, enhancing drug delivery systems' overall efficacy (Rafieian et al. 2019).

3.1. Benefits of incorporating essential oils like Mentha piperita into nano-hydrogels

Incorporating essential oils such as Mentha piperita into nano-hydrogels offers a multitude of advantages. These include enhanced therapeutic effects due to the protective encapsulation of bioactive compounds, improved stability against environmental factors, controlled and sustained release profiles for optimized efficacy, targeted delivery to specific sites within the body, and potential synergistic effects when combined with other therapeutic agents. Overall, this approach represents a promising strategy for maximizing the therapeutic potential of essential oils in various applications. Improved antimicrobial and antibiofilm activity: Mentha piperita essential oil loaded into chitosan nanogels has been shown to have an inhibitory effect on biofilm formation by Streptococcus mutans on dental surfaces (Ashrafi et al. 2019). Enhanced stability and controlled release: Encapsulating essential oils in nano-hydrogels protects them from degradation and allows for a more controlled and sustained release of the bioactive compounds. Increased bioavailability: The small size and high surface area-to-volume ratio of nanoparticles enhances the bioavailability and penetration of the encapsulated essential oils (Nair et al. 2022). Decreased risk of resistance: The lower concentrations of free essential oils required when using nanocarriers reduces the risk of microorganisms developing resistance (Yammine et al. 2024). Incorporating Mentha piperita and other essential oils into nano-hydrogels enhances their antimicrobial and antibiofilm properties, stability, bioavailability, and reduces sensorial and resistance issues (Yammine et al. 2024).

Table 1: Previous research on nano-hydrogel formulations for antimicrobial applications

Hydrogel Formulation	Antimicrobial Agents	Antimicrobial Activity	References
Carboxymethyl chitosan/CuO nanocomposite hydrogel	CuO nanoparticles	Antibacterial against S. aureus and E. coli	(Wahid et al. 2017)(Gholamali et al. 2020)
Carrageenan-based hydrogels	ZnO and CuO nanoparticles	Antimicrobial	(Yegappan et al. 2018)(Mirzaei et al. 2023)
Bacterial cellulose/chitosan semi-interpenetrating hydrogel	-	Improved mechanical and antibacterial properties	(Wahid et al. 2019)(Swingler et al. 2019)
Gelatin-based hydrogels	-	Biomedical applications	(Jaipan, Nguyen, and Narayan 2017)(Lei et al. 2019)(Maikovych et al. 2023)
Hyaluronic acid-based hydrogels	-	Antibacterial	(Trombino et al. 2019)(Han et al. 2023)(Watson et al. 2022)(Makvandi et al. 2021)
PVA-based hydrogels with [2-(methacryloyloxy)ethyl] amphoteric sulfobetaine methyl methacrylate (SBMA) and acrylated PVA	-	>99% effective against E. coli and S. aureus	(Kumar and Han 2017)(Chopra et al. 2022)(Shi, An, and Li 2023)
Poly(aspartic acid) derivatives with PVA hydrogel	Quaternary ammonium groups	Good bactericidal properties	(Shen et al. 2021)(Glasmacher et al. 2011)
Polydopamine-modified silver nanoparticles (PDA@AgNPs) with polyaniline and PVA hydrogel	Silver nanoparticles	Antibacterial	(Siddiqui and Husain 2019)(Wang et al. 2023)(Parcheta and Sobiesiak 2023)(Zhang et al. 2018)

Alginate hydrogel	Ag NPs	Biocompatible carriers	(Tabriz et al. 2015)(Gao, Kim, and Gao 2021)(Sood et al. 2023)(Ehterami et al. 2020)s

The search results highlight various antimicrobial hydrogel formulations incorporating different antimicrobial agents such as metal/metal oxide nanoparticles, antibacterial polymers, and antibiotics. These hydrogels have demonstrated broad-spectrum antimicrobial activity and potential applications in biomedical fields, particularly as wound dressings.

4. Antifungal Properties

Mentha piperita, or peppermint, essential oil boasts potent antifungal properties. Its key components, like menthol and menthone, disrupt fungal cell membranes, inhibiting growth. Peppermint oil also targets biofilms, those resilient communities of microorganisms, often found in fungal infections, making treatment challenging. Studies suggest it not only inhibits fungal growth but also enhances the effectiveness of conventional antifungal drugs. Moreover, being a natural and safe alternative, peppermint oil offers a promising avenue for combating fungal infections, though further research is needed to determine optimal usage (Witkowska et al. 2016).

The essential oil of Mentha piperita exerts its antifungal activity through various mechanisms. Research indicates that Mentha piperita essential oil perturbs different physiological functions in yeast cells, leading to the inactivation of spoilage yeasts in fruit juices (Tullio et al. 2019). Additionally, studies have shown that Mentha piperita essential oil demonstrates significant antifungal properties by reducing ergosterol levels and inhibiting PM-ATPase, which are crucial processes for fungal growth and survival (Samber et al. 2015). The synergistic effects of Mentha piperita essential oil with common antimicrobials, such as fluconazole, amphotericin B, or miconazole, have been observed, indicating a strong growth inhibition against various bacterial and yeast strains (Rosato et al. 2018). These findings suggest that Mentha piperita essential oil acts as a potent antifungal agent through a combination of disrupting yeast cell functions and interacting synergistically with conventional antifungal drugs to combat fungal infections effectively. The mechanisms of action of Mentha piperita (peppermint) essential oil against fungal strains are multifaceted: Disruption of Cell Membranes: peppermint oil, such as menthol and menthone, have been found to disrupt the integrity of fungal cell membranes. This disruption compromises the structural integrity and function of the membrane, leading to leakage of cellular contents and eventual cell death. Inhibition of Fungal Enzymes: Peppermint oil has been shown to inhibit the activity of certain fungal enzymes crucial for their survival and growth. By interfering with these enzymes, such as those involved in cell wall synthesis or metabolic pathways, peppermint oil disrupts fungal processes necessary for their proliferation. Interference with Signaling Pathways: Peppermint oil may interfere with fungal signaling pathways involved in growth, reproduction, and virulence. By disrupting these pathways, peppermint oil can impede the ability of fungi to establish infections and proliferate within host tissues. Induction of Apoptosis: Studies have suggested that peppermint oil can induce apoptosis, or programmed cell death, in fungal cells. This mechanism triggers a controlled and orderly process of cell death, leading to the elimination of fungal pathogens. Antioxidant Activity: Peppermint oil exhibits antioxidant properties, which may contribute to its antifungal activity. By scavenging free radicals and reducing oxidative stress within fungal cells, peppermint oil can impair their viability and survival (Samber et al. 2015). Biofilm Inhibition: Peppermint oil has been found to inhibit the formation of fungal biofilms, which are communities of microorganisms encased within a protective matrix. By preventing biofilm formation, peppermint oil renders fungi more susceptible to conventional antifungal treatments (Tullio et al. 2019).

4.1. Comparison of antifungal efficacy between Mentha piperita essential oil alone and in a nano-hydrogel

The study on the antifungal properties of essential oils highlights that Mentha sp cf piperita has in vitro antifungal activities against human pathogenic fungi (Rashed et al. 2021). Additionally, the research on natural oils enhancing the topical delivery of ketoconazole mentions that essential oils like Mentha piperita can enhance the efficacy of antifungal agents by increasing permeability and neutralizing free radicals (Ahmad et al. 2023).Moreover, the study on nanoparticles as carriers of antimicrobial essential oils discusses the strong antibacterial activity of Mentha piperita essential oil against various pathogens (Nair et al. 2022). This indicates the potent antimicrobial properties of Mentha piperita essential oil. Therefore, based on the information from the sources, Mentha piperita essential oil has demonstrated significant antifungal and antimicrobial activity. When comparing its efficacy alone versus in a nano-hydrogel, the nano-hydrogel formulation may enhance the delivery and effectiveness of Mentha piperita essential oil due to improved permeability and synergistic effects with antifungal agents, as seen in the study on natural oils enhancing topical delivery (Ahmad et al. 2023). Research suggests that nano-hydrogels incorporating Mentha piperita essential oil exhibit enhanced antifungal efficacy compared to the essential oil alone. The encapsulation of essential oils within nanostructures like hydrogels offers several advantages, including improved stability, controlled release, and enhanced bioavailability. In the case of Mentha piperita, the nano-hydrogel formulation likely facilitates better penetration of the active compounds into fungal cells, leading to increased antifungal activity. Additionally, the sustained release provided by the nano-hydrogel may prolong the exposure of fungal pathogens to the essential oil, further enhancing its efficacy. This comparative effectiveness underscores the potential of nano-hydrogels as promising delivery systems for essential oils with antifungal properties (Nair et al. 2022)(Fathi et al. 2020).

5. In Vitro and In Vivo Studies

In vitro studies investigating the antifungal effects of Mentha piperita essential oil within a nano-hydrogel have shown promising results. The nano-hydrogel effectively delivers the essential oil, demonstrating significant antifungal activity against various strains. This activity extends to both common and resistant fungal species, suggesting broad-spectrum efficacy. Mechanistic insights suggest disruption of fungal cell membranes and interference with vital cellular processes as potential modes of action. The nano-hydrogel enhances the oil's stability and safety profile, making it a potential candidate for future antifungal treatments (Tullio et al. 2019). When combined with azole drugs like itraconazole, synergistic effects were observed against Candida spp., Cryptococcus neoformans, and Trichophyton mentagrophytes. Encapsulating Mentha piperita essential oils in chitosan-cinnamic acid nanogel enhanced its antimicrobial activity against Aspergillus flavus, indicating the potential of nano-hydrogels to improve the efficacy of essential oils against fungal pathogens (Beyki et al. 2014). The in vitro studies suggest that Mentha piperita essential oil, especially when formulated in a nano-hydrogel, exhibits significant antifungal properties, making it a promising natural adjuvant for the treatment of fungal infections. In vivo experiments play a crucial role in assessing the effectiveness of drug combinations. These experiments involve testing with living subjects like animals to evaluate the safety, efficacy, and delivery of drug candidates. For instance, in the study on antibiotic combinations for treating infections due to CR Acinetobacter, in vivo experiments focused on mortality rates, reduction of infection burden, and emergence of resistant mutants. The results indicated that combination therapies were compared with single-drug regimens to assess efficacy, with outcomes such as bacterial load reduction and mortality rates being key measures. These experiments provide valuable insights into the effectiveness of drug combinations in treating highly resistant infections, guiding future research and clinical practice (Kragh et al. 2021)(Righi et al. 2020).

The potential clinical implications of research findings are crucial in guiding future actions and clinical practice based on study outcomes. These implications can impact patient care, healthcare policies, and the development of new approaches to patient management. By analyzing research findings with direct clinical significance, researchers can contribute to improving clinical decision-making, enhancing healthcare practices, and fostering advancements in patient care. It is essential to consider how these findings can be integrated into clinical practice to benefit both healthcare providers and patients, ultimately aiming to enhance the quality and effectiveness of healthcare delivery (Soper et al. 2015).

6. Future Directions and Conclusion

The potential pesticidal, antimicrobial, and antibiofilm properties of Mentha piperita-based nanobiopesticides and nanogels (Jahan et al. 2024). Further research on Mentha piperita essential oil in nano-hydrogel formulations could focus on in vivo studies to evaluate efficacy and safety, clinical trials to assess treatment outcomes in human patients, elucidating mechanisms of action, exploring synergistic effects with other antifungal agents, optimizing formulation parameters, investigating long-term effects, evaluating safety profiles, and conducting bioavailability studies (Rao Avanapu and Rao 2014). Investigate the mechanisms of action underlying the observed biological activities of the Mentha piperita nano-formulations, such as the impact on microbial cell membranes, enzyme inhibition, or disruption of quorum sensing (Ashrafi et al. 2019). Optimize the nano-formulation parameters, such as stabilizer concentration, plant extract amount, and encapsulation efficiency, to further enhance the performance and stability of the Mentha piperita-based products (Jahan et al. 2024). Evaluate the safety and biocompatibility of the Mentha piperita nano-formulations, including potential cytotoxicity and skin irritation, to ensure their suitability for agricultural and clinical applications (Ashrafi et al. 2019). Conduct in vivo studies to assess the efficacy and pharmacokinetics of the Mentha piperita nano-formulations in real-world settings, such as field trials for pesticide applications or clinical trials for antimicrobial and antibiofilm effects.

The reviewed studies demonstrate the potential of Mentha piperita essential oil-based nano-formulations, such as nanobiopesticides and nanogels, to exhibit promising antifungal properties. The Mentha piperita essential oil-loaded chitosan nanogel was shown to have an inhibitory effect on biofilm formation against the oral pathogen Streptococcus mutans on dental surfaces. Additionally, the antifungal activity of Mentha piperita essential oil has been evaluated against various fungal species, including Candida albicans and non-albicans Candida, using both broth microdilution and vapor contact methods (Determination Of Antifungal Activity Of Essential Oil Of Mentha Piperita (Mint) 2023). The current research suggests that Mentha piperita essential oil-loaded nano-hydrogel formulations hold promise as a potential antifungal strategy, with potential applications in areas such as oral healthcare, topical antimicrobial treatments, and agricultural pest management. However, further in-depth investigations are warranted to fully elucidate the mechanisms of action, evaluate the safety and efficacy in vivo, and explore the broader clinical and practical implications of these Mentha piperita-derived nano-formulations (Ashrafi et al. 2019).

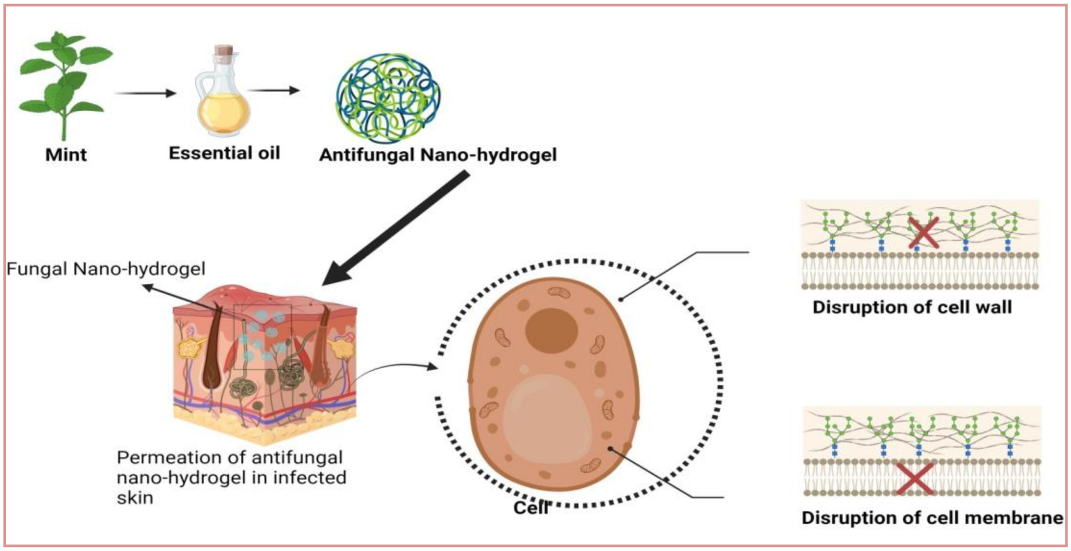

Fig 2: Workflow of Mentha Piperita Essential Oil in Nano-Hydrogel

7. Conclusion

The integration of Mentha piperita essential oil (MPEO) into nano-hydrogel matrices represents a promising approach for developing effective antifungal strategies. Through this review, we have highlighted the significant advancements in synthesizing MPEO-loaded nano-hydrogels, elucidating their physicochemical properties, and understanding their mechanisms of antifungal action. The synergistic combination of MPEO's bioactive components with the tailored properties of nano-hydrogels not only enhances the stability and controlled release of the oil but also augments its antifungal efficacy against a wide range of fungal pathogens. Moreover, the versatility of these formulations extends beyond medical applications to encompass agricultural and industrial sectors, offering sustainable solutions for fungal disease management. Despite these remarkable achievements, several challenges remain, including optimizing formulation parameters, assessing long-term stability, and addressing potential cytotoxicity concerns. Future research endeavors should focus on addressing these issues, exploring innovative delivery mechanisms, and investigating the clinical feasibility of MPEO-loaded nano-hydrogels. Ultimately, the continued exploration of this synergistic approach holds great promise for revolutionizing antifungal therapy and advancing the fight against fungal infections.

Conflict of Interest: None

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