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Review Article

Development and Optimization of Herbal Semisolid Formulation with Antifungal Activity of Peach (*Prunus persica*) and Mulberry (*Morus alba*) Extracts

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ABSTRACT

Fungal infections represent a significant global health burden, exacerbated by the emergence of drug-resistant strains and the side effects associated with synthetic antifungal agents. Herbal medicine offers a reservoir of bioactive compounds with potent antimicrobial properties. *Prunus persica* (Peach) and *Morus alba* (Mulberry) are two such botanical sources rich in polyphenols, flavonoids, and alkaloids that exhibit significant antifungal activity against dermatophytes and yeast species. This review focuses on the strategies for developing and optimizing semisolid dosage forms, specifically creams and gels, incorporating these extracts. It explores the phytochemical profiles of Peach and Mulberry, the mechanisms of their antifungal action, and the technological aspects of formulation optimization using Design of Experiments (DoE). Furthermore, evaluation parameters including physicochemical stability, rheological properties, and in vitro antifungal efficacy are discussed to provide a roadmap for the commercialization of standardized herbal antifungal topicals.

INTRODUCTION

The prevalence of superficial fungal infections, such as candidiasis, tinea pedis, and dermatophytosis, has increased significantly over the last few decades. While synthetic antifungal agents like azoles (fluconazole, ketoconazole) and allylamines are the standard of care, their long-term use is often limited by skin irritation, systemic toxicity, and the rapid development of

microbial resistance [1]. Consequently, there is a burgeoning interest in "Green Pharmacy," focusing on the development of herbal formulations that are biocompatible, cost-effective, and possess multi-target mechanisms of action.

Among various botanical candidates, *Prunus persica* (Peach) and *Morus alba* (Mulberry) have emerged as potent sources of antimicrobial agents.

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Peach kernels and leaves are traditionally known for their cyanogenic glycosides and phenolic acids, while Mulberry is celebrated for its high content of oxyresveratrol and morusin [2]. Integrating these extracts into a semisolid vehicle, such as a gel, cream, or ointment, provides a localized delivery system that enhances skin penetration and patient compliance. However, the development of herbal semisolids is fraught with challenges, including the stability of phytochemicals, the variability of extract composition, and the need for optimized drug release profiles. This review synthesizes current knowledge on the antifungal potential of Peach and Mulberry and provides a technical framework for optimizing their topical delivery systems.

Botanical and Phytochemical Profiles

A. *Prunus persica* (Peach)

Prunus persica, belonging to the family Rosaceae, is not only a nutritional fruit but also a source of secondary metabolites with therapeutic potential. The leaves, bark, and seeds contain bioactive compounds such as:

1. **Phenolic Acids:** Chlorogenic acid and gallic acid, which disrupt fungal cell membranes [3].
2. **Flavonoids:** Quercetin and kaempferol derivatives that inhibit the enzyme systems of pathogens.
3. **Cyanogenic Glycosides:** Amygdalin, primarily found in the seeds, which has demonstrated broad-spectrum antimicrobial activity in synergy with other phenols [4].

B. *Morus alba* (Mulberry)

Morus alba (family Moraceae) has been used in Traditional Chinese Medicine (TCM) for centuries. Its antifungal prowess is attributed to:

1. **Stilbenes:** Particularly oxyresveratrol and mulberroside A, which are potent inhibitors of tyrosinase and fungal growth [5].
2. **Prenylated Flavonoids:** Morusin and kuwanon G, which have shown strong activity against *Candida albicans* and *Aspergillus* species by inducing apoptosis-like cell death in fungi [6].
3. **Alkaloids:** 1-Deoxynojirimycin (DNJ), which interferes with glycoprotein processing in fungal cells.

Mechanism of Antifungal Action

The synergy between Peach and Mulberry extracts offers a multi-pronged attack on fungal pathogens:

1. **Cell Wall Disruption:** Phytochemicals like tannins and saponins from these extracts increase membrane permeability, leading to the leakage of intracellular contents (potassium ions and proteins) [7].
2. **Inhibition of Ergosterol Synthesis:** Certain flavonoids act similarly to azoles by inhibiting the cytochrome P450-dependent enzyme lanosterol 14 α -demethylase, essential for fungal cell membrane integrity [8].
3. **Induction of Reactive Oxygen Species (ROS):** Polyphenols from Mulberry induce oxidative stress within the fungal cell, leading to DNA damage and mitochondrial dysfunction [9].
4. **Enzyme Inhibition:** Peach extracts have been shown to inhibit extracellular proteases and lipases secreted by fungi to invade host tissues [10].

Development of Herbal Semisolid Formulations



To translate these extracts into a therapeutic product, the selection of the dosage form is critical.

A. Selection of Base

1. **Gels:** Aqueous-based gels (using Carbopol 934 or HPMC) are preferred for their non-greasy nature and superior cooling effect on inflamed fungal lesions. They allow for the rapid release of polar phytochemicals [11].
2. **Creams (O/W Emulsions):** Oil-in-water creams are suitable for extracts containing lipophilic compounds (like certain stilbenes from Mulberry). They provide an occlusive effect that enhances skin hydration and penetration [12].

B. Excipients and Penetration Enhancers

Herbal extracts often have large molecular weights or poor lipophilicity, hindering skin permeation. Incorporating penetration enhancers like propylene glycol, Tween 80, or natural oils (e.g., Eucalyptus oil) can temporarily disrupt the stratum corneum barrier to facilitate deeper delivery of Peach and Mulberry bioactives [13].

Optimization via Design of Experiments (DoE)

Optimization is essential to ensure that the formulation achieves maximum efficacy with minimum excipient concentration.

A. Factorial Design

A 2^3 or 3^2 full factorial design is often employed. Independent variables typically include:

1. Concentration of *Prunus persica* extract (X1)
2. Concentration of *Morus alba* extract (X2)
3. Polymer/Gelling agent concentration (X3)

Dependent variables (responses) measured include:

1. Viscosity (Y1)
2. Spreadability (Y2)
3. Zone of Inhibition (Y3)
4. *In vitro* drug release (%) at 8 hours (Y4) [14].

B. Response Surface Methodology (RSM)

RSM helps in identifying the interaction between Peach and Mulberry extracts. It has been observed in various studies that a 1:1 ratio of such extracts might not always be optimal; instead, a specific ratio may yield a synergistic "Checkerboard" effect, significantly lowering the Minimum Inhibitory Concentration (MIC) compared to individual extracts [15].

Evaluation Parameters

A. Physicochemical Evaluation

1. **Organoleptic Properties:** Color, odor, and texture. Herbal extracts often impart a distinct brownish hue; stabilization against oxidation is required using antioxidants like BHT or Vitamin E [16].
2. **pH Measurement:** Skin pH is approximately 5.5. Formulations must be adjusted using triethanolamine to ensure they are non-irritating [17].
3. **Rheological Studies:** Viscosity measurement using a Brookfield viscometer ensures the formulation remains stable during storage and spreads easily upon application.
4. **Spreadability:** Determined using the "Parallel Plate" method to ensure easy application over infected areas [18].



B. Phytochemical Standardization

High-Performance Thin Layer Chromatography (HPTLC) or HPLC must be used to quantify "marker compounds" (e.g., Oxyresveratrol for Mulberry and Quercetin for Peach) to ensure batch-to-batch consistency [19].

In Vitro Antifungal Activity

1. **Agar Well Diffusion Method:** The formulation is tested against *Candida albicans*, *Aspergillus niger*, and *Trichophyton rubrum*. The Zone of Inhibition (ZOI) is measured and compared against a standard (e.g., Clotrimazole cream) [20].
2. **Minimum Inhibitory Concentration (MIC):** Determined via broth microdilution to find the lowest concentration of the optimized formulation that prevents visible fungal growth.[21]

D. Stability Studies

As per ICH guidelines (Q1A), the formulation is subjected to accelerated stability ($40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{RH}$). Herbal semisolids are prone to microbial contamination and syneresis (liquid separation), necessitating the use of robust preservative systems like methylparaben and propylparaben or natural alternatives like Neem oil [22].

Factors Influencing Optimization and Efficacy

The optimization of a Peach-Mulberry formulation is influenced by several external and internal factors:[23]

1. **Extraction Method:** Ultrasound-assisted extraction (UAE) or Microwave-assisted extraction (MAE) typically yields higher concentrations of heat-sensitive antifungal

polyphenols compared to traditional maceration [24].

2. **Solvent Polarity:** Ethanol-water mixtures (70:30) are generally most effective for extracting the diverse range of flavonoids and stilbenes found in these species [25].
3. **Synergy with Excipients:** Certain surfactants used in cream bases can inadvertently sequester phenolic compounds, reducing their bioavailability. Therefore, the choice of non-ionic surfactants is critical for herbal efficacy [26].

Recent Advances: Nano-herbal Formulations

Current research is shifting towards "Nano-ethosomes" or "Solid Lipid Nanoparticles" (SLNs) loaded with Peach and Mulberry extracts. These nanocarriers can bypass the stratum corneum more effectively than traditional gels, providing a sustained release of antifungal agents and protecting the extracts from photodegradation [27-28]. Studies indicate that nano-encapsulation of Mulberry oxyresveratrol increases its antifungal potency by nearly 40% due to improved solubility and targeted delivery [29].

DISCUSSION

The integration of *Prunus persica* and *Morus alba* into a single semisolid matrix represents a holistic approach to fungal therapy. Peach extracts provide a high concentration of organic acids that lower the local pH, creating an inhospitable environment for fungi, while Mulberry extracts provide specific secondary metabolites that target fungal cell wall synthesis. The optimization process is not merely about mixing; it involves a delicate balance between the physical elegance of the cream/gel and the chemical stability of the bioactive markers.[30-31]



One significant challenge identified in the literature is the "browning effect" of Mulberry extract due to the oxidation of polyphenols. Optimization must, therefore, include the addition of chelating agents (like EDTA) and the use of opaque packaging to maintain the aesthetic and functional integrity of the herbal product [32]. Furthermore, the synergistic index (FICI) of Peach and Mulberry should be a primary response variable in future DoE models to mathematically prove the advantage of the combination over monotherapy.

CONCLUSION

Developing an optimized herbal semisolid formulation from Peach and Mulberry extracts holds great promise for the treatment of topical fungal infections. By utilizing systematic optimization techniques like Factorial Design and RSM, researchers can develop formulations that are not only stable and patient-friendly but also therapeutically superior to current synthetic options. The transition from traditional usage to evidence-based herbal medicine requires rigorous standardization of extracts and validated evaluation of antifungal kinetics. Future research should focus on clinical trials to establish the safety and efficacy of these optimized formulations in human subjects, paving the way for a new generation of green antifungal therapeutics.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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