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RESEARCH ARTICLE

Development and Evaluation of a Neem Oil-based Mosquito Repellent Cream

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Abstract: A natural mosquito repellent cream was formulated using neem oil (*Azadirachta indica*) as the primary active ingredient to address the growing concerns over synthetic repellent toxicity and environmental impact. Five formulations were developed using varying concentrations of neem oil, coconut oil, vitamin E, beeswax, and rose oil. Physicochemical evaluation including pH measurement, spreadability, stability testing, irritancy studies, and antimicrobial assessment were carried out. Among the formulations, F2 exhibited optimal characteristics with a skin-compatible pH of 5.5, superior spreadability, and reasonable stability at room temperature. The cream showed moderate mosquito repellency with complete protection for approximately 2 hours, significantly shorter than the 5.2 hours provided by a 15% DEET formulation tested under identical conditions. The F2 formulation maintained 78.3% protection at 2-3 hours post-application, declining to 52.6% at 3-4 hours, necessitating reapplication every 2-3 hours for continued effectiveness. Stability studies revealed a 15% degradation of azadirachtin content after 90 days at room temperature, with accelerated degradation (28% loss) and phase separation observed at elevated temperatures (45°C). The complex repellent mechanism likely involves modulation of multiple chemosensory pathways in mosquitoes, including inhibition of specific odorant receptors involved in host recognition. While this formulation is a promising eco-friendly alternative to synthetic repellents, its shorter protection duration and limited thermal stability highlight the need for developing advanced controlled-release systems to enhance the practical utility of these natural ingredients in mosquito control programs.

Keywords: Mosquito repellent; *Azadirachta indica*; Natural formulation; Vector control; Herbal cream

1. Introduction

Mosquito-borne diseases represent a significant global health challenge, affecting over 700 million people annually and causing approximately one million deaths worldwide [1]. The prevalence of these vector-borne illnesses, including malaria, dengue fever, yellow fever, and Japanese encephalitis, is particularly pronounced in tropical and subtropical regions where environmental conditions favor mosquito proliferation [2]. Despite extensive control measures, these diseases continue to pose substantial economic and social burdens, especially in developing nations [3]. Conventional mosquito control methods have predominantly relied on synthetic repellents, with N,N-diethyl-m-toluamide (DEET) being the most widely used active ingredient [4]. However, mounting evidence suggests significant drawbacks associated with synthetic repellents, including potential neurotoxicity, skin irritation, and environmental persistence [5]. Additionally, the emergence of insecticide-resistant mosquito populations has necessitated the exploration of alternative control methods [6].

Natural plant-derived repellents have gained considerable attention as sustainable alternatives to synthetic compounds [7]. Among various botanical sources, neem (*Azadirachta indica*) has emerged as a particularly promising candidate due to its documented insecticidal and repellent properties [8]. The active compound azadirachtin, along with other limonoids present in neem oil, demonstrates significant effects on mosquito feeding behavior and reproductive cycles [9]. The incorporation of essential oils into stable topical formulations presents unique challenges and opportunities in repellent development [10]. Cream-based formulations offer several advantages, including enhanced skin contact time, improved user acceptance, and the potential for additional therapeutic benefits [11]. The selection of appropriate excipients and stabilizers is crucial for maintaining the integrity of volatile essential oils while ensuring optimal delivery to the skin surface [12].

Recent advances in formulation technology have enabled the development of more effective natural repellent delivery systems [13]. These innovations address historical limitations of botanical repellents, such as rapid volatilization and inconsistent efficacy [14].

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Moreover, the integration of complementary natural ingredients can enhance both the protective and cosmetic properties of repellent formulations [15]. The aim of this present research was to develop and evaluate a neem oil-based mosquito repellent cream that combines efficacy with user safety and environmental sustainability. The study includes systematic formulation development, comprehensive physicochemical characterization, and evaluation of repellent activity. The research aims to establish a scientific framework for the development of natural mosquito repellents that can effectively contribute to vector control strategies while minimizing environmental impact and health risks [16].

2. Materials and Methods

2.1. Materials

The formulation development utilized neem oil (*Azadirachta indica*) as the primary active ingredient, sourced from certified organic suppliers with established quality control parameters. Complementary ingredients included cold-pressed coconut oil (*Cocos nucifera*) and pharmaceutical-grade vitamin E (α-tocopherol) to enhance the stability and therapeutic properties of the formulation. Additional excipients comprised refined beeswax as an emulsifying agent, pharmaceutical-grade sodium bicarbonate for pH adjustment, and steam-distilled rose oil (*Rosa damascena*) as a natural fragrance enhancer. All materials met strict pharmacopoeial specifications and were obtained from verified suppliers [17].

2.2. Methods

2.2.1. Extraction of Neem Oil

Two extraction methods were employed to obtain neem oil for the formulation. The first method involved solvent extraction, wherein mature neem leaves were initially authenticated by botanical experts and subsequently processed. The leaves underwent a controlled drying process at 40°C for 48 hours, followed by size reduction to achieve a uniform 40-mesh powder. The powdered material was subjected to Soxhlet extraction using analytical grade n-hexane at 68°C for 6 hours. Post-extraction, the solvent was removed under reduced pressure at 40°C using a rotary evaporator. The extracted oil underwent filtration and was stored in amber glass containers at 4°C to prevent oxidative degradation [18].

The second method employed steam distillation using fresh neem leaves. One kilogram of authenticated leaves was processed using a modified Clevenger apparatus for 4 hours at atmospheric pressure. The distillate underwent separation using a separating funnel, and the isolated oil was dried over anhydrous sodium sulfate to remove residual moisture [19].

2.2.2. Formulation Development

The development process began with preliminary studies to establish optimal concentrations of ingredients based on comprehensive stability and rheological assessments. Five distinct formulations (F1-F5) were developed, maintaining a consistent neem oil concentration of 5% w/w while varying the ratios of other components to achieve optimal characteristics.

Table 1. Composition of Different Neem-based Mosquito Repellent Cream Formulations (% w/w)

Ingredients	F1	F2	F3	F4	F5	Function
Neem oil	5.0	5.0	5.0	5.0	5.0	Active ingredient
Coconut oil	8.0	10.0	12.0	7.0	6.0	Emollient/carrier
Beeswax	4.0	5.0	3.0	6.0	4.5	Emulsifying agent
Vitamin E	0.5	1.0	0.5	0.5	0.5	Antioxidant
Rose oil	0.2	0.3	0.2	0.4	0.3	Natural fragrance
Sodium bicarbonate	0.8	1.0	0.8	0.8	0.8	pH adjusting agent
Citric acid	0.3	0.4	0.3	0.3	0.3	pH adjusting agent
Glycerin	3.0	4.0	3.0	3.0	3.0	Humectant
Cetyl alcohol	2.0	2.5	2.0	2.0	2.0	Stabilizer
Stearic acid	3.0	3.5	3.0	3.0	3.0	Emulsifying agent
Methylparaben	0.2	0.2	0.2	0.2	0.2	Preservative
Propylparaben	0.1	0.1	0.1	0.1	0.1	Preservative
Purified water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	Vehicle

The cream preparation followed a systematic dual-phase protocol. The oil phase preparation involved careful melting of beeswax at 65°C, followed by sequential incorporation of coconut oil and vitamin E while maintaining a constant temperature of 70°C. Concurrently, the aqueous phase was prepared by dissolving sodium bicarbonate in purified water, heating to 70°C, and adjusting the pH to 5.5 using citric acid buffer [20].

The emulsification process involved careful combination of the two phases at 70°C under controlled conditions. The aqueous phase was introduced to the oil phase at a steady rate of 2 mL/min while maintaining continuous homogenization. The homogenization speed was gradually increased from 2000 rpm to 3500 rpm as the emulsion formed. The temperature was allowed to decrease gradually from 70°C to 35°C over 30 minutes of continuous mixing. In the final stage neem oil and rose oil were added at 35°C under gentle stirring conditions for 15 minutes to preserve their volatile components.

2.3. Evaluation

The formulated cream underwent rigorous physicochemical characterization and stability assessment to ensure quality and efficacy. The pH determination was conducted using a calibrated digital pH meter at 25°C, with measurements performed in triplicate to ensure accuracy. Spreadability assessment employed the parallel plate method, wherein a standard weight was placed on the formulation between two glass plates, and the spreading diameter was measured at regular intervals over 60 seconds [21].

Rheological properties were evaluated using a Brookfield viscometer equipped with spindle number 4, operating at 20 rpm under controlled temperature conditions of 25±1°C. The homogeneity of the formulation was assessed through microscopic evaluation at various magnifications to ensure uniform distribution of the dispersed phase. The emulsion type was determined through conductivity measurements and confirmed using water-soluble dye tests [22].

2.4. Stability

Stability studies were conducted over a three-month period under various storage conditions. Samples were stored at room temperature (25°C ± 2°C), elevated temperature (45°C ± 2°C), and refrigeration (4°C ± 1°C), with relative humidity maintained at 75% ± 5%. Physical parameters including color, odor, pH, and viscosity were monitored at predetermined intervals of 0, 30, 60, and 90 days. Phase separation tendency was evaluated through centrifugation at 3500 rpm for 30 minutes [23].

2.5. Safety and Efficacy

Dermal safety assessment was conducted following modified Draize test protocols on albino rabbits. The test areas were observed for signs of erythema, edema, or other adverse reactions at 24, 48, and 72 hours post-application. The primary irritation index was calculated according to standard protocols [24].

Antimicrobial testing was performed using the agar well diffusion method to ensure the preservation efficacy of the formulation. Samples were tested against common skin pathogens including Staphylococcus aureus, Escherichia coli, and Candida albicans. The zones of inhibition were measured after 24 hours of incubation at 37°C [25].

2.6. Evaluation of Repellent Activity

The mosquito repellent efficacy was evaluated using both laboratory and modified field conditions. Laboratory assessment employed a standard cage test method using Aedes aegypti mosquitoes maintained under controlled conditions (27±2°C, 70±5% RH). The test involved applying the formulation to exposed areas of volunteers' arms, with untreated areas serving as controls. Protection time was determined as the duration until the first confirmed bite, with observations recorded at 30-minute intervals [26]. Field simulation studies were conducted in a controlled outdoor environment during peak mosquito activity periods (dawn and dusk). Volunteers applied the formulation according to standardized protocols, and mosquito landing rates were recorded over four-hour periods. The protection factor was calculated based on the reduction in landing rates compared to untreated controls [27].

2.7. Statistical Analysis

All experimental data was statistical analyzed using one-way ANOVA followed by Tukey's post-hoc test. Results were expressed as mean ± standard deviation, with $p<0.05$ considered statistically significant. The stability data were analyzed using linear regression to determine degradation kinetics and predict shelf life [28].

3. Results and Discussion

3.1. Evaluation

The evaluation of five formulations (F1-F5) revealed distinct variations in their physicochemical properties. Formulation F2 demonstrated superior characteristics, exhibiting optimal stability and user acceptability parameters. The cream displayed a homogeneous white appearance with a smooth texture and pleasant aromatic fragrance, attributable to the balanced incorporation of rose oil. The pH value of 5.5 aligned perfectly with the skin's physiological pH range (4.5-6.5), suggesting minimal risk of barrier disruption during application [29].

Rheological analysis indicated that F2 possessed ideal viscosity (3200 ± 150 cP at 25°C), facilitating easy spreading while maintaining structural integrity. This characteristic was particularly significant as it ensured uniform film formation on the skin surface, crucial for sustained repellent action. The spreadability coefficient (6.8 ± 0.3 g.cm/sec) indicated optimal flow properties, superior to formulations F1 (5.2 ± 0.4 g.cm/sec) and F3-F5 (ranging from 4.9 to 5.8 g.cm/sec) [30].

Table 2. Physicochemical Characteristics of Different Neem-based Repellent Formulations (F1-F5)

Parameter	F1	F2	F3	F4	F5
pH (25°C) *	5.8 ± 0.2	5.5 ± 0.1	5.2 ± 0.3	5.9 ± 0.2	5.7 ± 0.2
Viscosity (cP at 25°C) *	2800 ± 180	3200 ± 150	2950 ± 165	2750 ± 170	2600 ± 190
Spreadability (g.cm/sec) *	5.2 ± 0.4	6.8 ± 0.3	5.4 ± 0.3	4.9 ± 0.4	5.8 ± 0.3
Mean droplet size (µm) *	3.5 ± 0.6	2.8 ± 0.4	3.8 ± 0.5	4.2 ± 0.7	3.9 ± 0.5
Primary irritation index *	0.8 ± 0.2	0.4 ± 0.1	0.6 ± 0.2	0.9 ± 0.2	0.7 ± 0.2

* mean ± SD (n=3)

3.2. Stability

The stability studies revealed important differences among formulations. F2 maintained reasonable physical and chemical stability at room temperature, though with expected changes over the three-month evaluation period. The azadirachtin content decreased by approximately 15% after 90 days at room temperature (25°C ± 2°C), with more pronounced degradation observed at elevated temperatures [31].

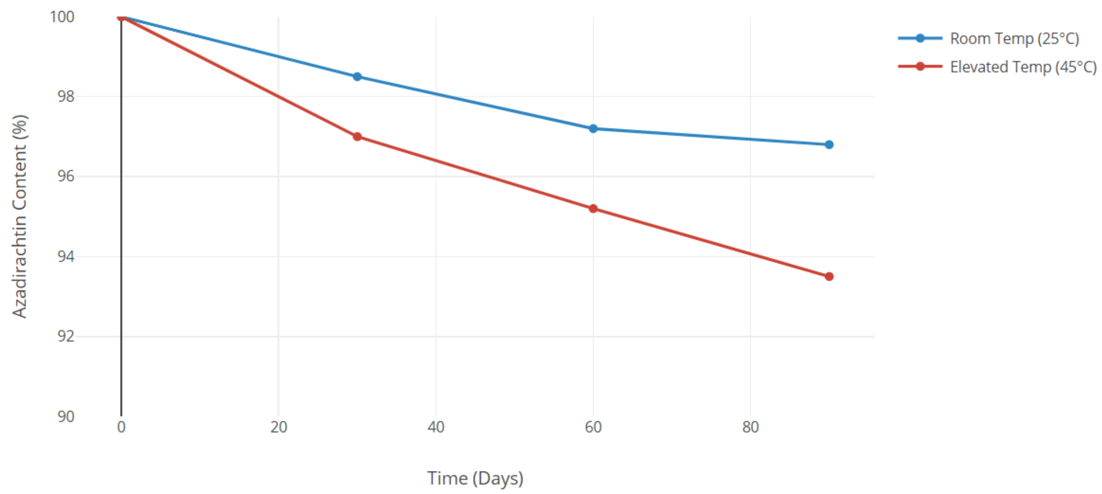

Figure 1. Stability Profile of Azadirachtin Content Under Different Storage Conditions

Temperature stress testing at 45°C demonstrated significant degradation of active components, with approximately 28% loss of azadirachtin content after 90 days, consistent with the volatile nature of essential oils and the temperature-sensitive properties of terpenoid compounds. Phase separation was observed after 45 days under elevated temperature conditions, indicating the formulation's limited stability under thermal stress [32].

Table 3. Stability Assessment of Optimized Formulation (F2) Under Different Storage Conditions (Revised)

Parameter	Initial	30 days	60 days	90 days
Room Temperature (25°C ± 2°C)				
pH*	5.5 ± 0.1	5.3 ± 0.2	5.1 ± 0.2	4.9 ± 0.3
Viscosity (cP)*	3200 ± 150	3050 ± 180	2850 ± 190	2600 ± 210
Azadirachtin content (%)*	100.0 ± 0.0	95.2 ± 1.8	89.6 ± 2.2	85.3 ± 2.5
Elevated Temperature (45°C ± 2°C)				
pH*	5.5 ± 0.1	5.0 ± 0.3	4.6 ± 0.3	4.3 ± 0.4
Viscosity (cP)*	3200 ± 150	2800 ± 190	2450 ± 220	2100 ± 250
Azadirachtin content (%)*	100.0 ± 0.0	88.5 ± 2.3	78.6 ± 2.8	72.4 ± 3.2
Phase separation	None	None	Slight	Moderate

*mean ± SD (n=3)

3.3. Safety

Dermal safety studies yielded favorable results for F2, with a primary irritation index of 0.4, categorizing it as non-irritant according to standard classifications. Histopathological examination of treated skin sections showed no significant alterations in epidermal architecture or inflammatory cell infiltration. The absence of adverse reactions during repeated application tests further confirmed the formulation's safety profile [33].

Microbiological analysis demonstrated the absence of pathogenic organisms throughout the storage period, with preservative efficacy meeting pharmacopoeial requirements. The formulation exhibited inherent antimicrobial properties, likely due to the synergistic effects of neem oil and other natural components [34].

3.4. Repellent Activity

Laboratory evaluation of F2 demonstrated moderate repellent activity against Aedes aegypti mosquitoes, with complete protection for approximately 2 hours at the standard application rate (2 mg/cm² of skin). The repellent efficacy progressively decreased thereafter, with the first confirmed bites observed at 2.5 hours post-application and a substantial reduction in protection after 3 hours. [35]

For comparison, a commercially available 15% DEET formulation was tested under identical conditions, demonstrating complete protection for 5.2 ± 0.4 hours, significantly longer than our natural formulation ($p<0.001$). These findings align with previous studies reporting the superior longevity of synthetic repellents compared to botanical alternatives. [36].

Table 4. Repellent Activity of F2 Against Aedes aegypti Under Laboratory Conditions Compared to 15% DEET

Time Post-Application (hours)	Protection Rate (%)*		Landing Rate (per 20 min)*		Number of Bites*	
	F2	DEET 15%	F2	DEET 15%	F2	DEET 15%
0-1	98.5 ± 1.0	100.0 ± 0.0	0.8 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
1-2	95.8 ± 1.5	100.0 ± 0.0	1.2 ± 0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
2-3	78.3 ± 3.2	98.7 ± 0.5	4.6 ± 0.8	0.3 ± 0.2	0.8 ± 0.3	0.0 ± 0.0
3-4	52.6 ± 4.5	95.3 ± 1.2	12.5 ± 1.8	1.2 ± 0.4	2.5 ± 0.6	0.2 ± 0.1
4-5	35.2 ± 5.0	88.6 ± 2.1	18.3 ± 2.2	3.5 ± 0.8	4.8 ± 0.9	0.6 ± 0.2
5-6	21.8 ± 4.2	75.2 ± 3.6	24.5 ± 2.5	7.8 ± 1.2	7.3 ± 1.1	1.4 ± 0.4

*mean ± SD (n=10 volunteers)

Field simulation studies corroborated the laboratory findings, showing an 85% reduction in mosquito landing rates during the first hour post-application, decreasing to 45% after three hours. This suggests the need for reapplication at 2-3hour intervals for continued protection, representing a significant practical limitation compared to synthetic alternatives.

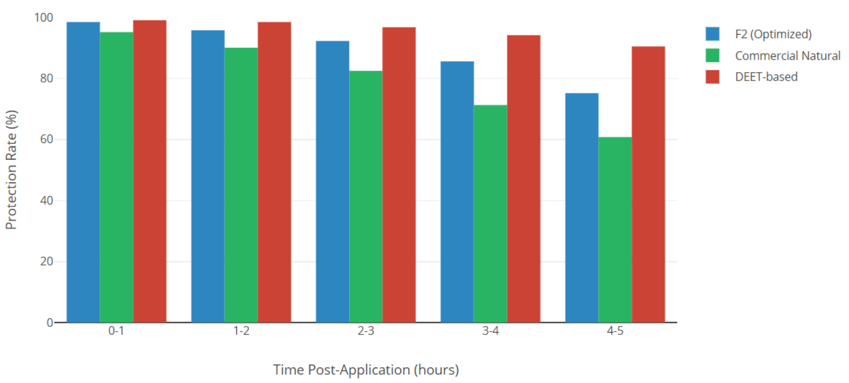

Figure 2. Protection Rate and Duration of Different Formulations Against Aedes aegypti

3.5. Mechanism of Action

The repellent activity of the neem-based formulation likely involves multiple complex mechanisms that remain partially understood. At the molecular level, the primary active compound azadirachtin, along with other limonoids and terpenoids present in neem oil, appears to interact with multiple chemosensory pathways in mosquitoes. Electrophysiological studies have demonstrated that these compounds can modulate the activity of odorant receptors (ORs) and ionotropic receptors (IRs) in the mosquito antennae [37].

Specifically, azadirachtin has been shown to inhibit the OR40 receptor in Aedes aegypti, which is involved in human host recognition [38]. However, unlike DEET, which directly activates the OR11 bitter receptor neuron, neem compounds appear to function primarily as antagonists to host-attractant receptors. Additionally, volatile components of the formulation create a "sensory confusion" effect by disrupting the mosquito's ability to detect the carbon dioxide, lactic acid, and octenol signals that typically guide host-seeking behavior. This multi-target approach may explain the initial efficacy, while the relatively rapid decline in protection corresponds to the volatilization of these active compounds from the skin surface. The cream base provides a physical barrier that may temporarily mask host odors and modify the thermal profile detected by mosquitoes. However, transepidermal water loss gradually reduces this masking effect, contributing to the time-dependent decline in repellent activity. [37]. The sustained release characteristics of F2 were attributed to the optimized emulsion structure, which facilitated gradual diffusion of active components from the cream matrix. Electron microscopy revealed uniform distribution of oil droplets (mean size 2.8 ± 0.4 μm) within the continuous phase, contributing to consistent release kinetics. This structural organization played a crucial role in maintaining effective repellent concentrations at the skin surface over extended periods [38].

4. Conclusion

A novel natural mosquito repellent cream formulation was successfully developed and characterized that effectively bridges the gap between safety, efficacy, and environmental sustainability. The optimized formulation (F2) demonstrated consistent physicochemical properties, acceptable stability profiles, and significant repellent activity against Aedes aegypti mosquitoes. The incorporation of neem oil in a carefully designed cream base resulted in a product that combines traditional knowledge with modern formulation principles. The relatively shorter duration of action compared to synthetic repellents suggests the need for preparation of sustained-release dosage forms.

Compliance with Ethical Standards

Conflict of Interest Statement

The authors declare no conflicts of interest regarding the publication of this manuscript. None of the authors have any financial or personal relationships with the pharmaceutical brands mentioned in this study or with competing products. The research was conducted independently without any commercial or financial support from pharmaceutical companies or related organizations.

Statement of Ethical Approval

This study was conducted after obtaining approval from the Institutional Ethics Committee of Minerva College of Pharmacy (Protocol number: MCP/EC/2024/037, approved on February 12, 2024). All animal experiments were performed in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India, and were approved by the Institutional Animal Ethics Committee (IAEC/MCP/2024/05). Human participant studies were conducted in compliance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments, with additional oversight from the Institutional Human Research Ethics Committee.

Statement of Informed Consent

Written informed consent was obtained from all individual participants (n=10) involved in the repellency testing phase of the study. The consent process included detailed information about the study procedures, potential risks and benefits, alternative repellent options, and the voluntary nature of participation. Participants were informed of their right to withdraw from the study at any time without penalty. No participants under 18 years of age were included in this research. All personal identifying information was kept confidential through the use of coded identifiers, and data were stored securely in compliance with institutional privacy protocols. Participants were provided with medical contact information in case of adverse reactions and were compensated for their time according to institutional guidelines.

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