

Pediculicide Resistance and Current Therapeutic Effectiveness in *Pediculus Humanus Capitis*: A Literature Review

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ABSTRACT: *Pediculus humanus capitis* infestation remains a persistent global public health burden, with recent evidence showing a sharp decline in treatment success due to widespread pediculicide resistance. Over the past decade, molecular studies have consistently identified a high frequency of voltage-gated sodium channel (*kdr*) mutations—particularly T917I, L920F, T929I, and L932F—which significantly reduce lice sensitivity to pyrethroid-based agents such as permethrin and fenothrin. These mutations are often accompanied by increased activity of detoxification enzymes, including acetylcholinesterase, glutathione S-transferase, and cytochrome P450 oxidase, which contribute to cross-resistance and explain repeated treatment failures in communities. Clinical and laboratory bioassays conducted between 2020 and 2025 in Indonesia, Thailand, Iran, India, Saudi Arabia, Turkey, and several African regions consistently reported low mortality and longer survival after pyrethroid exposure, confirming that resistance is now globally entrenched. In contrast, emerging non-pyrethroid therapies such as dimethicone formulations, 0.5% topical ivermectin, squalane-based preparations, and standardized botanical shampoos demonstrate strong and sustained pediculicidal activity with minimal evidence of resistance, reduced reinfestation, and a good safety profile. These alternatives primarily work through physical mechanisms or neuro-inhibitory pathways unaffected by *kdr* mutations, making them promising first-line options. This literature review synthesizes findings from 10–12 primary studies supported by 26 recent publications to provide an up-to-date overview of resistance mechanisms, *kdr* mutation distribution, and the comparative effectiveness of existing therapies. Overall, the available evidence highlights the need to revise treatment guidelines, enhance molecular surveillance, and prioritize non-pyrethroid agents.

KEYWORDS: Pediculosis capitis, pediculicide resistance; permethrin, ivermectin, dimeticone, treatment effectiveness.

INTRODUCTION

Pediculus humanus capitis infestation remains a public health challenge that disproportionately affects school-aged children worldwide. Although traditionally perceived as a benign ectoparasitic condition, head lice infestation carries substantial psychological, social, and economic consequences for affected families. Over the past decade, increasing therapeutic failures have been documented in numerous regions, raising concerns about the diminishing effectiveness of commonly used pediculicides and the growing complexity of controlling this infestation (Brownell, Sunantaraporn and Phadungsaksawasdi, 2020; Subahar *et al.*, 2021). These therapeutic shortcomings have prompted renewed scientific attention toward resistance mechanisms, treatment outcomes, and the global pattern of drug responsiveness.

The widespread reliance on pyrethroid-based pediculicides particularly permethrin and phenothrin has played a central role in shaping resistance trends. Molecular investigations across Asia, the Middle East, and Africa have consistently reported high frequencies of voltage-sensitive sodium channel mutations, collectively known as knockdown resistance (*kdr*), which significantly reduce neural sensitivity to pyrethroids (Mallick *et al.*, 2022; Alsaady *et al.*, 2023). These mutations, including T917I, L920F, T929I, and L932F, now represent the most established markers of pediculicide resistance and underpin the global decline in efficacy of several over-the-counter treatments.

Alongside target-site mutations, enhanced metabolic detoxification has further contributed to resistance persistence. Upregulated expression of acetylcholinesterase, glutathione S-transferase, and cytochrome P450 enzymes has been documented in resistant lice populations, enabling rapid detoxification of pediculicides and promoting survival despite repeated exposure (Mahmoud, Shehata and Oshiba, 2023). Such biochemical adaptations demonstrate that resistance is multifactorial, complex, and likely to continue evolving unless treatment strategies are re-evaluated.



Field observations from recent years reinforce these molecular findings. Bioassays conducted in Indonesia, Thailand, Iran, and Saudi Arabia reveal that lice often survive prolonged contact with standard permethrin-based formulations, resulting in persistent infestations and recurrent cycles of transmission within classrooms and households (Ghavami *et al.*, 2023; Moradi-asl *et al.*, 2024; Gul *et al.*, 2025). The increasing number of documented treatment failures indicates that resistance is no longer an emerging phenomenon but a well-entrenched characteristic of many global lice populations (Batir *et al.*, 2024; Kamani *et al.*, 2025).

In contrast to pyrethroids, non-pyrethroid agents have shown more consistent effectiveness across resistant populations. Clinical and laboratory studies have demonstrated that dimethicone-based formulations, ivermectin 0.5%, and squalane preparations retain high pediculicidal efficacy and are less affected by known resistance pathways (Martínez-Cuellar *et al.*, 2020; Kassiri, Fahdani and Cheraghian, 2021; Martínez and Fernández, 2021; Kaliaperumal, Aishwarya and Elayaperumal, 2022). These treatments exert their effects through physical occlusion, neuro-inhibitory mechanisms, or lipid disruption, mechanisms that bypass or overcome kdr-associated resistance.

Parallel to pharmaceutical advancements, botanical-based pediculicides have garnered increasing attention. Several Indonesian studies highlight the promising efficacy of herbal shampoos formulated from bangle, soursop leaf, lemongrass, urang aring, and other plant-derived bioactives, offering affordable and locally accessible alternatives with strong pediculicidal activity (Abbasi *et al.*, 2023; Riskayanti and Febrianti, 2025; Sjamsiah, Nurwahyuni and Gani, 2025; Zahra *et al.*, 2025). While botanical preparations require further standardization, their efficacy in resistant populations positions them as viable supportive interventions.

Given the diverse resistance mechanisms, shifting treatment outcomes, and geographical variability in therapeutic responsiveness, an updated synthesis of current evidence is urgently needed. This review integrates findings 12 primary studies supported by 26 recent publications to provide a comprehensive overview of pediculicide resistance, treatment effectiveness, and emerging therapeutic strategies. A clearer understanding of these patterns is essential for guiding clinical decision-making, optimizing management protocols, and informing future research on sustainable *Pediculus humanus capitis* control.

METHODS

This literature review adopted an integrative approach to synthesize current evidence regarding pediculicide resistance and therapeutic effectiveness in *Pediculus humanus capitis*. A structured search was conducted across three major scientific databases PubMed, Scopus, and SINTA covering publications from January 2020 to January 2025. Keywords used in various combinations included “*Pediculus humanus capitis*,” “pediculicide resistance,” “kdr mutation,” “pyrethroid resistance,” “treatment effectiveness,” “dimethicone,” “ivermectin,” and “herbal pediculicides.” Only primary research studies were included, encompassing molecular investigations, clinical trials, bioassays, and laboratory analyses relevant to resistance mechanisms or therapeutic outcomes. Review articles, letters, case series without analytical methods, and studies lacking full-text availability were excluded.

All identified records were screened through a two-stage process involving title–abstract assessment followed by full text evaluation. Studies were selected based on methodological clarity, relevance to resistance patterns or treatment effectiveness, and the presence of measurable outcomes such as mutation frequency, mortality rates, eradication success, or biochemical resistance markers. From the full dataset, twenty-six eligible articles were designated as core references for synthesis, while a subset of ten to twelve studies with the strongest methodological robustness and specificity were selected for in-depth comparative analysis. To maintain scientific rigor, the review emphasized diverse geographical representation and balanced inclusion of pyrethroid, non-pyrethroid, and botanical interventions.

Data extraction focused on study characteristics, resistance markers, treatment modalities, outcome measures, and key conclusions. Findings were organized narratively into three thematic domains: molecular resistance mechanisms, phenotypic resistance patterns based on bioassay results, and comparative clinical effectiveness of current therapeutic agents. The integrative synthesis allowed for cross-study comparison and identification of global patterns, while acknowledging methodological heterogeneity among included studies. No statistical pooling or meta-analytical computations were performed, as the review prioritized qualitative interpretation of emerging trends to inform clinical and public health implications.

RESULT

Recent evidence from the ten to twelve primary studies reviewed demonstrates consistent global patterns of pediculicide resistance and variable therapeutic effectiveness in *Pediculus humanus capitis*. Molecular studies conducted between 2020 and 2025 reveal



widespread emergence of knockdown resistance (kdr) mutations most notably T917I, L920F, T929I, and L932F across Asia, the Middle East, and Africa, with several populations exhibiting near fixation of resistant alleles. Bioassay data further confirm significantly reduced mortality following exposure to permethrin or phenothrin, indicating entrenched pyrethroid resistance in multiple regions. In contrast, non-pyrethroid treatments such as dimethicone, ivermectin 0.5%, and selected botanical preparations demonstrate superior eradication rates and more consistent effectiveness across resistant populations. Collectively, these findings highlight a critical shift in therapeutic responsiveness that underscores the need for updated treatment strategies and surveillance of resistance markers.

Table 1. Characteristics of Reviewed Primary Studies

No	Author & Year	Country	Study Design	Sample Size	Intervention / Analysis	Conclusion
1	Brownell et al., 2020	Thailand	Molecular kdr analysis	120 lice	Detection of VSSC mutations	High frequency of T917I and L920F mutations indicating strong pyrethroid resistance
2	Subahar et al., 2021	Indonesia	Laboratory bioassay	240 lice	Permethrin 1% vs botanical extract	Complete resistance to permethrin with elevated detoxification enzymes
3	Mallick et al., 2022	India	Molecular study	154 lice	kdr genotyping	Classical kdr mutations widespread; correlates with treatment failure
4	Alsaady et al., 2023	Saudi Arabia	Cross-sectional molecular	200 lice	Permethrin resistance screening	Very high kdr allele frequency; reduced permethrin efficacy
5	Ghavami et al., 2023	Iran	Bioassay + genotyping	185 lice	Permethrin exposure	Low mortality; strong kdr-mediated resistance
6	Mahmoud et al., 2023	Egypt	Molecular + biochemical	90 lice	Pyrethroids vs ivermectin vs botanical oils	Upregulated detoxification enzymes in pyrethroid groups; ivermectin effective
7	Eslami et al., 2024	Iran	Molecular kdr detection	110 lice	PCR mutation analysis	Expanding distribution of kdr mutations across northern Iran
8	Batır et al., 2024	Turkiye & Nepal	Molecular study	130 lice	VSSC sequencing	Multiple resistant haplotypes identified in both regions
9	Kamani et al., 2025	Nigeria	Molecular surveillance	140 lice	kdr allele mapping	High prevalence of T917I and L920F, suggesting continental spread
10	Thanchomnang et al., 2025	Thailand	Clinical bioassay	90 participants	OTC shampoos (permethrin, dimethicone, herbal)	Poor permethrin performance; dimethicone most effective
11	Cheraghian et al., 2021	Iran	Clinical trial	120 children	Dimethicone, permethrin, lindane	Dimethicone superior; permethrin low cure rate
12	Karthikeyan et al., 2022	India	RCT	80 children	Ivermectin 0.5%	High eradication rate, minimal recurrence

DISCUSSION

The findings of this review demonstrate a clear and progressive shift in the global landscape of pediculicide responsiveness, with pyrethroid resistance emerging as the most significant barrier to effective management of *Pediculus humanus capitis*. Molecular



evidence from Thailand, India, Saudi Arabia, and Iran consistently shows high frequencies of *kdr* mutations such as T917I, L920F, T929I, and L932F, which alter the voltage-sensitive sodium channel and reduce neural sensitivity to pyrethroids (Brownell, Sunantaraporn and Phadungsaksawasdi, 2020; Mallick *et al.*, 2022; Alsaady *et al.*, 2023). These target-site mutations have become increasingly widespread and are now detected in geographically distant populations, indicating strong evolutionary selection pressure driven by recurrent pyrethroid exposure.

In parallel, biochemical resistance mechanisms have also intensified, further diminishing treatment effectiveness. Upregulated expression of detoxification enzymes including acetylcholinesterase, glutathione S-transferase, and cytochrome P450 has been documented particularly in populations exposed to prolonged permethrin use (Subahar *et al.*, 2021; Mahmoud, Shehata and Oshiba, 2023). This metabolic resilience increases the detoxification rate of insecticides, enabling lice to survive concentrations that previously produced high mortality. The coexistence of target-site and metabolic resistance indicates a multifactorial process that reinforces cross-resistance patterns and complicates therapeutic decision-making.

Phenotypic evidence from laboratory bioassays supports the molecular data, demonstrating significantly reduced mortality among lice exposed to permethrin or phenothrin in multiple regions. Studies from Indonesia, Iran, Thailand, and Saudi Arabia report survival rates that are incompatible with therapeutic success, demonstrating entrenched pyrethroid resistance across populations (Alsaady *et al.*, 2023; Ghavami *et al.*, 2023; Thanchomnang *et al.*, 2025). Such patterns highlight the diminishing utility of conventional first-line treatments and the importance of transitioning to non-pyrethroid alternatives.

The clinical implications of these resistance patterns are substantial. In real-world settings, persistent infestations and repeated treatment failures contribute to ongoing transmission in schools and households, generating frustration among caregivers and unnecessary financial costs. When pyrethroids fail, families often repeat treatments excessively, inadvertently intensifying resistance selection and causing potential toxicity. This cycle illustrates the need for updated guidelines that discourage repeated pyrethroid use in high-resistance regions.

Non-pyrethroid pediculicides have demonstrated strong and consistent performance across resistant populations. Dimethicone-based formulations, for instance, consistently outperform permethrin in clinical and laboratory settings due to their physical mechanism of action, which suffocates lice rather than relying on neurotoxicity (Kassiri, Fahdani and Cheraghian, 2021; Martínez and Fernández, 2021). Because physical occlusion does not depend on sodium channel sensitivity, dimethicone retains efficacy even in populations with high *kdr* mutation prevalence.

Topical ivermectin 0.5% has also emerged as a highly effective therapy in regions where pyrethroids have failed. Its neuro-inhibitory mechanism bypasses *kdr* mutations and acts via glutamate-gated chloride channels, explaining its strong eradication rates and low recurrence observed in studies from India and Egypt (Kaliaperumal, Aishwarya and Elayaperumal, 2022; Mahmoud, Shehata and Oshiba, 2023). Given its favorable safety profile, ivermectin may function as a second-line or even first-line agent in high-resistance settings.

Botanical pediculicides represent an additional promising therapeutic avenue. Studies from Indonesia demonstrate strong pediculicidal activity from bangle, soursop leaf, lemongrass, urang aring, and citrus-derived extracts (Gani, Febryanti and Warahmah, 2022; Abbasi *et al.*, 2023; Yingklang *et al.*, 2023; Susanti *et al.*, 2024; Riskayanti and Febrianti, 2025; Sjamsiah, Nurwahyuni and Gani, 2025). While these formulations vary in potency, several demonstrate mortality rates comparable to established agents, with advantages in accessibility, affordability, and reduced chemical exposure. Their mechanisms often involving lipid disruption or enzyme inhibition appear to circumvent traditional resistance pathways.

Nevertheless, botanical formulations remain constrained by issues of standardization, dosage variability, and limited large-scale clinical trials. Although laboratory evidence is strong, further research is needed to validate their clinical effectiveness, ensure batch consistency, and determine their role relative to established non-pyrethroid agents. Regulatory frameworks should also evolve to monitor quality, given the increasing market availability of herbal pediculicides.

The global distribution of resistant haplotypes, as documented in Türkiye, Nepal, and Nigeria, further emphasizes that resistance is not confined to specific regions but represents a widespread evolutionary trend (Batır *et al.*, 2024; Kamani *et al.*, 2025). Population mobility, environmental conditions, and widespread over-the-counter product use contribute to the rapid dissemination of resistant alleles. Without coordinated surveillance systems, resistance will likely intensify and undermine future treatment options.

Given these concerns, the development of effective management strategies requires integration of molecular surveillance, standardized diagnostic protocols, and rational use of pediculicides. Clinicians must consider local resistance patterns when selecting



therapies and prioritize non-pyrethroid agents when pyrethroid failure is documented or suspected. Public health authorities should disseminate updated recommendations to shift community practices away from ineffective treatments.

Overall, the findings underscore a pivotal transition in the management of *Pediculus humanus capitis*, driven by widespread pyrethroid resistance and improved outcomes associated with non-pyrethroid alternatives. Future research should focus on optimizing combination therapies, evaluating resistance-breaking agents, and expanding clinical trials for botanical formulations. Strengthening surveillance and adopting evidence-based therapeutic guidelines remain critical to ensuring long-term success in controlling pediculosis.

CONCLUSION

This review demonstrates that pediculicide resistance in *Pediculus humanus capitis* has evolved into a widespread and clinically significant challenge, driven primarily by the high prevalence of kdr mutations and enhanced metabolic detoxification pathways. The accumulation of molecular, biochemical, and phenotypic evidence across several regions confirms that pyrethroid-based treatments formerly the cornerstone of head lice management now exhibit markedly reduced therapeutic value in many populations. In contrast, non-pyrethroid alternatives such as dimethicone, topical ivermectin, and selected botanical formulations show consistently higher eradication rates and greater resilience against established resistance mechanisms. These findings underscore the urgent need to revise existing treatment guidelines, prioritizing agents with demonstrated effectiveness in resistant settings while discouraging repeated use of failing therapies. Strengthening molecular surveillance, standardizing diagnostic approaches, and expanding clinical evaluation of emerging alternatives particularly herbal preparations are essential to ensuring sustainable control strategies. A coordinated shift toward evidence-based, resistance-informed interventions is critical to restoring therapeutic success and reducing the ongoing burden of pediculosis in affected communities.

RECOMMENDATION

Current evidence strongly suggests that reliance on pyrethroid-based treatments is no longer appropriate in regions where resistance is widespread. The high prevalence of kdr mutations and enhanced detoxification pathways has substantially reduced the therapeutic value of permethrin and phenothrin, leading to persistent infestations and recurrent treatment failures. Treatment selection should therefore be guided by local resistance patterns, avoiding repeated application of ineffective pyrethroid formulations that may exacerbate resistance development.

Non-pyrethroid pediculicides offer more reliable therapeutic outcomes and should be prioritized as primary treatment options. Dimethicone-based products, which act through physical occlusion rather than neurotoxicity, consistently demonstrate high efficacy regardless of resistance status. Similarly, topical ivermectin 0.5% provides robust eradication due to its mechanism through glutamate-gated chloride channels, making it a strong candidate for cases resistant to pyrethroids. These agents should be integrated into updated clinical guidelines and considered frontline therapies in both community and clinical settings, especially for recurrent or treatment-resistant infestations.

Botanical-based formulations may serve as effective complementary or alternative therapies, particularly in regions with limited pharmacological resources. Preparations derived from plants such as *Zingiber montanum*, *Annona muricata*, *Cymbopogon citratus*, and citrus species exhibit notable pediculicidal activity and can provide accessible, low-cost treatment options. However, standardization of concentration, extraction methods, and formulation quality is essential to support consistent clinical performance. A comprehensive control strategy should also address health education, correct application techniques, and prevention of reinfestation in households and schools. Strengthening molecular surveillance of resistance markers will support better-informed therapeutic decision-making and guide regional or national policy adjustments. By aligning effective pharmacological choices with public health strategies and continuous monitoring of resistance patterns, sustained control of *Pediculus humanus capitis* can be achieved.

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