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Advancements in Arthropod Repellent Strategies for Public Health

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ABSTRACT:

Arthropod bites pose a substantial risk to human health, potentially causing infectious or inflammatory effects and transmitting severe diseases such as malaria, Chikungunya and dengue. Minimizing human-mosquito contact is essential to prevent disease transmission. Understanding the history of Insect Repellents (IRs) informs the development of effective modern strategies. DEET, botanicals, and citronella are vital ingredients in existing IRs, with DEET being the primary and widely used repellent for over six decades. Additionally, the Environmental Protection Agency (EPA) has approved various IR ingredients for topical use due to their low toxicity and effectiveness. Despite extensive global efforts, finding absolute preventive measures against arthropod bites remains challenging. Appreciating how repellents impact olfactory and gustatory processes lays the groundwork for enhancing existing repellents and uncovering novel compounds. The present review presents the latest information on repellents, including recent discoveries and areas that require attention, such as novel formulations, aiming to advance scientific knowledge in this field.

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Introduction

Mosquitoes, known for transmitting various diseases, can cause infections, allergic reactions, and other health concerns upon biting, threatening humans and livestock [1]. The ability of mosquitos to transmit diseases like malaria, dengue, and Zika virus has elevated the importance of effective preventive measures [2,3]. Preventive strategies against mosquito, black fly, and tick bites include using skin-based insect repellents (IRs), protective clothing, and limiting outdoor activities during peak biting times. However, the persistent use of synthetic insecticides has led to resistance and environmental concerns, prompting a shift toward environmentally safe control methods and the study of alternative repellents [4,5]. This comprehensive review examines repellents' historical, current, and future use for personal protection against mosquito-borne diseases.

History

Historically, various insect repellents (IRs) like tars, smoke, and plant oils have been used. The discovery of citronella oil in 1901 was a significant breakthrough, although its effectiveness has diminished over time, offering only 20 to 30 minutes of limited protection. In 1946, the US Department of Agriculture introduced N, N-Diethyl-3-Methylbenzamide (DEET), which revolutionized the field, becoming the most widely used and potent IR due to its capability to create a repellent vapor barrier with an unpleasant scent and taste [6].

Classification of Repellents

Repellents are grouped based on insect behavior into five categories: (a) true repellents that deter insects without direct contact; (b) contact irritants repellents, prompting insects to withdraw upon contact; (c) deterrents, preventing specific behaviors like blood-feeding or ovipositional; (d) odor maskers, diminishing host appeal or disrupting host localization through odors; and (e) visual maskers, interfering with visual cues to impede insect host localization [5].

Efficacy of Repellent:

Several factors impact the efficacy of repellents, including type, environmental conditions, inherent properties, application method, and individual susceptibility to insects [7]. The effectiveness against mosquitoes depends on the delivery rate, evaporation rate, and the ability to induce repellent behavior [8]. Ideal repellents release volatiles within the boiling point range of 230-260°C to ensure sustained performance [6]. Evaluating repellent efficacy involves assessing protection time and levels across mosquito species [9]. External factors like temperature, humidity, and wind speed can affect longevity and necessitate frequent reapplication, especially in warm, humid climates with high winds [10].

Desirable Attributes of an Effective Repellent

An ideal insect repellent should provide prolonged protection against various arthropods without causing toxic reactions [11]. It should also exhibit chemical stability, a pleasant or odorless scent, non-irritating properties, inertness, cost-effectiveness, and leave no residues [12,13]. These requirements are incorporated into diverse anti-mosquito formulations like sprays, creams, lotions, aerosols, oils, evaporators, patches, and canisters to meet usability standards, including vapor pressure, safety, smell, and solubility.

Botanical Fumes

Derived from ancient practices, repellents have evolved from plant-based smoke and extracts to formulations with single active ingredients designed to repel or eliminate insects. Smoke, frequently generated from burned plants in rural tropical regions, has been used to repel mosquitoes for a long time [14]. Citronella oil and other plant-based solutions were the primary choices for mosquito repellents before World War II [15].

Initial synthetic repellents

Post-World War II, synthetic repellents gained prominence, including chemicals like Dimethyl Phthalate (DMP), discovered in 1929, Indalone® (Butyl-3,3-dihydro-2,2-dimethyl-4-oxo-2H-Pyran-6-Carboxylate) in 1937, and Rutgers 612 (Ethyl Hexanediol) from 1939. A combination of these products (6-2-2 of M-250) was subsequently developed for military use [8].

Dimethyl Phthalate (DMP)

From 1940 to 1980, DMP was extensively used as a broad-spectrum repellent, especially in China, before being replaced by Quwenling (PMD; Para-Menthane-3,8-Diol), which became the standard in India until the advent of DEPA (N, N-Diethylphenyl Acetamide) [8]. However, due to its reduced effectiveness, DMP is no longer used as a repellent [16].

Indalone

Indalone (butyl 3,4-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylate) showed potent repellent properties against mosquitoes and ticks, initially perceived as more effective than DEET, but some studies revealed its inefficacy [17]. Classified as a gustatory or contact repellent because of its low volatility, Indalone was considered safe for use on clothing or directly on the skin [18].

Rutgers 612

Like DMP, Rutgers 612 (2-ethyl-1,3-hexanediol) was initially developed as a solvent and added to different

repellent formulations [6]. While Rutgers 612 is effective against mosquitoes, information on its efficacy against other arthropods is limited [19]. Despite being marketed as a black fly repellent in the US and Canada, it was discontinued in 1991 due to observed toxicity in laboratory animals.

DEET

Synthetic repellents, initially vital for safeguarding military personnel, were superseded by DEET (N, N-Diethyl-Meta-Toluamide/N, N-Diethyl-3-Methylbenzamide) in 1946, establishing itself as the standard for arthropod repellents [17]. Studies have proposed two hypotheses on the receptors and molecular mechanisms underlying DEET repellency: activation of ionotropic receptor Ir40a and odorant receptor(s) pathway mediating non-contact DEET repellency [20]. As both a repellent and antifeedant upon contact, DEET forms a vapor barrier that repels insects through its offensive odor and taste [6]. Despite its effectiveness against various arthropods, its use is restricted due to high cost, unpleasant odor, and the need for frequent, high-concentration applications [5]. Reports of DEET resistance in mosquitoes and flies have emerged, raising concerns about its potential damage to specific fabrics and materials [21].

Nevertheless, the Environmental Protection Agency (EPA - US) has deemed DEET safe for cotton, wool, and nylon use. Caution is advised when using DEET alongside certain topical retinoid or sunscreen products, as it can enhance systemic absorption and increase toxicity [22]. Despite its six-decade dominance, newer ingredients with improved characteristics may eventually surpass DEET's popularity in the future.

Permethrin

Derived from Chrysanthemum cinerariifolium, permethrin, a synthetic pyrethroid insecticide, offers superior tick protection compared to DEET [23, 24]. Registered as a repellent and insecticide in the US since 1979, it is commonly applied to fabrics like clothing and bed nets, acting as both a contact insecticide via neural toxicity and an insect repellent [25]. Permethrin hinders sodium ion movement into nerve cells, inducing paralysis in various arthropods, effectively safeguarding against mosquitoes, ticks, sand flies, tsetse flies, chigger mites, fleas, lice, and kissing bugs [26]. Its use in mosquito nets has notably reduced disease-related morbidity and mortality in tropical regions [27]. Though permethrin-treated clothing is a crucial method for arthropod protection, potential neurotoxic side effects are rarely reported [28].

Picaridin

To counter increased DEET resistance, Picaridin, an odorless piperidine analog introduced by Bayer in the 1980s, serves as an alternative known as KBR 3023, Icaridin, and Bayrepel TM [14, 29]. Its precise mode of action remains uncertain, but it is believed to deter biting by creating a vapor barrier akin to DEET, targeting the odorant receptor CquiOR136 in arthropod vectors [20]. Offering efficacy comparable to DEET, a 20% picaridin spray provides superior protection with lower dermatologic and olfactory irritation and a non-greasy feel [30,31]. Unlike DEET, Picaridin does not harm plastics or synthetic materials, making it an appealing option for combatting vector-borne diseases in endemic regions [32]. In 2000, the World Health Organization endorsed Picaridin for its safety, effectiveness, and cosmetic properties, noting its potential superiority to DEET under specific conditions [33].

DEPA

DEPA (N, N-Diethyl-2-Phenyl-Acetamide), a cost-effective multi-insect repellent synthesized by Kalyansundaram in 1982, has regained popularity in developing countries due to its affordability compared to DEET [14]. It is a practical option in regions like India, where DEET production components are scarce [34]. While the specific olfactory receptors activated by DEPA remain largely unknown, it is believed to trigger irritation in insect antennal senses [35]. DEPA demonstrates no cytotoxicity or mutagenicity, making it suitable for direct skin application [36,37]. Additionally, acute and subacute inhalation toxicity studies suggest its potential in aerosol formulations [38].

Plant-Based Repellents

Exploration of natural mosquito repellents has increased, although their commercialization remains limited [39]. Lemon eucalyptus, soybean oil, cinnamon oil, clove oil, rose merry oil, and geraniol are botanical alternatives offering safety advantages over non-biodegradable compounds like DEET [40]. Glyceridic oils from various plant fruits, including castor, mustard, neem, margosa,

olive, and soybean, exhibit individual repellent activity against mosquitoes, tested topically and in burned sticks. Mosquitoes have shown sensitivity to free long-chain fatty acids. Recent research found that combining free fatty acids from coconut oil demonstrated robust and lasting repellency against blood-sucking insects, surpassing DEET's effectiveness. Synergistic effects were observed, with the combined free fatty acids showing superior repellent activity compared to individual components. Plant extracts such as Zanthoxylum limonella, Citrus aurantifolia, and Artemisia vulgaris display significant repellent activity against mosquitoes. Still, challenges like extraction costs, low compound yields, and potential contact dermatitis may limit their widespread use [14, 40].

Neem

Neem oil's limonoids act as potent insect growth inhibitors. Azadirachtin, a highly oxidized triterpenoid and an essential active compound of neem extract, is present in higher concentrations (0.2–0.6%) in neem seeds than in other parts of the tree [41]. It disrupts insect hormone balance by interfering with the endocrine system, constituting its primary mode of action [42].

Pyrethrum

Pyrethrum, an insecticide derived from Tanacetumcinerariifolium flower heads, contains six active ingredients from esters of chrysanthemic acid (pyrethrin I, cinerin I, and jasmolin I) and esters of pyrethric acid (pyrethrin II, cinerin II, and jasmolin II) [43]. These compounds act on the insect nervous system by blocking voltage-gated sodium channels in nerve axons, resulting in hyperactivity and convulsions, producing a rapid knockdown effect [44].

Alkaloids

Alkaloids, nitrogen-containing natural products found in bacteria, fungi, animals, and plants, are frequently used in traditional insect repellents [45]. They act through various modes, disrupting essential cellular and physiological functions by affecting AChE receptors in the nervous system, regulating hormonal activity, and inducing toxicity [46].

Flavanoids

Flavonoids exhibit larvicidal activity by inhibiting AChE in mosquito larvae and can further act as respiratory inhibitors, disrupting the larval respiratory system [47].

Garlic

Garlic is recognized for its potential as a mosquito repellent, although conclusive evidence supporting its systemic efficacy is limited [48]. The shift from natural source-based to synthetic production of arthropod repellents has facilitated the extraction of highly pure active compounds, exemplified by substances like P-Menthane-3,8-Diol (PMD) and insect repellent 3535 (IR3535), representing a contemporary trend [8,32].

PMD

PMD (P-Menthane-3, 8-Diol) gained notable recognition in commercial US repellents after its registration by the US EPA. It was endorsed by the US CDC in 2005 as highly effective against mosquitoes and ticks, alongside Picaridin and DEET [30,49]. Derived from C. citriodora, the essential oil exhibits significant repellent properties against mosquitoes and ticks, providing extended protection due to its low volatility as a monoterpene [50,51]. While the specific mechanism behind its repellency remains unknown, its interaction with the odorant receptor CquiOR136 in Culex quinquefasciatus has been suggested [20]. PMD boasts an excellent safety profile and minimal toxicity, such as eye irritation [52].

IR 3535

Insect repellent 3535 (Ethyl 3-[acetyl(butyl)amino]-propanoate), known as IR 3535 or Merck 3535, shares structural similarities with beta-alanine, developed by Merck in 1970 [53]. Registered as a biopesticide by the US EPA, it effectively repels various insects, including mosquitoes and ticks, although its specific mode of action is still under investigation [54]. One hypothesis suggests it functions similarly to DEET, utilizing the odorant receptor CquiOR136 in the southern house mosquito Culex quinquefasciatus [20]. Offering protection comparable to DEET, IR

3535 requires reapplication every 6–8 hours, causing less irritation to mucous membranes and exhibiting safer oral and dermal toxicity than DEET.

Newer Generations

Balancing investment recovery with product affordability is challenging, as repellents are hypothesized to primarily act through sophisticated olfactory systems in mosquitoes, involving hundreds of receptor proteins from the ionotropic receptor (Ir), odorant receptor (Or), and gustatory receptor (Gr) families [55].

Olfactory receptor proteins

Recent research emphasizes the olfactory binding protein (OBP) as a critical target in the search for the next generation of insect repellents (IRs), disrupting the mosquito's olfactory pathway and potentially reducing mosquito bites. Hallem has examined human-specific odorants, particularly the protein Or1 in Anopheles gambiae, which binds to human sweat components. Targeting OBP offers an efficient airborne repellent release approach, eliminating the need for direct skin application and facilitating broader protection across larger areas. Recent advances in molecular and computational tools have enabled detailed investigations into the mosquito olfactory system, resulting in several groundbreaking discoveries [56].

Anthranilate-based InsectRrepellents (ABIRs)

ABIRs, a new entomological group recognized as enhanced alternatives to DEET, were discovered via virtual chemical library screening. Four ABIRs—ethyl anthranilate, butyl anthranilate, methyl N, N-dimethyl anthranilate, and 2,3-Dimethyl-5-isobutyl-pyrazine—have shown potential as insect repellents, activating specific receptors and inducing avoidance behavior in Aedes aegypti mosquitoes while inhibiting their oviposition behavior. Unlike DEET, ABIRs have gained approval from the FDA, WHO, and EFSA, and they do not harm synthetic fabrics or surfaces, broadening their applications [57]. Incorporating novel ABIRs with other control measures, such as CO_2 masking and population control, indicates their potential in managing DEET-resistant strains [58,59]. Affordability, safety, and approval for human consumption make these DEET substitutes compelling options [57].

2,3-Dimethyl-5-Isobutyl-Pyrazine (DIP)

DIP, a new insect repellent, mimics ABIRs by targeting the Ir40a receptor proteins of the fruit fly Drosophila melanogaster, exhibiting repellency against Aedes aegypti mosquitoes [57,60]. Unlike DEET, DIP is not authorized for human use but offers the advantage of compatibility with synthetic fabrics, plastics, and diverse surfaces. Currently, DIP is undergoing assessment for its potential as a mosquito repellent for human application and in agricultural contexts.

4-Methylpiperidine (MP)

MP, a recent finding, exhibits potent repellent properties against fruit fly Drosophila melanogaster and Aedes aegypti mosquitoes by strongly targeting the Ir40a receptor proteins. Its unique chemical structure distinguishes it from DEET and other Ir40a receptor agonists like ABIRs and DIP. MP boasts a notably higher vapor pressure, extending its repellent effect over a larger spatial zone against hematophagous insects and fruit flies [61]. Although not suitable for direct human skin application, MP holds potential in identifying novel classes of Ir40a neuron activators, offering the prospect of developing repellents with enhanced spatial ranges and prolonged efficacy.

Methyl Jasmonate (MJ)

MJ, or Methyl jasmonate, shows tick aversion in various species, including nymphal I. ricinis and Hyalomma marginatum rufipes Koch [8]. The non-volatile jasmonic acid-derived MJ has recently displayed mosquito-repellent properties, notably against the southern house mosquito Culex quinquefasciatus, targeting the CquiOR136 receptor [20]. Further investigation into potential MJ receptors in other vectors presents a significant research and development opportunity.

Significance of Formulations of Mosquito Repellents

Despite significant advancements in insect-repellent research, controlling vector-borne diseases remains challenging primarily due to poor user compliance [62]. Prioritizing user compliance and acceptability in formulations can enhance mosquito repellents, potentially by using additional classes of volatile repellents, facilitating the creation of diverse formulations for various surfaces like clothes, bed nets, candles, and house entryways. Understanding the physicochemical properties and manufacturing conditions is critical in creating efficient and safe insect-repellent formulations [63]. Traditional burning coils offer long-lasting protection, while polymer-based controlled release formulations, such as nano and microcapsules, hydrogels, films, papers, and patches, are gaining traction due to their performance, low toxicity, and biodegradability [64]. These formulations ensure continuous release without electricity, improving safety profiles by minimizing dermal absorption and inhalation exposure [65]. High-throughput chemical informatics screening and a structure-activity approach have identified environmentally safe and cost-effective novel insect repellents that activate similar chemosensory pathways as DEET [57].

Conclusion and Prospective

Despite significant progress in repellent research and the availability of potential solutions, their limited utilization persists due to the incomplete understanding of insect chemical ecology and repellent mechanisms. With a growing focus on "green technologies," the future development and use of repellents are likely to be influenced. The scientific community must raise awareness and actively educate the public on effective and safe methods for personal protection to minimize adverse effects. Public perception significantly impacts repellent use and the spread of vector-borne diseases, underscoring its critical importance regardless of repellent effectiveness.

Conflicts of interest

The authors declare no conflicts associated with this work.

Abbreviations:
IR: Insect Repellent
DEET: N,N-Diethyl-3-Methylbenzamide
EPA: Environmental Protection Agency
US: United States
DMP: Dimethyl Phthalate
PMD: P-Menthane-3, 8-Diol
DEPA: N, N-Diethyl-2-Phenyl-Acetamide
KBR: All-Family Insect Repellent Aerosol Spray
CDC: Centers for Disease Control and Prevention
OBP: Olfactory Binding Protein
ABIR: Anthranilate-based InsectRrepellents
WHO: World Health Organization
FDA: Food and Drug Administration
EFSA: European Food Safety Authority (EFSA)
MP: Methylpiperidine
MJ: Methyl Jasmonate

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