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Phytochemistry, Efficacy and Safety Evaluation of Polyherbal Insect Repellent Formulations

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Abstract

Insect-borne diseases continue to impose a substantial global health burden, particularly in tropical and subtropical regions where vector exposure is persistent. Although synthetic repellents such as N,N-diethyl-meta-toluamide (DEET) and pyrethroids remain effective, concerns regarding dermal irritation, neurotoxicity, environmental persistence, and emerging insect resistance have accelerated interest in plant-based alternatives. Polyherbal insect repellent formulations, which combine multiple plant extracts or essential oils, represent a promising strategy for achieving broad-spectrum protection with improved safety and sustainability. This review critically examines the phytochemical foundations, mechanisms of action, efficacy, formulation advances, and safety considerations associated with polyherbal repellent systems. Key bioactive constituents include volatile terpenoids (e.g., citronellal, linalool, eucalyptol), phenolics, flavonoids, alkaloids, and limonoids, which collectively exert olfactory disruption, neurophysiological interference, anti-feeding, and anti-oviposition effects. Laboratory and in vitro studies commonly demonstrate protection levels ranging from 70% to 95%, with efficacy strongly influenced by phytochemical composition and delivery system. Recent innovations such as nano-emulsions, gels, sprays, and transdermal platforms have markedly enhanced stability, controlled release, and duration of repellency. Safety evaluations generally indicate low dermal toxicity, minimal sensitization, rapid biodegradability, and reduced ecological impact compared to conventional synthetic agents. Nevertheless, significant challenges persist, including variability in phytochemical profiles, lack of standardized extraction and quality control protocols, limited long-term clinical data, and regulatory ambiguity. Addressing these limitations through rigorous phytochemical characterization, harmonized testing methodologies, and controlled human studies is essential for the translation of polyherbal repellents into reliable public health tools. Overall, polyherbal formulations offer a scientifically credible, eco-friendly alternative for integrated vector management.

Keywords: Polyherbal formulations; Insect repellents; Essential oils; Phytochemicals; Nano-formulations

1. Introduction: Insect-borne diseases such as malaria, dengue, chikungunya, filariasis, leishmaniasis, and Japanese encephalitis remain major public health challenges, particularly in tropical and subtropical regions[1,2]. Chemical insect repellents such as DEET, permethrin, and synthetic pyrethroids are effective but are associated with adverse effects including skin irritation, neurotoxicity, environmental persistence, and insect resistance. These concerns have driven growing interest in plant-based and polyherbal insect repellent formulations, which are traditionally used, biodegradable, and generally considered safer[3].

Polyherbal formulations combine multiple plant extracts or essential oils to achieve broad-spectrum repellency, prolonged protection, and reduced toxicity. Advances in phytochemical characterization, bioassays, and formulation technologies have strengthened the scientific basis for these traditional preparations[4,5]. This review critically evaluates the phytochemical composition, repellent efficacy, mechanisms of action, formulation strategies, and safety aspects of polyherbal insect repellent systems.

2. Phytochemical Basis of Polyherbal Insect Repellents

Major Classes of Phytochemicals Involved: Polyherbal insect repellents derive activity from diverse secondary metabolites, which act synergistically to deter, confuse, or kill insects.

- **Terpenoids and Essential Oil Constituents:** Terpenoids constitute the most prominent group in herbal repellents. Monoterpenes and sesquiterpenes such as citronellal, citronellol, limonene, linalool, eucalyptol, camphor, thymol, carvacrol, and α-pinene are volatile compounds responsible for strong odor-mediated repellency. These compounds disrupt insect olfactory receptors, masking host-derived attractants such as carbon dioxide and lactic acid. Essential oils from *Cymbopogon spp.*, *Eucalyptus spp.*, *Ocimum spp.*, *Mentha spp.*, and *Thymus spp.* are particularly rich in terpenoids and form the backbone of many polyherbal formulations[6,7].
- **Phenolics and Flavonoids:** Phenolic acids and flavonoids contribute both repellent and insecticidal effects. Compounds such as quercetin, kaempferol, rutin, caffeic acid, and ferulic acid interfere with insect nervous signalling and act as feeding deterrents. Their antioxidant nature also stabilizes volatile oils in formulations, enhancing shelf life.

- **Alkaloids:** Certain alkaloids exhibit contact toxicity and behavioral repellency. Alkaloids from *Azadirachta indica* and *Piper spp.* affect insect growth, reproduction, and feeding behavior. In polyherbal combinations, alkaloids enhance long-term protective effects by acting as insect growth regulators[8].
- **Limonoids and Other Triterpenoids:** Limonoids such as azadirachtin play a pivotal role in polyherbal repellents. These compounds disrupt molting hormones, inhibit oviposition, and reduce larval viability. Though not highly volatile, they contribute sustained insect control when combined with essential oils[9].

Rationale for Polyherbal Combinations: Single-plant formulations often suffer from short duration of action due to rapid evaporation of volatile constituents. Polyherbal systems offer:

- Multi-target action (olfactory disruption + neurotoxicity + growth inhibition)
- Extended repellency duration
- Reduced concentration of individual oils, lowering irritation risk
- Broader efficacy against mosquitoes, flies, ticks, lice, and mites[8,10.]

Synergistic interactions among phytochemicals result in enhanced efficacy compared to mono-herbal preparations.

3. Efficacy Evaluation of Polyherbal Insect Repellent Formulations

3.1 In Vitro and Laboratory Bioassays

Efficacy is commonly assessed using:

- Arm-in-cage tests
- Landing and biting inhibition assays
- Olfactometer-based repellency studies
- Larvicidal and ovicidal assays

Polyherbal formulations have demonstrated 70–95% protection for periods ranging from 2 to 8 hours, depending on formulation type and plant composition[11].

3.2 Mechanisms of Repellent Action

- **Olfactory Receptor Disruption:** Insects rely heavily on a highly sensitive olfactory system to locate hosts, mates, and oviposition sites. Host-seeking behavior in mosquitoes and other vectors is primarily mediated by detection of carbon dioxide, lactic acid, ammonia, and skin-derived volatiles through specialized odorant receptors (ORs) and odorant-binding proteins (OBPs) present in antennal sensilla.

  Volatile terpenoids present in polyherbal insect repellents—such as citronellal, citronellol, limonene, linalool, eucalyptol, thymol, and carvacrol—interfere with this

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chemosensory process. These compounds bind competitively or non-competitively to insect OBPs, preventing the normal transport of host odor molecules to olfactory receptors. As a result, signal transduction to the insect nervous system is disrupted, leading to confusion, loss of orientation, and failure to recognize the human host[12].

Additionally, many terpenoids act as olfactory masking agents, overwhelming insect sensory perception with strong odors that suppress or override host cues. Some phytochemicals also cause desensitization of olfactory neurons after repeated exposure, reducing responsiveness over time. In polyherbal formulations, the presence of multiple volatile compounds enhances this effect by targeting different receptor subtypes simultaneously, resulting in broader and more sustained repellency compared to single-component systems[11,12].

- **Neurotoxic Effects:** Beyond sensory disruption, several phytochemicals exert direct neurotoxic effects on insects by interacting with molecular targets that are either absent or less prominent in mammals, thereby offering selective toxicity[11,13].

  A key target is the octopaminergic system, which plays a role analogous to the adrenergic system in vertebrates. Octopamine regulates insect locomotion, feeding, learning, and stress responses. Phytochemicals such as monoterpenes and phenylpropanoids modulate octopamine receptors, leading to abnormal neurotransmission. This results in hyperexcitation, tremors, loss of coordination, paralysis, and eventual death in insects.

  - In addition, certain plant-derived compounds interfere with:
  - Voltage-gated sodium channels, altering action potential propagation
  - Calcium ion channels, impairing neurotransmitter release
  - GABA-gated chloride channels, leading to neuronal overstimulation[13,14]

  These effects collectively disrupt synaptic signaling and neuromuscular function. Unlike synthetic neurotoxic insecticides, phytochemicals typically produce reversible and dose-dependent effects, reducing the risk of long-term environmental accumulation. In polyherbal formulations, simultaneous modulation of multiple neural targets lowers the likelihood of resistance development and enhances efficacy against resistant insect populations.

- **Anti-Feeding and Anti-Oviposition Effects:** A critical long-term advantage of polyherbal insect repellents lies in their ability to modify insect behavior and reproductive success, rather than relying solely on immediate repellency or lethality[14].

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- **Anti-Feeding Activity:** Limonoids, alkaloids, tannins, and bitter terpenoids act as antifeedants by stimulating gustatory receptors that signal aversion. These compounds interfere with the insect's chemosensory perception of food, leading to reduced probing, biting, and blood-feeding behavior. In hematophagous insects, impaired feeding directly affects survival, energy balance, and pathogen transmission capacity[15].

  Additionally, anti-feeding phytochemicals inhibit digestive enzymes and disrupt nutrient assimilation, resulting in growth retardation and reduced fitness.
- **Anti-Oviposition Activity:** Limonoids such as azadirachtin and related triterpenoids exert profound effects on insect reproduction. These compounds interfere with juvenile hormone and ecdysteroid signaling, which are essential for egg development, maturation, and molting. Exposure leads to:
  - Reduced egg-laying
  - Production of non-viable or malformed eggs
  - Disruption of larval development and pupation

Phytochemicals also alter surface chemistry of treated substrates, making them unsuitable for oviposition. This behavioral deterrence significantly reduces vector population density over successive generations, contributing to sustained control[16].

Integrated Impact in Polyherbal Systems When combined in polyherbal formulations, olfactory disruption, neurotoxicity, anti-feeding, and anti-oviposition mechanisms operate synergistically. Immediate repellency prevents insect contact, while sub-lethal effects impair feeding, reproduction, and population growth. This multi-level interference reduces reliance on high-dose chemical insecticides and supports eco-friendly, resistance-mitigating vector control strategies[16].

3.3 Role of Advanced Formulations

Nano-emulsions, gels, creams, sprays, and patches improve:

- Controlled release of volatile oils
- Skin adhesion
- Thermal and oxidative stability
- Duration of repellency

Nano-herbal repellents often show 2–3 fold enhancement in protection time compared to conventional oils[16,17].

4. Safety Evaluation of Polyherbal Insect Repellents

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4.1 Dermal Safety

Most herbal repellents show minimal irritation in patch tests when used within recommended concentrations. Polyherbal systems reduce the required dose of individual oils, further improving tolerability[18].

4.2 Toxicological Considerations: Safety evaluation includes:

- Acute dermal toxicity
- Skin sensitization studies
- Eye irritation tests
- Inhalation exposure assessment

Plant-based repellents generally exhibit low systemic toxicity, rapid biodegradability, and minimal environmental accumulation[19].

4.3 Environmental Safety: Unlike synthetic repellents, polyherbal formulations are:

- Non-persistent
- Eco-friendly
- Safe for non-target organisms when properly formulated[20,21].

5. Challenges and Standardization Issues

Despite promising results, challenges remain:

- Variability in phytochemical composition
- Lack of standardized extraction and quality control protocols
- Limited long-term human safety data
- Regulatory ambiguity for herbal repellents

Addressing these gaps is essential for global acceptance[22].

6. Conclusion: Polyherbal insect repellent formulations represent a scientifically credible and environmentally sustainable alternative to synthetic repellents. Their efficacy arises from synergistic interactions among terpenoids, phenolics, alkaloids, and limonoids, acting through multiple behavioral and physiological mechanisms. Advances in formulation science have significantly improved stability, safety, and duration of protection. However, standardized phytochemical profiling, rigorous safety evaluation, and controlled clinical studies are necessary to translate these formulations into widely accepted public health solutions[20,23].

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