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Review on various Pharmaceuticals and their Pharmacology of Anti-repellents- As a Preventive aspect of Vector (*mosquito species)* borne Disease

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Abstract

Mosquito is one of the most vexing bloodsucking insects. Malaria, Filariasis, Japanese Encephalitis, Dengue fever, Yellow fever, Chikungunya, and Zika are all transmitted by mosquito species belonging to the genera Anopheles, Culex, & Aedes. Mosquitoes alone infect almost 700 million people each year, resulting in one million fatalities. Malaria, which is caused by Plasmodium parasites and transmitted by female Anopheles mosquito bites, is still a substantial illness that impacts the development of infants and kids. Present review work aims to review various pharmaceutical dosage forms of anti-repellent products and their molecules, mechanism of repellent activity as a preventive of different vector bone diseases. Malaria cases were over 207 million in 2012, with 627,000 deaths reported. In addition, Yellow fever, which is spread by the Haematologus and Aedes mosquitoes, causes 200,000 instances of disease and 30,000 fatalities worldwide each year. Dengue fever is spread by Aedes aegypti and Aedes albopictus mosquitos, which are responsible for more than 100 million infections yearly. Furthermore, more than 2.5 billion individuals, or about 40% of the world's population, are now in danger of contracting Dengue fever. This review helped to understand the various kinds of vector bone disease and the surveillance of disease data. In addition, the review revealed the various pharmaceutical products would help control the Mosquitoes bits and related disease as preventive aspects and the components of pharmaceutical and their mechanism of action to inhibit the spread of various insects' related disease.

Keywords: *Anti-repellent, Mosquitoes, Anopheles, Vector bone disease, DEET, Permethrin, Neem oil, Citronella oil.*

1. Introduction

Mosquitoes are one of the most vexing bloodsucking insects that torment the general public. Malaria, filariasis, Japanese encephalitis, Dengue fever, yellow fever, Chikungunya fever, and Zika are all transmitted by mosquito species belonging to the genera Anopheles, Culex, & Aedes. Mosquitoes alone are responsible for transmitting diseases to about 700 million people worldwide, with one million deaths reported each year. Malaria, which seems caused by Plasmodium parasites & transmitted by female

Anopheles mosquito bites, continues to be a significant illness burden on newborns & small children. As a result, mosquito control is a major public health concern around the world. Interrupting disease transmission by killing mosquitos or preventing them from biting people is one method for controlling mosquito-borne diseases. Knowledge, attitude and practice of vectors were more important to understand the vector-borne diseases. [1]

Malaria is a mosquito-borne infectious disease, fever, tiredness, vomiting, and headaches are the immediate symptoms. [2]. Lymphatic filariasis, classified as parasitic disease which is caused by microscopic, thread-like worms. Most cases symptomless. Rarely, long-term damage causes swelling in the legs, arms and genitalia and also increases the risk of frequent bacterial infections that harden and thicken the skin (elephantiasis). [3] Japanese encephalitis (JE) is a kind of brain infection which is caused by the Japanese encephalitis virus (JEV). The symptoms, occasionally inflammation in the brain. In addition may occur headache, vomiting, fever, confusion and seizures.[4, 5] Dengue fever is caused by Flaviviridae virus family with four serotypes (DENV-1, DENV-2, DENV-3, DENV-4) and symptoms like high fever, Headache, Muscle, bone or joint pain, Nausea, Vomiting, Pain behind the eyes, Swollen glands, Rash etc.[6-10] Chikungunya virus (CHIKV) transmitted by arbovirus of *Aedes* mosquitoes. Characterized by an intense joint pain of abrupt onset, high fever, and rash.[11-13]. Yellow fever (YF) virus is a mosquito-borne flavivirus. Mild cases symptoms like fever, headache, nausea and vomiting. Serious condition fatal heart, liver and kidney. [14-16] Zika virus (ZV) is the *Flaviviridae* family symptomos like fever, rash, or arthralgia possibilities. [17-18]

WHO surveillance:

Vector-borne infections account for roughly 17 percent of all contagious diseases and 700,000 mortality per year. Parasites, germs, and viruses will spread them. Malaria is a parasite ailment that is transmitted by Anopheline mosquitos. It is believed that there are 219 million cases worldwide, with about 400,000 deaths every year. The majority of deaths among children under the age of five occur in this age group. Dengue fever is the most common viral infection transmitted by Aedes mosquitos. Dengue fever affects over 3.9 billion people in 129 countries, resulting in 96 million symptomatic cases and nearly 40,000 deaths per year. Chikungunya fever, Zika virus fever, yellow jack, West Nile fever, Japanese encephalitis (all spread by mosquitoes), and tick-borne encephalitis are some of the other viral diseases spread by vectors (transmitted by ticks). Chagas disease (spread by triatomine bugs), leishmaniasis (sandflies), & schistosomiasis (snails) are all vector-borne diseases that impact millions of people around the world. Many vector-borne illnesses can be prevented or controlled by taking precautions & mobilizing the community. [19, 20]

Table No: 1: Typical classifications of Mosquito Vector by WHO [21]

1	*Aedes*	Chikungunya	Virus
		Dengue	Virus
		Lymphatic filariasis	Parasite
		Rift Valley fever	Virus
		Yellow Fever	Virus
		Zika	Virus
2	*Anopheles*	Lymphatic filariasis	Parasite
		Malaria	Parasite
3	*Culex*	Japanese encephalitis	Virus
		Lymphatic filariasis	Parasite
		West Nile fever	Virus

Control of Mosquitoes:

Inhibiting mosquito vector populations and preventing mosquito bites is the most effective way to control these diseases. Insect repellents, according to studies, have a critical role in stopping mosquito vectors from flying to, settling on, or biting humans and animals. Synthetic chemical repellents are the most often used insect repellents. However, they have the problem of being unsafe for humans, particularly children and livestock, as they induce skin irritation, hot sensations, rashes, & allergies. [22]

1. DEET, Permethrin - Synthetic repellents
2. Neem oil, Citronella oil- Natural repellents:
3. Mosquito traps, medicated nets, & nonmedicated nets - Physical methods
4. Mechanical treatments include the use of an electric mosquito zapper and a mosquito magnet.
5. Biological solutions include rearing mosquito larvae-eating fish in bodies of water. [23]

Different Pharmaceutical dosage forms of anti-repellent products in the market:

Spray mosquito repellents:

Mosquito repellents that are sprayed on clothing or skin are the most frequent. Some of the effective sprays have high DEET concentrations and are effective for several hours, even when strolling through dense woods with hundreds of mosquitos.

Mosquito repellent clothing:

Mosquito repellent apparel is made with a tight weave & is injected with a long-lasting natural mosquito repellent to keep mosquitoes at bay.

Mosquito coils:

Mosquito coils were well-known as one of the most effective repellents. With concentrations of 0.3-0.4 percent of coil mass, the main active element in mosquito coils is similar Pyrethrums. When a mosquito coil is burned, the insecticides in the coil evaporate with the smoke, preventing mosquitoes from entering the room and swarming all around the surroundings. Nevertheless, the drawback is that when mosquito coils are burned, they emit a foul odour, making people believe that the coils are dangerous to their health since they produce headaches, nausea, & disorientation.

Mosquito repellent liquidizers:

Synthetic Pyrethroids are used in mosquito repellent liquidizers, which can induce neurological damage if consumed accidentally. Studies have recently revealed that these are becoming a source of hydrocarbon toxicity.

Physical methods:

Some physical insect repellents, including such mosquito nets, are believed to be superior to mosquito repellent than coils and other repellents that pose health risks. Sleeping beneath mosquito netting ensures mosquito defense & greater protection without posing any risks. Some mosquito nets are currently medicated with 25% Deltamethrin. All these nets are thought to be safer than mosquito coils, liquidizers, & inhalation of chemicals from coils & liquidizers, which can induce respiratory system illnesses, including headaches.

Mechanical methods:

Electric Mosquito Zappers, for example, use ultraviolet light to attract mosquitos & afterward kill them when they come into touch with a lethal dosage of electrical current. In another way, some of mosquito repellent products are available based on ultrasound. Female mosquitoes will not mate with males again after mating once, and they will avoid being in the vicinity of males. Females detect the presence of males by feeling the ultrasonic emitted by the males. As a result, an ultrasound generator imitates the sound waves produced by male mosquitoes beating their wings, potentially repelling female mosquitoes.

Synthetic organic insecticides:

Mosquito control methods have nearly entirely relied on synthetic organic insecticides since the invention of DDT. Nevertheless, during the past five decades, the widespread use of synthetic insecticides has resulted in environmental risks and the development of physiological resistance in important vector species. Some synthetic mosquito repellents have impressive safety ratings, but they are hazardous to the human skin and neurological system, causing rashes, swelling, & irritants to the eye.

Natural herbal formulation:

Research and development efforts are currently being directed on an alternative approach for environmentally safe, biodegradable, low-cost, and indigenous vector control approaches that may be utilized with minimal care by individuals and communities worldwide. Some of the plant essential oils reported higher mosquito repellent activities.[24] In indigenous medicine; plant-based repellents have been utilized for generations as a personal defense measure against host-seeking mosquitoes. Knowledge of indigenous mosquito repellent plants gleaned from ethnobotanical studies is a crucial resource for developing novel natural mosquito repellents [25]

Mechanism and Chemical structure of Pharmaceutical Mosquitorepellents:

DDT (Dichlorodiphenyltrichloroethane)

DDT (Chemical Abstracts Service Registry Number 50-29-3) was employed as a highly effective pesticide & insect repellent for the control of disease-carrying insects (e.g., mosquitoes for malaria and lice for typhus) and later for agricultural and residential applications [26]. DDT activates sodium ion channels in neurons, causing them to fire spontaneously, resulting in spasms and final death in insects [27]

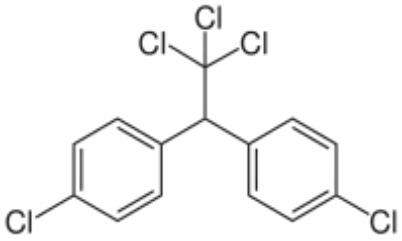


Fig No: 1: Dichlorodiphenyltrichloroethane

Pyrethrins/Pyrethroids

The most extensively used insecticides and insect repellents are natural pyrethrins and synthetic pyrethroids. Pyrethrins are botanical insecticides that come from the pyrethrum flower of Chrysanthemumcineraria folium. Pyrethroids are synthetic compounds that act as insect repellents. Pyrethroids exert their insecticidal effect on the voltage-gated sodium channel (VGSC) located on the membrane of neurons. When pyrethroids bind an open channel, they prevent its closure, thus prolonging the action potential and resulting in the insect's rapid paralysis, known as "knockdown" or kdr, and death.[28-34]

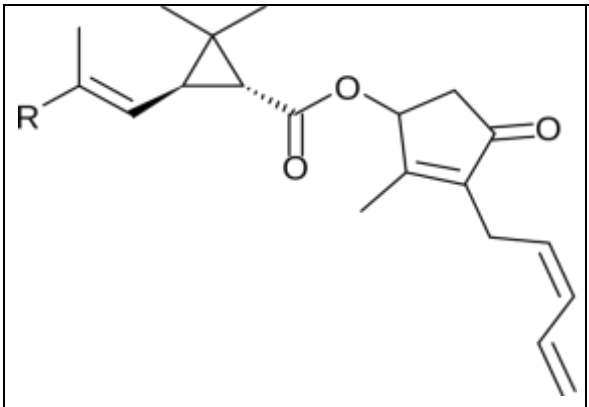
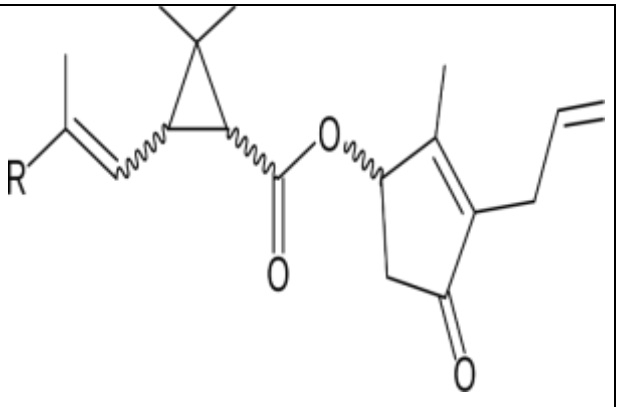
 **Pyrethrins**	 **Pyrethroids**

Fig No: 2: Pyrethrins/Pyrethroids

DEET (N, N-diethyl-3-methylbenzamide)

DEET is thought to work by inhibiting the olfactory receptors of insects for 1-octen-3-ol, a volatile chemical found in human perspiration & breath. DEET's inhibition theory effectively "blinds" or "confuses" the insect's senses, preventing the biting/feeding impulse from being triggered by compounds found in human or animal perspiration & breath. DEET binds to Anopheles gambiae odorant binding protein 1 (AgamOBP1) with good form complementarity, according to a 2011 structural analysis (PDB: 3N7H), suggesting that AgamOBP1 could be a molecular target of DEET and possibly other repellents [35]According to a 2019 study, neurons on the tarsi (feet) of yellow-fever mosquitoes respond to DEET and repel mosquitoes when they come into touch with it.[36-37]

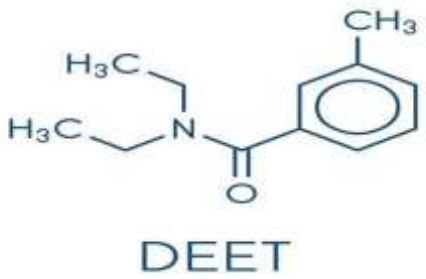


Fig No: 3: N, N-diethyl-3-methylbenzamide

Picaridin

Picaridin (Lcaridin) is classified as a potent broad-spectrum arthropod repellent. Chemically (1-piperidine carboxylic acid 2-[2-hydroxyethyl]-1-methlypropylester) the repellent and deterrent activities of Picaridin by olfactory sensing in mosquitoes, and ticks, via their interactions with odorant receptor proteins. Picaridin has an amide moiety. Small amide derivatives have been shown to affect a wide range of molecular pathways through allosteric regulation of various proteins including proteases, the cannabinoid receptor 1 (CB1), the α7 nicotinic acetylcholine and $GABA_A$ receptors [38-43]

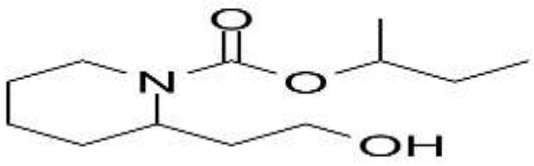


Fig No: 4: Picaridin

Permethrin

Permethrin is a 3rd synthetic pyrethroid that has been certified by the Environmental Protection Agency for use as an insecticide. It may be found in many households and agricultural insecticidal formulations. [44] Permethrin comes under the type I pyrethroid category, and it primarily targets an insect's nervous system, which will produce muscle spasms. Permethrin (and other pyrethroids) is acts as a toxin to nerve membrane sodium channels. Permethrin binds to sodium channel proteins, slowing the rate of sodium current inactivation caused by membrane depolarization. Finally, the sodium channel is opened

for an extended period of time. Permethrin is the most effective clothing impregnant available, exhibiting protection from a wide variety of arthropods. [45]. Permethrin's primary mode of action is contact toxicity; however it also exhibits contact repellency effects. [46, 47]

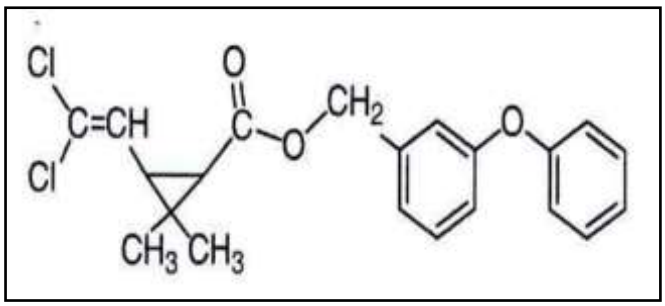


Fig No: 5: Permethrin

Natural products (essential oils):

Citronella

In 20th century citronella was used as mosquitoes repellent by Indian army.[48]Today, citronella is one of the most widely used natural repellents on the market, used at concentrations of 5-10%. [49] Citronella oil has exhibited good efficacy against mosquitoes and it is a mixture of components which includes citronellal, citronellol, and geraniol as major constituents. Citronella oil mainly contributing to various activities (antimicrobial, anthelmintic, antioxidant, anticonvulsant antitrypanosomal and wound healing), besides mosquito repellent action. [50] The formulation of encapsulated citronella oil nano emulsions using high-pressure homogenization at various surfactant and glycerol concentrations was investigated. The release profile rate was found to be closely connected to mosquito protection time, with a drop-in release profile rate extending mosquito residence time. [51]. The nano emulsions were made from citronella oil, hairy basil oil, and vetiver oil, with mean droplet sizes ranging from 150 to 220 nm, and they have been created & studied in vivo & in vitro. After high-pressure homogenization, larger emulsion droplets (195-220 nm) moved toward a smaller size (150-160 nm), resulting in a more significant release rate profile. Thin films made from nano emulsions with smaller droplet sizes would have high-level integrity, allowing more essential oils to be vaporized and the mosquito repellent activity to last longer. [52]

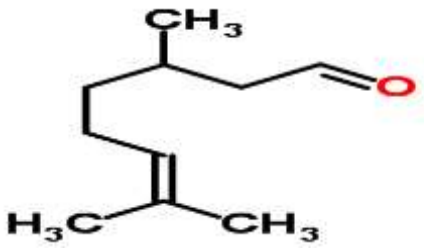
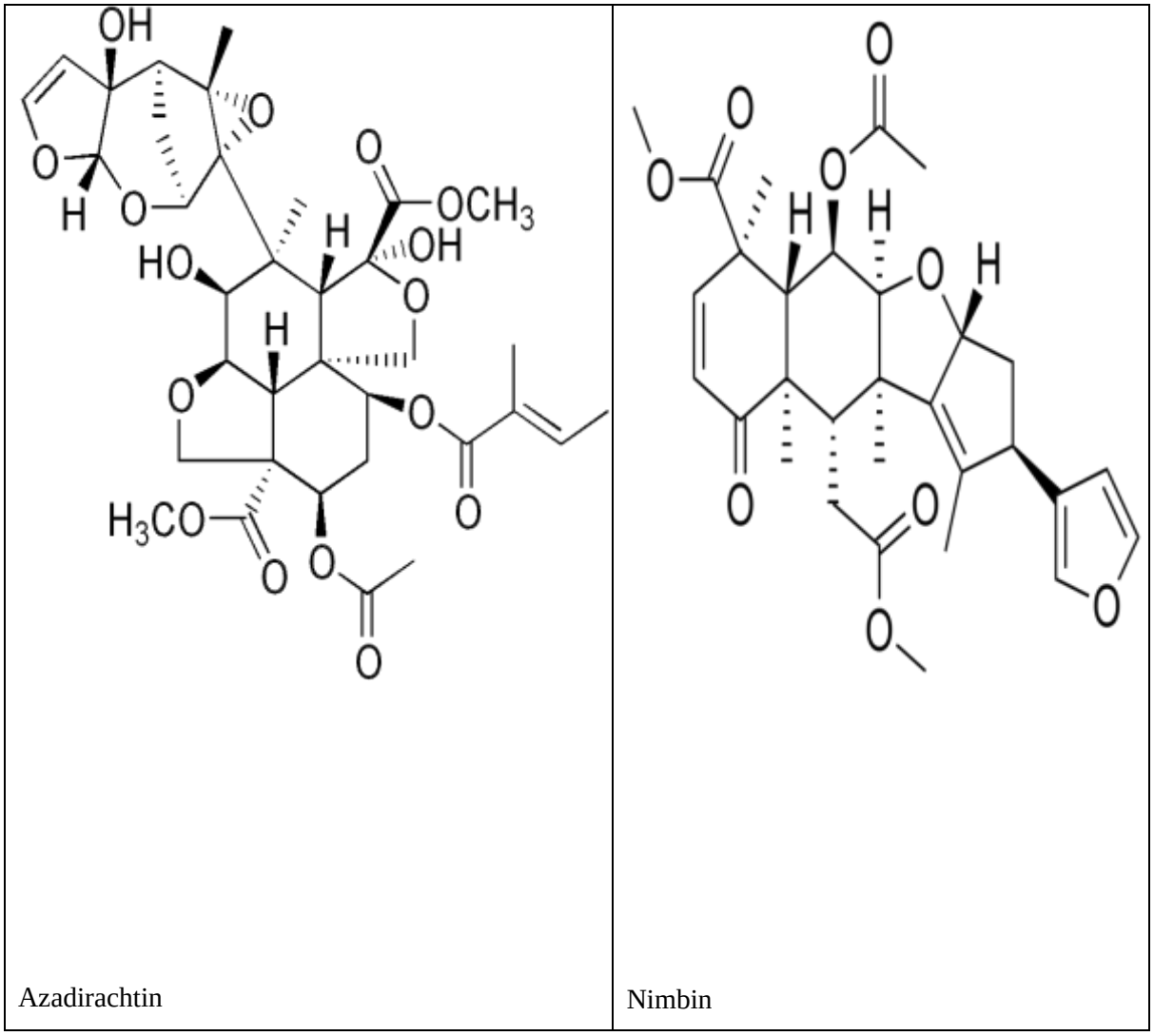


Fig No: 6: Citronella oil

Neem oil

The seeds of neem trees are used to extract neem oil using a crushed-out physical procedure. Azadirachta indica is a plant that belongs to the Azadirachta family. [53] Over 100 pesticide formulations included neem oil and its refined components. Neem oil has been used to control insects in a wide range of crops and ornamental plants. Neem oil has been manufactured as granules, dust, wettable powders, and emulsifiable concentrates, among other forms. "Neem oil, which includes several insect components," the National Pesticide Information Center said. One of the most active compounds is Azadirachtin. It decreases insect feeding & works as a repellant, according to the mechanism of action.

It also works by interfering with insect hormone systems, making it more difficult for insects to grow and produce eggs." According to the Environmental Protection Agency (EPA), "Azadirachtin works by deterring specific insects from feeding, such as locusts, and interfering with the regular life cycle of insects, such as feeding, moulting, mating, & egg-laying .[54]



Azadirachtin | Nimbin

Fig No: 7: Neem oil

Lemongrass oil

Lemongrass oil is made from the aerial portions of Cymbopogon citratus (DC.) Stapf. a Poaceae plant [55] Lemongrass oil has two primary active principal components: geranial (-citral) and neral (-citral), as well as geraniol and citronellol, which are both tiny percentages of established repellents (Diptera: Culicidae) and house flies (Diptera: Muscidae) [56-58]. Lemongrass oil as an insecticide approach to management of A. ipsilon. Lemongrass oil caused significant effects on the mortality, developmental duration, and expression level of CAT and lipid peroxidase after 96 h post treatment. [59]

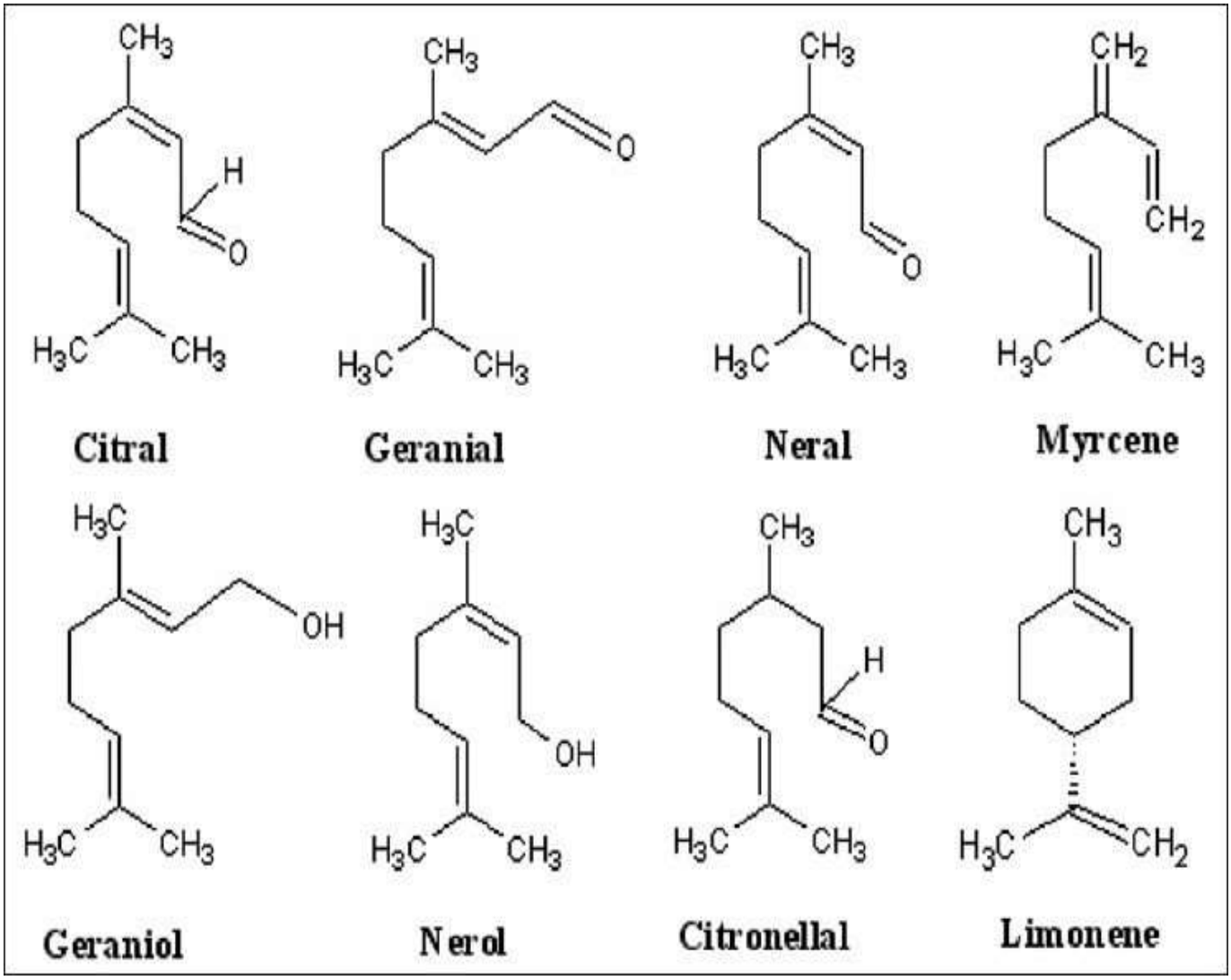
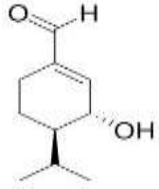
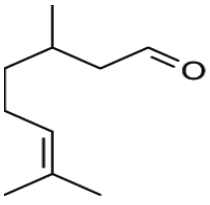
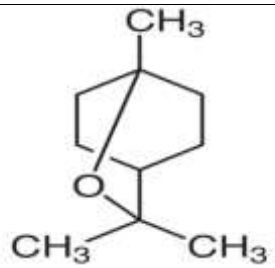


Fig No: 8: Lemon grass oil

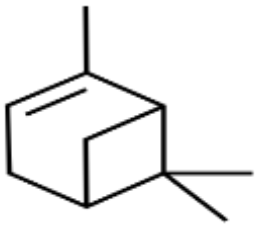
Eucalyptus oil

Eucalyptus, an Australian native, belongs to the family of Myrtaceae. Antimicrobial, fungicidal, insecticidal/insect repellant, herbicidal, acaricidal, and nematicidal are just a few of this oil's biological properties.[60]. Eucalyptus oil is a natural insect repellent that protects against mosquitoes and other dangerous arthropods while acting as an antifeedant against herbivores. Eucamalol, Citronellal, 1, 8-Cineole, a-Pinene, and gamma-Terpinene are some of the active constituents present in Eucalyptus oil and reported as insect activity.

 Eucamalol	 Citronellal



1, 8-Cineole



a-Pinene

Fig No: 9: Eucalyptus oil

The mosquito repellent efficacy was determined and the rate of results as : Cymbopogon nardus and Eucalyptus globulus (100%) >Ocimum sanctum (97.94%) > Syzygiumaromaticum (95.81%) > Citrus sinensis (93.75%) > Curcuma longa (89.56%) > Vitex negundo (85.44%) > Azadirachta indica (81.25%) by 1 ml of 10% (v/v%) extract / essential oil containing ethanol solutions prepared using each plant extract / essential oil was tested for mosquito repellent activity using arm-in1cage method.[62] Another herbal study of Homalomena aromatica, Ocimum basilicum and Ageratum conyzoides powder together with the powdered bark of Litsea glutinosa as a binder to prepare cakes is able to repel mosquito's effectively.[63, 64, and 65]

Table No: 2: Herbs of mosquito repellent activity [66]

SNO	BIOLOGICAL NAME
1	Acorus Calamus
2	Addathoda Vasika/ Justicia adhatoda L
3	Anacardium Occidentale
4	Anaphalis contorta (D. Don) Hook. f.
5	Azardirachta Indica A.Juss
6	Acacia nilotica (Linn.) Willd
7	Andrographis paniculata(Burm.f.)Wall.ex.Nees
8	Artemesia parviflora Roxb
9	Arundo donax Linn
10	Allium sativum
11	Ageratum conyzoides L
12	Arisaema concinnum
13	Anisomeles malabarica (L.)
14	Argemone mexicana L.
15	Artemesia nilagirica (Clarke) Pamp
16	Acorus calamus Linn
17	Anabasis aphylla
18	Atherosperma moschatum
19	Artemisia arborescens (L.)
20	Artemisia Vulgaris
21	Aloe vera (L) Burm.f.
22	Anisomeles indica (L.) Kuntze.
23	Adhatoda Zeylanica Medic. Adulsa
24	Annona squamosa (L.)
25	Artemisia abrotanum (L.)
26	Anthemis cotula Linn.
27	Allium sativem (L.)
28	Barleria prionitis L.
29	Albizialebbeck (L.)

30	Butea monosperma
31	Bixa orellana (L.)
32	Backhousia myrtifolia
33	Bosewellia serrata Roxb. Ex Colebr
34	Coronopus didymus (L.) Sm.
35	Croton bonplandianus Baill.
36	Cassia alata Linn
37	Canarium strictum Roxb.
38	Cannbis sativa
39	Catunaregam spinosa (Thunb.)
40	Chenopodium ambrosioides Linn
41	Clerodendrum viscosum Vent
42	Clerodendrum indicum(L.)Kuntze
43	Curcuma aromatic
44	Curcuma Longa
45	Celastrus paniculatus Willd
46	Cymbopogon martini (Roxb.)/ Cymbopogon winterianus
47	Coronopus didymus (L.) Sm
48	Chloroxylon swietenia DC
49	Canarium bengalense Roxb
50	Calotropis procera
51	Commiphora wightii or Commiphora mukul (Guggul)
52	Callitris glauca
53	Cymbopogan citratus Stapf./ Cymbopogon flexuosus (Linn.) Rendie
54	Cellastrus paniculata Willd
55	Cissampelos pareira L.
56	Clousena anisata
57	Clousena anisata (Burm) L
58	Citrus sinensis (L.)
59	Cassia fistula (L.)
60	Clinopodium nepeta (L.)
61	Calamintha acinos (L.)
62	Colotropis procera (L.)
63	Diospyros melanoxylon Roxb.
64	Dalbergia sissoo DC
65	Dipterocarpus spp
66	Diospyros melanoxylon Roxb.
67	Euphorbia milli Des.
68	Eclipta alba (L.)Hassk.
69	Erigeron linifolius Willd.
70	Elsholtzia blanda (Benth)
71	Eugenia bracteata (Willd.) DC
72	Eucalyptus globules Labill
73	Eugenia carypphyllata (L.)
74	Ficus banghalensis (L.)
75	Ficus hispida L.
76	Glycosmis pentaphylla(Ret z.)DC
77	Hyptis suaveolens (L.) poit.

78	Hemizonia Fuchii
79	Helicteres isora L.
80	Homalomena aromatic schott.
81	Jatropha gossypifolia L.
82	Jacobaea vulgris (L.)
83	Kalanchoe pinnata Pers
84	Kaempferia galanga L
85	Kaempferia rotunda Linn
86	Lavendula angustifolia (L.)
87	Leucas aspera (Willd.) Link
88	Litsea citrata Bl
89	Lantana Comara
90	Melia dubia L
91	Matricaria chamomilla
92	Myrica Gale
93	Melaleuca Bracteata
94	Michelia champaca L
95	Melia azedarach
96	Mentha piperita (L.)
97	Mentha pulegium (L.)
98	Monarda punctata (L.)
99	Melia azadirachta L
100	Nicotiana tabacum Linn
101	Nyctanthes arbor-tristis L
102	Ocimum sanctum
103	Ocimum americanum
104	Ocimum canum Sims
105	Oroxylon indicum (Linn.) Vent
106	Origanum vulgare
107	Ocimum Basilicum
108	Ocimim Tenuiflorum L
109	Ocimum gratissimum
110	Oroxylon indicum (Linn.) Vent
111	Prunus persiaca (Linn.) Batsch
112	Psidium guajava (L.)
113	Piper nigrum (L.)
114	Pongamia pinnata (Linn.) Pierre
115	Pentanema indicum (Linn.) Ling
116	Premna latifolia Roxb
117	Pandanus odoratissimus L.f.
118	Rosmarinus officinalis
119	Randia longiflora Lamk.
120	Ricinus communis (L.)
121	Santalum album
122	Solanum khasianum Clarke
123	Solanum nigrum Linn
124	Swertia angustifolia Buch.- Ham.ex D.Don
125	Salvia longifolia Nutt.
126	Sassafras albidum (L.)

127	Salvia officinalis (L.)
128	Santolina chomaecyparissos (L.)
129	Salvia longifolia Nutt
130	Tinospora cordifolia(Willd.) Hook .f. & Thoms.
131	Trychnos nux vomica L.
132	Tridex procumbens (L.)
133	Tribulus terrestris (L.)
134	Trachyspetmum ammi (L.)
135	Tanacetum cinerarifolilum (L.)
136	Urena lobata
137	Vitex negundo L.
138	Vetiveria Zizanioides (Linn)/ Chrysopogon zizanioides (L)
139	Woodfordia fruticosa(L.)Kurz
140	Zingiber oficinalis (L.)
141	Murraya koenigii
142	Blumea eriantha DC / Blumea Lacera (Burm.f.) DC
143	Clausena anisata

4. Conclusion

Malaria was reported in roughly 207 million cases in 2012, with an estimated 627,000 deaths worldwide. Every year, approximately 200,000 cases of disease and 30,000 deaths are caused by yellow fever, which is spread between monkeys and humans by mosquitoes of the Haematologus and Aedes species [World Health Organization, Yellow Fever, 2008]. The mosquitos that spread Dengue fever, Aedes aegypti, and Aedes albopictus, are responsible for more than 100 million infections each year, resulting in thousands of fatalities, and more than 2.5 billion people, or more than 40% of the world's population, are now at danger. [61] This review helped to understand the various kinds of vector bone disease and the surveillance of disease data. In addition, the review revealed the various pharmaceutical products would help control the Mosquitoes bits and related disease as preventive aspects and the components of pharmaceutical and their mechanism of action to inhibit the spread to various insect-related diseases. There is a need to create more awareness of these insect-related diseases and the medication remedy available in the pharmaceutical market in the current scenario. In addition, this revealed the synthetic insects and chemical-based repellent is more available in the market. Also, there is a need to initiate research on alternate herbal-based formulations to overcome the issues of synthetic chemical repellents. The protocol of standard quality guidelines is necessary, specific to insect repellent pharmaceutical products to enhance the quality of products to the consumers and safety aspects to improve the healthily and insect-free environments.

Availability of data and materials

Not applicable to this review topic.

Competing interests

The authors declare that they have no competing interests

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