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Natural repellents a topic not to be neglected in a quest for new effective mosquito repellent: A review on *Azardirachta indica* (neem) and *Citrus sinensis* (sweet orange)

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Abstract

The current rise in insecticide resistance of mosquitoes to synthetic compounds that used to be very effective is of great concern to malaria control. Several bio-compounds from plants and essential oils have insecticidal or repellent potencies. However, lack of harmonization and complete research on insecticides from plant origin have obscured the breakthrough of discovering an alternative plant-based mosquito repellent to the synthetic DEET-based repellents. This review seeks to provoke the drive for finding an alternative and effective mosquito repellent from plants or essential oil sources with focus on *Azadirachta indica* and *Citrus sinensis*.

Keywords: *Azadirachta indica*; *Citrus sinensis;* Mosquito repellent

1. Introduction

The use of derivatives and bio compounds from plants as insect repellents, especially against mosquitoes is a potential option that can be exploited in the midst of the current rising insecticide resistance in mosquitoes [1–3]. This calls for finding alternative effective vector control approaches [4, 5]. Moreover, repellents from natural or plant origin are easily degradable and environmentally friendly unlike the synthetic ones [6]. Plants such as *Azadirachta indica* and *Citrus sinensis* have demonstrated repellent properties [7, 8]. This review seeks to provoke the drive for finding an alternative and effective mosquito repellent from plants or essential oil sources with focus on *Azadirachta indica* and *Citrus sinensis*.

2. History of repellent

Traditionally in many parts of the world, some plants were used as repellent against insects in order to prevent biting [9]. These were used as plant oils, smokes or tars and many more [10]. Even though much studies have been made into artificial (synthetic) repellents, less strides have been made in the area of natural (plant) repellents [9].

Citronella oil was the first among four others that were recorded in history to be used as insecticide and at times for the treatment of hair to prevent head lice before the Second World War. The three others are dimethyl phthalate, Indalone and Rutgers 612 were discovered, patented and available respectively in 1929, 1937 and 1939. During the World War II, combined formulation of the later three components in the ratio 6-2-2: dimethyl phthalate, Indalone and Rutgers 612 respectively was quickly prepared for the military yet it could not produce the expected protection of the military personnel across the globe [11, 12].

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Synthetic insect repellent made of N, N-diethyl-m-toluamide (DEET) was for military use only and its first product was introduced for civilian use in 1956 [11]. DEET currently remains the gold standard for mosquito repellent irrespective of the reported toxic side effects, which include skin rashes and itches, encephalopathy in children, serious allergic response, low blood pressure and reduce heart rate, it has been generally regarded as safe [13] .

2.1. Mechanism of action by insect repellents

According to Acree *et al.*(1968), *Aedes aegypti* is attracted to lactic acid which is a component of human sweat. Studies done by others on the behaviour of mosquitoes indicated that lactic acid was only slightly attractive alone. This therefore proves its synergistic effect with carbon dioxide and other unidentified components of human odour that may be essential. Compounds such as steroids, phenols, carboxylic acids, indoles that exude from animals attracts mosquitoes [15, 16].

Physiological sensory studies on insect gives the impression that mosquito repellent reduce biting rate by interfering with host-enticing signals and change a sensual information to a repulsive one due to activation of many sensory receptors leading to confusion of the mosquito [17]. The mosquito as a result is not able to detect host attractants such as carbon dioxide, lactic acid, ammonia and other compounds hence protecting the host [14, 18].

2.2. Synthetic repellent

DEET repels insects and does not kill them, and it is considered the gold standard of repellents [19]. Though discovered in 1953, the general public and the United State government accepted it's use in the year 1957 [11]. Over 200 insect repellents products which are in the market contain DEET as their main active ingredients with concentrations starting from 5-100%. People with defected ammonia metabolism are susceptible to the negative effects from DEET exposure [13, 19]. The mechanism of DEET tends to give a vapour barrier that prevents the mosquito from coming into contact with the host's skin[20].

Permethrin is used in the treatment of mosquito nets and clothing [19]. Another example of synthetic repellent is Picaridin (2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester) [21]. However, neurotoxicity is the most common reported systemic toxic effects of DEET but unfortunately the mechanism is unknown. Additionally, ingestion of DEET often result in nausea, vomiting, hypotension, seizure, and ataxia. Excessive application on the skin, especially in children has led to loss of body control movement, lethargy, vomiting, bullous eruption, and other negative effects. There has also been report of disturbance of the development of embryo or foetus in pregnant women as well [10, 22].

2.3. Natural insect repellents

Between 1953 and 1974, 872 synthetics and 29 plant-based oil were tested for repellent efficacy on four outstanding species of cockroaches by the US Department of Agriculture (USDA) [11]. Citronella oil was used as active ingredient in insect repellent formulations in the United States [8, 23]. In 1901, the insecticidal properties were discovered and processed into candles and incense, insect repellent and hair control of flea and lice. Even though popular, little studies have been made to assess the effectiveness of such products [24]. Citronella oil used as air freshener showed intriguing results of repellent activity against mosquitoes [25]. Cedar wood, eucalyptus, lavender, cajuput, safrole-free, peppermint and bergamot oils according to a laboratory olfactometer were combined in various proportions but failed to produce repellency effect in olfactometer than DEET [26]. Leaves from the neem tree (*Azadirachta indica*) and herbs from *Ocimum spp* are commonly used as larvicide and repellent as well [27].

In China, Artemisia and Calamus species of herbs were burnt to drive away mosquitoes and for treatment of malaria infection in the rural areas [28]. In 1994, a trial was conducted on an insect repellent branded Quwenling which was produced from *Eucalyptus* oil. The active ingredient in the oil responsible for the repellent effect is p-menthane-3,8-diol (PMD). Outcome of the trial proved *Eucalyptus*-based repellent very effective, comparable to DEET which led to the popularity and registration of PMD upon further researches [29].

According to Abduelrahman H.[30], *Ocimum basilicum* (Labiatae) oil was used traditionally in Sudan communities to repel mosquitoes whiles another research showed it's larvicidal effect [31]. Ethiopia villages were not an exception in using natural repellents in the form of burning. A research conducted by Karunamoorthi and Hailu[32] showed that 70% and 90% of the participants in the survey from Bechobore Kebele in Ethiopia were aware and used plants as mosquito repellent respectively. In South Africa, plant species from two families, Meliaceae and Anacardiaceae were the most used. *Sclerocarya birrea, Lippia javanica, Melia azedarach, magnifera indica, Balanite maughamii*, and nine other

new species were used in the Mkhanyakude district with most of them used in the dry form by burning to repel mosquitoes [33].

Another pilot efficacy study of *Lantana camara* (Lantana) demonstrated the repellent effect of the living plant. In this study, some houses were made to plant Lantana and other selected houses were not. The density of anopheles indoor were assessed and it showed that the houses with the plant had reduced mosquito density indoors. This suggested that living plant repellents could be used as natural reduction method for mosquito control in rural communities and which was cost effective [34].

3. Neem tree

Dryer or semiarid regions of Asia and Africa are very suitable for the planting of *Azadirachta indica* from the family Maliaceae because it adapts naturally [35]. Neem is evergreen tree whose size ranges from medium to large with dark brown to grey bark and straight trunk. It can grow to a height of about 40 meters and at the same time several centimetres in width or diameter. An annual rainfall of between 500 to 1150 mm is usually required. Neem is able to accommodate drought but difficult to withstand water-logged and soils that drain poorly [36]. It has dark green pinnate leaves that are brightly coloured with 9-15 serrated leaflets each of 7 cm long. The flowers are small, white, sweet scented and in clusters that are excellent nectar-producing grounds for bees. Trees usually blossoms between February and May in India. The fruits are green drupes which are elliptical and smooth with a seed that is covered by a pulp. Upon ripening the fruit turns golden yellow often within the months of June through to August [36, 37].

Studies have been made on the pesticidal properties of six species in the family Meliaceae in different parts of the world. The most promising phytochemical pesticides studies in recent studies, however, are those based on extracts of *Azadirachta indica* (neem) [37, 38].

Indian scientists were the first to research into the benefits of neem even though in the 1920s, there was virtually little global recognition until a German entomologist found out in 1959 that neem trees in Sudan were resistant to the attack of migratory locusts. It was from this time that considerable research and commercialization activities on the products of neem became visible [39].

3.1. Uses of neem

Neem has been the most preferred tree, in different cultures it is referred to as miracle tree in the region of Sahel because it responds to so many needs of the people in the following ways [35]. People take rest under the beautiful canopy of neem tree due to its large cover. It also serves as wind-breaks to protect food crops and buildings from winds from the desert [7]. The flower attracts bees that at the end produce a very delightful and delicious honey [40].

Neem kernels produce oil, which is used in the production of soap and other toiletries, fuels for lighting lamps and heating whereas the left over from the kernels after extraction of the oil could be used as fertilizer [41]. These were commonly known and used by indigenes in India and the tree was planted all over every community. Moreover, the proteinaceous residue from the kernel was also used to feed poultry as well. This indicates that every part of the seed and the whole plant remains useful to humans and animals [40, 42].

Since ancient times in India, various parts of neem tree have been used traditionally as medicine that heals the whole body [35]. Also, the roots, bark, leaf and fruits of neem are considered the major constituents in medicine [42], ailments such as leprosy, intestinal infestation by worms, constipation, cough and respiratory problems were treated with neem oil and leaf extract. It is also generally known to promote the health of people [36]. Eczema and many other skin infections were also controlled by the oil in addition to the treatment of rheumatism, chronic sores from syphilis and ulcers [43].

Work done by Suryawanshi [44] further confirmed the spermicidal effect of neem oil that was speculated traditionally and the research of earlier studies. He realized that within 20 seconds, as little as 3mg of neem oil was able to kill sperms completely in a laboratory experiment conducted without any negative side effect. In another vivo studies conducted earlier in the 1990s exhibited that intra-vaginal use of neem oil before sexual intercourse was able to prevent pregnancy completely. Another revealing discovery from the same study was the reversibility of the antifertility effects of neem [44–46].

Also, neem seed and leaf extracts were used as a powerful remedy to some fungal infection of human such as Trichophyton, Epidermophyton, Microsporum, Candida and many others [47]. Essentially, the seed and leaf extract of

neem have been effective against malaria parasites [48]. The rise of Chloroquine and other drug resistant strains of malarial parasites has raised several concerns for continuous surveillance for effective treatment of malaria [49]. An in-vitro experiment using ethanolic extracts of neem leaf demonstrated antimalaria activity [49]. Oocyte blocking and reduction of *Plasmodium falciparum* in the midguts of female *Anopheles* mosquito was recently identified with blood treatment of ethyl acetylated neem leaf extract. This is a novel outcome which can be exploited for new drug development against malaria [50].

Antimicrobial efficacy of neem in bacteria and viruses is also worth noting. The oil from the leaves, seeds and bark serve as a source of broad spectrum of antibacterial activity against both Gram-negative and positive micro-organisms [43, 51, 52]. The bark, seed and leaves are not only having bactericidal effect but antiviral activity against herpes simplex virus and other viruses as well [53].

Finally, to mention just a few of the numerous medical benefits of neem was the research in which ethanolic neem extract at a pH of 7.4 was able to cause cytotoxic effect on breast cancer cells [54].

3.2. Chemical component of neem oil

Azadirachtin, a complex terpenoid-limonoid from the seeds of neem, is the main constituent that gives both feeding reduction and toxic effect in insects [55]. Other limonoid containing compounds are also responsible for the repellent, antipyretic, contraceptive, antiparasitic and antiseptic properties that are found in the other parts of the tree thus root, bark, leaves and flowers [56]. *A. indica* produces a large volume of triterpenoids which are biosynthesis that accumulates in azadirachtin [57]. The production of azadirachtin begins with a steroid precursor (examples are azadirone and azadiradione) and C-ring opening (example are nimbin and salannin) and then goes through dimensions of structural complexity: furan-ring formation results azadirachtin (Okonkwo et al., 2013).

The neem seed yields up to 45% oil upon extraction, and this makes the seed a very important component together with other active molecules. Thus, research has increased on the study of the seed after azadirachtin is removed [56]. There are many active compounds such as triterpenoids, limonoids, azadirachtin which are effective in pest control just to mention few [58].

Moreover, the mode of operation of the active ingredient in the oil of neem (limonene and azadirachthin) is presumed to interfere with the neuromodulator, octopamine of the mosquitoes[59]. Octopamine is responsible for many physiological and neurological control activities of insects [60]. A tamper by active constituents in essential oils affects its activation leading to reduce or complete change of behavioural pattern of attraction and biting humans. This makes the oil an idea active ingredient for mosquito repellent [61].

4. The orange tree

The orange tree is from the family Rutaceae, of which the most important genus is Citrus [62]. The sweet Orange is called *Citrus sinensis,* a fruit tree that is very commonly grown in the world. It adapts to wide range of environmental conditions subtropical and tropical climate and well-drained soil [63]. The average height of an orange tree is around 10m with an engulfed conical apex and usually spiny branches which takes between 5 and 18 months after flowering for the development of fruits. It has fragrant flowers which produces berry fruit from a single ovary but its ripe fruits are reddish-green to yellow in colour [62]. Brazil is the leading producer of orange in the whole world, thus producing about 36 million ton per annum and exporting 95% in the form of frozen orange juice [64]. Between 2016 and 2017, the second leading producer of orange in the world was the United States of America [62] .

Citrus tangerine (Tangerine), *Citrus paradise* (Grapefruit), *Citrus sinensis* (Sweet orange), *Citrus lemon* (Lemon), are some species of the genus Citrus[62].

4.1. Uses of orange

The tree, fruits and peels of orange are important source of nutrition, medicine and great economic value [62]. The orange trees are potential source of firewood. At other times its wood is processed into boards and paneling. They are sometimes planted in garden as amenity tree. The tree also provides shade for people and animals and serves as wind breaks in the rural areas [65].

Moreover, the fruits serve as a source of dietary fiber with the juice used for the manufacture of many drinks and flavoring substance [66]. One of the most important components of *Citrus sinensis* is it's peel oil and the therapeutic effect [63]. The oil was effective against *Aedes* and *Culex* as mosquito repellent which can be exploited for a novel

repellent [67]. Even in the engineering field, sweet orange peel oil improves the performance of gasoline in engines [68, 69].

4.2. Chemical component of orange peel oil

Sweet orange oil has a nice fresh and sweet smell and is yellow to orange in colour and watery in viscosity [67]. The shelf life is about 6 months. Orange oil is used in flavouring food, confectionery, and drink. It helps protect furniture against insects' damage when added to polish [63]. The following are some of the medicinal properties of the oil: antiseptic, reduction of depression, antispasmodic, relieving flatulence, increase the flow of urine, anti-inflammatory, sleep-inducing and tonic [70–72]. The major chemical constituents of orange oil are limonene, a-pinene, citronellal, geranial, myrcene, linalool and sabinene. It is neither toxic nor irritant and also non-sensitizing safe oil, better still caution must be taken because it can have a little phototoxic effect [66, 73]. The repellent properties cannot be ignored due to the presence of limonene [74, 75]. Dry peels of orange were traditional burnt to repel mosquitoes in Ghana and Sierra Leone while others applied the fresh peel on the skin [76].

5. What is the way forward?

A heavy metal analysis done on sweet orange peel oil and neem oil creams showed significant safety for topical application [77]. A further investigation proved comparable repellent effect of combined neem seed oil at 15% and orange peel oil at 15% cream to DEET [74]. The issue of the current insecticide resistance of mosquitoes against the commercial synthetic active ingredients demand thorough search for active ingredients of plant-based, essential oil or natural origin [78, 79]. However, there is the need to standardize research in this area to ensure good comparison of results across the globe as it is done for insecticide resistance testing.

6. Conclusion

It is important to explore plant sources for new and very effective mosquito repellents that would mitigate the impact of insecticide resistance which threatens malaria vector control. However, harmonization of the preparation and testing of repellents from plants origin is necessary to comparably measure the efficacy of bio compounds across the globe.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no competing interests

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