HERBAL ESSENTIAL OILS AS THE ALTERNATIVE REPELLENT AGAINST MOSQUITOES

TINH DẦU THỰC VẬT, CHẤT ĐUỔI MUỖI THẾ HỆ MỚI

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Abstract - Mosquitoes are vectors of serious human diseases, *i.e.*, dengue fever, malaria, and yellow fever. The number of dengue fever cases has seen 30 times increase in the previous 50 years. The research and development of mosquito repellents as personal care products is an approach for preventing diseases spread by mosquitoes, besides others for killing larvae. Most commercial mosquito repellents today are derived from chemical synthesis associated with many risks of adverse effects on human health, particularly for the nervous system. Natural products are appraised to be a tremendous means of overcoming these restrictions and shortcomings. The ability of essential oils extracted from herbs to repel mosquitoes has drawn much more attention recently. In this review, we have summarized the chemical composition, the mosquito repellent capacity, and the application of essential oils.

Key words - Essential oil; natural repellents; mosquito repellent; citronella oil; mint oil

Tóm tắt - Muỗi là vật truyền nhiều bệnh nguy hiểm cho con người như sốt xuất huyết, sốt rét và sốt vàng da. Số ca mắc bệnh sốt xuất huyết đã tăng gấp 30 lần trong 50 năm qua. Việc nghiên cứu và phát triển thuốc đuổi muỗi như sản phẩm chăm sóc cá nhân là một cách tiếp cận nhằm ngăn ngừa các bệnh lây lan do muỗi, bên cạnh các biện pháp khác để tiêu diệt ấu trùng. Hầu hết các loại thuốc đuổi muỗi thương mại hiện nay đều có nguồn gốc tổng hợp hóa học với nhiều nguy cơ ảnh hưởng xấu đến sức khỏe con người, đặc biệt là hệ thần kinh. Các sản phẩm tự nhiên được đánh giá là một giải pháp hiệu quả để khắc phục những hạn chế này. Khả năng đuổi muỗi của tinh dầu chiết xuất từ thảo dược đang được chú ý trong thời gian gần đây. Trong bài đánh giá này, chúng tôi đã tóm tắt về thành phần hóa học, khả năng đuổi muỗi và các sản phẩm đuổi muỗi từ tinh dầu.

Từ khóa - Tinh dầu; chất chống côn trùng tự nhiên; chất đuổi muỗi; dầu sả chanh; tinh dầu bạc hà

1. Introduction

Mosquitoes, borne vectors of dangerous diseases (*i.e.*, malaria, yellow fever, Japanese encephalitis, and dengue fever [1]), are responsible for the major death of human beings and animals [2], especially malaria in tropical and subtropical climates (106 endemic countries) [3]. Approximately 500 *Anopheles* mosquito species are globally identified and more than 50 ones are recognized to be able to transmit malaria, up till now, there is, unfortunately, no vaccine to prevent this disease in the early stage [4]. Hence, prevention from the bite of *Anopheles* species is the most effective method. In the continuous efforts to reduce malaria by at least 90% by 2030, mosquito repellent is the most preferable option [1, 5].

Most of the dominant ingredients in the mosquito repellent of commercial products are synthesized compounds, *i.e.*, *N*,*N*-diethyl-meta toluamide (DEET), allethrin, and dimethyl phthalate [2]. The mosquito repellents containing these substances above for habitual use strictly require medical indications because of adverse effects on human health, *e.g.*, allergies, dermatitis, cardiovascular, and neurological disorder, *etc*. [4]. In addition, these synthesized chemicals also adversely affect the environment, changing the natural ecosystem, causing drug resistance, adversely affecting non-target insects, *etc*. [4, 6].

The mosquito repellents, in recent decades, derived from essential oils have attracted the attention and concernment of the scientific and research community. They have been gradually exploited and utilized for commercial purposes instead of synthesized mosquito repellents. The advantages of these products can be found. These products could be regularly utilized for a long time and have many beneficial biological activities rather than synthesized chemicals. In addition, they have moderate pharmacological properties, and are safe for humans. Essential oils do not adversely affect mammal and feather animals, and aquatic ecosystems [1, 5, 7]. Mosquito repellents accommodating essential oils as the main ingredients have been proven and published in many scientific reports, in which the most effective mosquito repellent belongs to the essential oil of *Ligusticum sinense*, followed by lemongrass (*Cymbopogon citratus*), pine, North Indian rosewood (*Dalbergia sissoo*), mint, and mangrove [8].

In this review, the characteristics of the chemical ingredients in marketable mosquito repellent products, the main chemical compositions and biological activities of the citronella and mint oils were introduced. The recent development of mosquito repellent derived from citronella oil followed by mint oil in 2020 until now was summarized.

2. The most common essential oils for mosquito repellents

The repellency of herbal essential oils has been exploited for thousands of years by humans, most simply by burning dried bark or leaves, a practice that is still in wide use throughout developing countries, especially in rural areas. Their effectiveness in repelling mosquitoes with different formulations has also been demonstrated by many studies (see Table 1).

Almost all the herbal essential oils used as repellents are customary and used for food flavoring and/or in the perfume industry for a long time (see Table 1 also), which may explain the association with these oils as safer natural alternatives rather than synthesized repellent, *e.g.* DEET, allethrin, and dimethyl phthalate. One of the main disadvantages of using essential oils as a mosquito repellent is the short duration of agility because essential oils evaporate quickly and do not stick for long on the surface of the skin. The duration of most essential oil is around 20 - 30 mins [21]. However, this issue could be overcome by using fixatives, *e.g.*, 5% vanillin mixed with oils from turmeric and hairy basil repelled mosquitoes for a period of 6 - 8 hours depending on the mosquito species [23]. Another option is using carriers, usually oils, to increase the adhesion of essential oils on the skin's surface and reduce evaporation. Some plant-based oils such as soybean, coconut, and palm nut oils are good candidates for that. Although all these oils are far less effective than DEET, they may be helpful as carriers for other repellent actives. The listed oils are available *vide infra*, low cost, and contain emulsifiers that improve repellent coverage and slow evaporation of volatile repellent molecules (Table 1) [24].

Table 1. *The overview of repellency of some common herbal essential oils*

Essential oil	Concentration	Duration	Protection percentage	Major constituents	Reference
DEET (synthesized chemicals)	40%	7 hours	100%		[9]
Lemon eucalyptus oil	32%	3 hours	95%	1,8-cineole citronellal; Z- and α- citral; α-pinene	[9]
Thyme oil	5%	1.5 hours	85%	thymol, *p*-cymene, carvacrol, linalool, and α -terpinene	[10, 11]
Greek catmint oil	-	2 - 3 hours	-	4α,7α,7aβ-nepetalactone (36.8%), 1,8-cineole (25.5%), and 4α,7β,7β-nepetalactone (11.1%)	[12]
Lemongrass oil	15%	2 - 3 hours	$\geq$ 50%		[13]
Citronella	30%	1 hour	86%	citronellal, geraniol, and citronellol	[14, 15]
Tea tree oil	5%	3 hours	98.1%		[16]
Neem	20%	3 hours	> 70%		[17]
Clove essential oil	10%	2 hours	> 90%	eugenol (76.8%), β-caryophyllene (17.4%), α-humulene (2.1%), and eugenyl acetate (1.2%)	[18, 19]
Cinnamon oil	10%	2 hours	> 90%	eugenol (76.60%), linalool (8.5%) and piperitone (3.31%)	[19, 20]
Cornmint oil	10%	4 hours	> 90%		[21]
Peppermint oil	100%	3.5 hours	100%		[22]

3. Citronella oil

3.1. Chemical composition and biological activities of citronella oil

Numerous commercial repellents contain several herbal essential oils either for fragrance and/or as repellents including peppermint, lemongrass, geraniol, pine oil, pennyroyal, cedar oil, thyme oil, and patchouli. The most effective of these include thyme oil, peppermint oil, clove, and citronella oil which have been found to repel malaria, filarial, and yellow fever vectors for a period of 60-180 mins. In the following articles, we only focus on citronella, which is common and cheap in Southern-east Asia.

Two commercially available essential oils are distilled from the Ceylon and Java citronella species. In the early 20th century, Ceylon citronella was widely used, however, Java citronella gradually prevailed due to higher yields [25]. Citronella oil is an essential oil extracted from the stem or leaves of the different species of *Cymbopogon*. The citronella oil on the global market is more than 2000 tons/year. The main suppliers are Taiwan, Guatemala, Malaysia, Brazil, Ceylon, India, Argentina, Ecuador, Madagascar, Mexico, and the West Indies [26]. Citronella oil is used as an antiseptic, antispasmodic, diuretic, and astringent. Citronella oil has also attracted great attention for mosquito repellent products [15]. The main constituents of citronella oil are citronellal, geraniol, and citronellol [27, 28].

Cymbopogon accounts for about 28 - 45% of citronella oil given the highest percentage [29]. The repelling insect is an outstanding characterization of citronellal, especially dangerous one in terms of mosquitoes. Moreover, citronellal also has anti-inflammatory and antioxidant properties [30]. The experiment carried out by OuYang *et al.* demonstrated that citronellal was able to destroy the cells of *Penicillium Digitatum*, therefore, anti-mold is clarified for the biological activity of this chemical [31]. Furthermore, scavenging free radicals is also identified in this regard [32].

Geraniol was first reported in 1871 by the German chemist Oscar Jacobsen. Geraniol is the major component that can be found in lemongrass and rose essential oils. Geraniol could kill and repel insects, the mosquito-repellent property is very strong as its application is mentioned in the published chemical database of this chemical [33]. Antibacterial activity toward many different bacteria species, *e.g.*, *Pseudomonas*, *Staphylococcus*, and *Escherichia* is also reported for geraniol. Synergistic effect in combination with other drugs to enhance the

effectiveness of antibiotics is also an emphasized characterization of geraniol [34, 35].

Another constituent in citronella oil is citronellol which can also be found in rose and geranium. The mosquito-repellent activity of citronellol was reported in an article published by Seidel *et al.* [36]. In addition, the antibacterial, antifungal, antispasmodic, anti-inflammatory, anti-infective, anticonvulsant, and anti-anxiety properties of citronellol were also reported by Priscila *et al.* [37].

The major components found in citronella oil can repel insects, especially mosquitoes, and are an outstanding property for natural products. These ingredients of citronella oil also have good medicinal properties. Therefore, mosquito repellent derived from citronella oil not only repels mosquitoes but is also beneficial for human health.

3.2. The novel development of mosquito repellent from citronella oil

Citronella oil has been used as a mosquito repellent for such a long time and recently it has been intensively investigated and published in many scientific reports [5]. The group of Sharma *et al.* compared the mosquito-repelling activity of mosquito coils developed based on citronella, eucalyptus, and rosemary. The results show that the mosquito repellent made from citronella has a higher physical strength and repealing mosquito activity than the rest of the essential oil plants, especially commercial products [38]. Enhancing the economic value of the agricultural industry is recently drawn the interest of the research community. Therefore, Elhamida *et al.* developed one type of mosquito repellent coil by combining citronella oil and tapioca stem powder, which is a waste resource in Lampung province, Indonesia. The results show that the mosquito oil developed by this research group meets the Standard Industri Indonesia (SII) No. 1113-84 criteria [39].

The ability to repel mosquitoes of citronella oil obviously depends on the concentration of the essential oil and the *Anopheles* species. This has been illustrated in the work of Kweka *et. al* and Solomon *et al.* that citronella oil concentration from 52 to 85% gave the highest mosquito repellent capacity [40, 41]. The derivative of citronellal, *i.e.*, hydroxylated cyclic acetals, synthesized by Immacolata *et al.* in 2022 to improve repellency with outstanding characterization, *e.g.*, lower volatility, more mosquito repellent activity, and odor. A pleasant feeling for the user due to a weaker scent is also seen in these derivatives. Regarding *Anopheles* species hydroxylated cyclic acetals show the ability to repel *Aedes albopictus* mosquitoes better than that of *N*,*N*-diethyl-metatoluamide at the same concentration at the laboratory scale. When research was conducted on real conditions (where there is a high density of *Aedes albopictus*), the ability of citronellal derivatives to repel mosquitoes is fourth times higher than that of *N*,*N*-diethyl-metatoluamide at the same concentration [42].

The property of rapid evaporation from the skin surface makes citronella oil lose its activity quickly, increases waterproofing time, and minimizes toxicity as highlighted in the work of Higuchi *et al*. in 2023 [43]. Also, citronella oil is packed in microcapsules poly-ε-caprolactone, a highly biodegradable substance [44], by electronic injection technique to increase the evaporation capacity, optimal ratio 3:1 (v/v) of poly-ε-caprolactone and citronella oil at given electric field of 10 kV for the best quality product reported by Francisco *et al*. [43]. In the study of Willy *et al.*, the ability of citronellol and geraniol to repel *Aedes aegypti* was better than that of citronellal. In addition, a deodorant gel with citronella oil mixed with carrageenan, gum, sodium benzoate, ethylene glycol, polysorbate 20, sodium chloride, and distilled water, at different concentrations, was also developed in this work [44]. Another method to develop mosquito repellents is to encapsulate citronella oil with cellulose ethyl by the printing technique proposed by Merih *et al.* in 2022. Mosquito-repellent products developed based on citronella essential oil packaging with cellulose ethyl achieved 72% after five washing cycles [45].

β-cyclodextrin was used as a carrier to produce mosquito repellent containing citronella oil by cross-linking, the results showed that β-cyclodextrin was 23.05 ± 3.88 nm in size gave the product has a high ability to repel mosquitoes for 24 h, this method was developed by Dubey *et al.* [46]. Mosquito repellent formulated by encapsulating citronella oil in a nano-lipid as a carrier to increase the protection time and limit the penetration of citronella oil into the surface of skin was developed by the research group of Higuchi *et al.* The results showed that the ratio of nano-lipid carriers and citronella oil was 1:1 for a mosquito repellent with high physicochemical stability and high repellency [47]. Skin irritation and volatilization of citronella oil were significantly minimized when the mosquito repellent was produced by the dispersive emulsion method reported by Manish *et al.* However, the experiment only stops at the level of animal testing, this research needs to be conducted on humans before being applied [48].

4. Mint oil

4.1. Chemical composition and biological activities of mint oil

Various mints are perceived for their high essential oil (EO) content, which is deposited mainly on the axial surface of the leaves. There are two notable species of mint in cultivation, *i.e.*, *Mentha x piperita* L. as peppermint and *Mentha arvensis* L. (synonym *M. canadensis* L., Japanese mint) as cornmint.

The most common species among the mint family in mosquito repellent is peppermint oil extracted from *Mentha x piperita* L.. This species has been reported and agreed to be a hybrid of mint, a cross between watermint and spearmint. It is more productive in temperate climates with higher rainfall. *Mentha arvensis* L. originates from the temperate climates, it has higher yields under the subtropical conditions of Asia.

Both varieties of mint have been successfully spread and cultivated in some areas of Vietnam. However, because the essential oil content in *Mentha x piperita* L. is not high, it is

less planted commonly than *Mentha arvensis* L.. The significant component of mint oil is presented in Table 2. Menthol is the most important substance found in mint oil, bringing a cool feeling, fresh, and minty taste. This compound is recommended for the treatment of inflammation related to digestive and respiratory tract systems [52]. Hence, this chemical is a paramount ingredient in many medicines. Because of these characteristics and its antibacterial effects, it is also often replaced by a less expensive version in air fresheners, perfumes, and toothpaste as well as in chewing gum [53, 54]. On another approach, menthol is used in many mosquito repellent products with different formulations [55].

Menthone is a mint plant's ketone, one of the two most toxic compounds to insects [56]. L-menthone significantly exhibited insecticidal activity toward *Tribolium castaneum*, *Lasioderma serricorne*, and *Liposcelis bostrychophila* adults [57]. In addition, menthone had shown the potent antibacterial effect on methicillin-resistant *Staphylococcus aureus*, the most infected bacteria in hospital due to the alteration of membrane structural components of bacteria [58]. Therefore, the main component of drugs for treating rheumatoid arthritis is menthone. *In vivo*, vigilant observations demonstrated that menthone alleviates collagen II-induced arthritis in mice [59]. In addition, menthone inhalation reduces local and systemic allergic inflammation in asthmatic mice [60].

Table 2. *The main constituents of essential oil are extracted from two species of mint.*

The main constituents	**Cornmint oil (*Mentha arvensis* oil) (%)** [49]	**Peppermint oil (*Mentha* × *piperita* oil) (%)** [50, 51]
Menthol	65.0 - 85.0	30.0 – 55.0
Methone	4.0 - 20.0	14.0 – 32.0
Menthyl acetate	0.4 - 6.4	2.8 – 10.0
Menthofuran	0.0 - 1.6	1.0 – 9.0
1,8-cineol	0.1 - 0.3	3.5 – 4.0

Menthofuran is a highly toxic organic compound and the main poison in gotu kola responsible for its potentially fatal effects. After oral administration of menthofuran, the effect of this chemical is activated and menthofuran is metabolized to mediators of hepatotoxic chemical reactions [61]. However, there is no evidence of the toxicity of the menthofuran via breathing.

4.2. The novel development of mosquito repellent from mint oil

Mint oil is quite a common one utilized in insecticides, including mosquito repellent also. The duration of pure essential oils or diluted with water as an adopted solvent is quite short and apparently depends on the concentration. The complete protection time increases gradually from 45, 90, and 165 mins at 25, 50, and 100% concentration, respectively in concern to the essential oil extracted from *Mentha arvensis* L.. To reduce the amount of essential oil and increase the protection time, vanillin or an oil carrier is the prestigious substance. The complete protection time of the developed essential oil by adding 5% vanillin to the corn mint oil (at 25%) increased up to 120 mins [62].

Mint oil has just been used in a small amount in the most current mosquito repellents available in the market due to its high cost. Typically, the concentration of these mosquito repellents is from 0.3 - 2%. In this case, the mosquito repellency is not the main reason for their presence in the products, but the cool and fresh feeling from menthol.

5. Discussion

Commercial mosquito repellents usually contain one of the main ingredients, *i.e.*, *N*,*N*-diethyl-meta toluamide, allethrin, and/or dimethyl phthalate [2], which have many adverse effects on human health. Regular use of allethrin-based mosquito repellents will cause metabolic disorders as a conclusion in the work of Narendra *et al.* [63]. The experiments were conducted on mice as the target animal, Abdulla and his colleagues had shown that mosquito repellent incense containing allethrin would increase the concentration of liver enzymes (alanine transaminase - 89%, aspartate transaminase - 85%), cholesterol - 36%, triglycerides (30%), and low-density lipoproteins (48%) [64]. The recommendation proposed by Al-Sagaff and co-workers is that mosquito repellents containing dimethyl phthalate should not be used when a severe adverse effect of dimethyl phthalate on rabbit skin was depicted during their experiments and this effect persisted for two months even though the impact of mosquito repellents containing dimethyl phthalate was ceased [65]. The toxicity of dimethyl phthalate to human erythrocytes was emphasized by the group of Li *et al.* when the antioxidant and immune capacity of erythrocytes would be impaired, destroying the structure of human erythrocytes when they are exposed to dimethyl phthalate [66]. Chi's group had the same conclusion as Li *et al.* while they concluded the red blood cells' oxygen-carrying capacity, oxidative stress on erythrocytes, and erythrocyte iron release under dimethyl phthalate [66].

N,*N*-diethyl-meta toluamide, a major ingredient of many commercial repellents (more than 100 products on the market present-day), was first synthesized by the American chemist Samuel Gertler in 1944 [67]. A report by Swale *et al.* has shown that *N*,*N*-diethyl-meta toluamide is an acetylcholinesterase inhibitor resulting neurotoxicity [68]. The scientific results pointed out that chronic exposure to *N*,*N*-diethyl-meta toluamide increases the risk of coronary heart disease/human cardiovascular diseases [69].

Mosquito repellent with natural ingredients (plant essential oils), will be an alternative effective one to preserve human health rather than these commercial mosquito repellents [1, 5, 7]. The main components in citronella and mint oils, in addition to the ability to repel mosquitoes, also have good both biological and medicinal properties (see sections 3.1 and 4.1).

One study was conducted on 20 common essential oils to investigate their mosquito repellency by using an organic lotion base containing 10% of each essential oil. The study revealed that the most effective ones belong to cinnamon and clove oil following one is peppermint oil.

Citronella oil is less protection time than peppermint oil in both species, mosquitoes and ticks [19]. However, many critical points need to be under stringent consideration regarding research and development of novel repellent products, not only the effectiveness but also the economic aspect. Especially, the toxicity of essential oil is also the most challenge for natural products, *e.g.*, drinking 0.2 - 0.4 mL of peppermint oils three times daily is recommended and safe for reducing some of the common symptoms of irritable bowel syndrome, but peppermint oil can be toxic and even lethal, it has been thought interstitial nephritis and acute renal failure are associated with excessive doses of peppermint oils [70]. Citronella oil is approved by the Environmental Protection Agency after having confident scientific documentation as having minimal or no risks to human and wildlife health and is safe even for children and other sensitive populations [71]. Therefore, citronella oil is a common ingredient in many natural mosquito repellents. However, products based on citronella at lower concentrations have a limited duration of action and higher concentrations can cause skin irritation. Therefore, citronella may be acceptable for brief exposure to nuisance mosquitoes, but it is not recommended for protection against disease-carrying mosquitoes [72]. Natural mosquito repellents usually should be a mixture of some essential oils to get the best protection and safety to overcome this shortcoming. The combination of essential oils increases the duration with less concentration [8]. The mixture of peppermint and patchouli oil at a 1:1 (*v/v*) ratio increased the time of protection against *Anopheles dirus* by more than 200 minutes, while the protection time of pure peppermint oil was 180 minutes and patchouli essential oil was 120 minutes. This essential oil blend contains only 50% of each essential oil, and so reduces their unwanted side effects. The mechanism that increases the mosquito repellency time of the essential oil mixture has not been elucidated. However, this may be due to the interactions between the ingredients that slow down the release of some substances, like those in perfumery.

6. Conclusion

In this review, the chemical composition of citronella and mint oils and their biological activities were introduced in parallel to the main synthesized substance of commercial mosquito repellents. The research and development of novelty natural mosquito repellent based on essential oil from 2020 were summarized. The toxicity of synthesized chemicals contained in commercial mosquito repellent products to living organisms was identified. As a result, the current general trend for research and development of mosquito repellent products containing natural essential oils is attracting the attention and interest of the scientific community. We suppose that further developments for natural mosquito repellent will be coupled with a better understanding of biological mechanisms and improvement of physical characterization. This will also result in a great expansion of the applications in the field of green organic components.

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