Malaysian Journal of Analytical Sciences (MJAS)
Published by Malaysian Analytical Sciences Society

ACETAL DERIVATIVES OF HYDROXYCITRONELLAL: A REVIEW ON SYNTHESIS, CHARACTERIZATION AND THEIR MOSQUITOE REPELLENT ACTIVITIES

(Terbitan Asetal Hidroksisitronelal: Ulasan ke atas Sintesis, Pencirian dan Aktiviti Penghalau Nyamuk)

Ariff Mahtar and Juliana Jumal*

Faculty of Science and Technology
Universiti Sains Islam Malaysia 71800 Nilai, Negeri Sembilan, Malaysia

**Corresponding author: juliana.j@usim.edu.my*

Received: 7 September 2022; Accepted: 20 December 2022; Published: 22 February 2023

Abstract

Mosquitoes represent the deadliest animal species in tropical regions because they can affect human health. Personal protection which is mosquito repellent has been used since 20^{th} century. Mosquito repellent which contains plant-based ingredients has high demand from consumers since its efficacy is as good as synthetic ones. Citronella genus plants are originally extracted to be used in perfumery, then they were used for ingredients of plant-based mosquito repellents as they have repellent properties. Citronellal-based repellent has an effective dose such as *N,N*-diethyl-meta-toluamide dose. However, the oil content has high volatility causing it to reduce its efficacy because the oil evaporates. Recently, the structure of citronellal compound has been modified into hydroxycitronellal by adding some functional groups to reduce the release rate, prolong the protection time and improve the stability of the compound. The release rate properties are affected by functional groups and the molar mass of the compounds. This paper presents a summary of recent catalyst and solvent usage during synthesis, characterization and comparison of mosquito repellents.

Keywords: synthesis, hydroxycitronellal, acetal derivatives, mosquito repellent

Abstrak

Perlindungan diri iaitu penghalau nyamuk telah digunakan sejak abad ke-20. Nyamuk mewakili spesies haiwan yang paling mematikan di kawasan tropika kerana ia boleh menjejaskan kesihatan manusia. Ubat nyamuk yang mengandungi bahan berasaskan tumbuhan mendapat permintaan tinggi daripada pengguna memandangkan keberkesanannya setanding dengan sintetik. Tumbuhan genus *Citronella* pada asalnya diekstrak untuk digunakan dalam minyak wangi, kemudian ia digunakan untuk bahan-bahan penghalau nyamuk berasaskan tumbuhan kerana ia mempunyai sifat penghalau. Penghalau berasaskan sitronelal mempunyai dos berkesan seperti dos *N,N*-dietil-meta-toluamida. Walau bagaimanapun, kandungan minyak mempunyai kemeruapan yang tinggi menyebabkan ia mengurangkan keberkesanannya kerana minyak menyejat. Struktur sebatian sitronel telah diubah suai dengan menambah beberapa kumpulan berfungsi untuk mengurangkan kadar pelepasan, memanjangkan masa perlindungan dan meningkatkan kestabilan sebatian. Sifat kadar pelepasan dipengaruhi oleh kumpulan berfungsi dan jisim molar sebatian. Kertas ini membentangkan ringkasan penggunaan pemangkin dan pelarut terkini semasa sintesis, pencirian dan perbandingan penghalau nyamuk.

Kata kunci: sintesis, hidroksisitronelal, terbitan asetal, penghalau nyamuk

Introduction

Mosquitoes represent the deadliest animal among other species in the tropical regions as they can affect human health [1]. They can spread the pathogens among human in the regions because of the powerful vectors [1]. Malaria, oestridean parasites which can cause myasis, Japanese and encephatilis and the parasites come from the mosquito themselves [2]. Aedes albopictus is one of the common example of Asian tiger mosquito which can cause several reported severe disease cases [3]. There are many strategies which help to reduce infection by and transmission of vector disease especially in tropical regions, such as chemical control, genetic control and personal protection [4]. The use of insecticides represents the chemical control of mosquitoes in order to kill the adults [5]. There are many ways for environmental controls such as the removal of disused tires, draining of ponds and introducing predatory fish [6]. In addition, genetic control mosquito population can also be implemented by reducing mosquitoes's lifespan [7]. However, personal protection is the best way to protect user from mosquito bites as well as to reduce mosquito-borne disease outbreaks potential of user's surrounding [8].

Personal protection which commonly used by individual is mosquito repellent. Mosquito repellent is a key recommendation of health authorities to reduce the potential of mosquito-borne disease. *N,N*-diethyl-m-toluamide (DEET), picaridin and p-menthane-3,8-diol (PMD) are the most commonly used repellent products. The common repellent products have high demand from users because they have good efficacy since 1950s [9]. One of the repellent products which gains the highest demands from users and commonly commercialized by mosquitos repellent industries is DEET [10]. However, DEET can lead to negative impacts to humans [10]. It is reported that DEET can lead to neurotoxic effects not only to insects but as well as human because it can disturb the acetylcholinesterase's activity which is a key enzyme of synaptic transmission [1]. Besides, it can affect the channels of Na^+ and K^+ which are located at cortical neurons in mammalian and it can cause the pro-angigenic effects to human because DEET acts as an allosteric modulator of M3 mAchR [11]. Picaridin also one of the repellents which can cause dermatitis on our skin [12].

Therefore, there has been an effort to seek for environment-friendly repellent [13]. Plant-based repellents is an alternative mosquito repellent to be used for personal protection [13]. Geranyl acetate, citronellal, 6-methyl-5-hepten-2-one and geranyl acetone [8] give response to odor receptors of mosquito which the receptor also can receive the same respond from the gold-standard repellent DEET [14]. Citronellal is reported to be one of the plant-based repellent which has most effective repellent properties because it is monoterpenoid aldehyde and there is a carbonyl group [13]. On the other hand, the two functional or substituent groups of citronellal contributes to biological interaction towards mosquito receptor as mosquito repellent. On the other side of coin, citronellal has high release rate and high volatility because of the presence of carbonyl group [15] and low molecular weight [16]. The structure of citronellal can be modified by adding a functional group [14] and undergoes an acetalization in order to increase its molecular weight and protection time [15].

Acetal, ketal and their derivatives

Acetal and ketal

Acetal (Figure 1) or ketal (Figure 2) can be formed via the reaction between carbonyl and alcohols, for instance methanol or ethanol (Scheme 1) [7]. The reaction is catalysed by acid catalyst. The formaldehyde or higher aldehydes with diols such as 1,2-diols or 1,3-diols in the presence of an acid catalyst can react to form cyclic acetal (Figure 3) [17]. Usually, carbonyl compound will react with an alcohol and aided by catalyst such as Lewis acid to form acetal or ketal [18]. The reaction is stereotypically undergoes with homogenous catalysis; sulphuric acid and phosphoric acid which are mineral inorganic acids [19]. It is important to choose a suitable azeotropic solvent from ketone or aldehyde solution to aid in the process of water removing. Besides, acetal or cyclic acetal can act as protecting group of carbonyl group against an attack by reagents, for example, reducing agents, basic, nucleophiles, catalytic and oxidant [20].

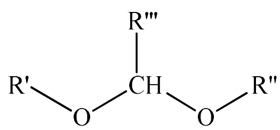


Figure 1. Structure of acetal [21]

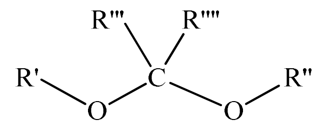
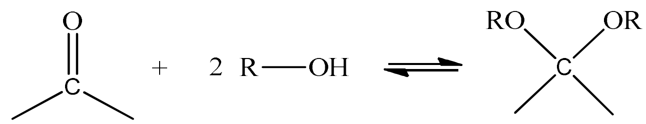


Figure 2. Structure of ketal [21]



Scheme 1. Chemical reaction on synthesizing ketal or acetal [21, 22]

Acetal and ketal can also be synthesized from orthoester carbonyl compound with the presence of glycol and a catalyst [23]. The structures of 1,3-dioxane and 1,3-dioxalane can be formed if the reaction undergoes between polyol and suitable ketone and aldehyde with the used of glycerol in the presence of catalyst [24]. The reaction produces 6 membered ring of 1,3-dioxane or 5 membered ring of 1,3-dioxalane because of the reaction between glycerol and steric blocking of hydrogen atom and radical. The reaction of diol will form a ketal or cyclic ketal (Fig. 4).

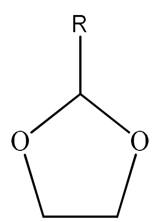


Figure 3. Structure of cyclic acetal [17]

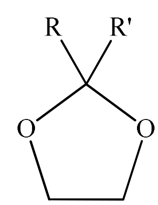


Figure 4. Structure of cyclic ketal [17]

Derivatives of acetal and ketal

Different substituents such as methanol or ethanol have been used in the reaction with aldehyde or ketone to produce our desired acetal or ketal derivatives [25]. The process of acetalization can modify the functional groups of compound in order to provide better efficiency and transformations of subsequent synthetic flexibility [26]. The characteristics of aroma, vapour pressure, flavour and solubility can be modified by using different methods in carbonyl compound conversion, for instance, the compound process is commonly called as attenuation in perfumery industry [23]. Besides, different methods also have been used to synthesize acetal or ketal derivatives by using different catalyst such as β-cyclodextrin. The use of this catalyst has been proven to reduce the release rate, the volatility and to prolong its insect repellent activities [27] in insect repellent industry. On the other hand, the process of synthesizing allysine ethylene acetal (Figure 5) can be simplified using amination method instead of using 8-step process to produce the acetal [28].

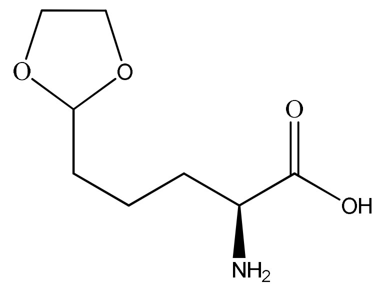


Figure 5. Structure of allysine ethylene acetal [29, 30]

In a view of pharmaceutical industry, the acetal derivatives can improve the activity of anti-inflammatory [31]. The binding of the acetal derivatives to skin which has thiol groups can accumulate in the skin which resulted by the ring-opening of an intermediate of Schiff base. Ethylene ketal derivatives of prostaglandin E2 can also contribute in stability of solid-state improvement. The hydrocortisone 21-acetate spirothiazolidines and hydrocortisone spirothiazolidines have been prepared to be reacted to the substituents of cysteine esters or β-aminothiols and produce the derivatives [31].

Properties of acetal:

Physicochemical properties of acetal

Acetal is an organic compound which has pleasant odor such as earth, nutty, green, sweet [32] and ethereal [33]. The color of acetal in liquid form is colorless at standard state. Acetal has moderate toxicity and narcotic at high concentration [34]. Table 1 lists the physicochemical properties of acetal.

Synthesis:

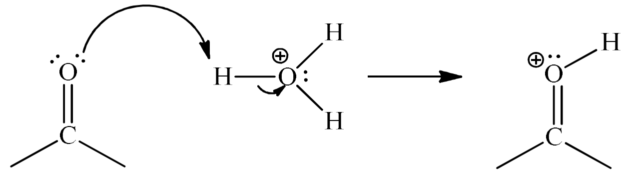
Mechanism of formation of acetal

There are 7 steps of mechanism in the formation of hemiacetal and acetal. Scheme 2 displays the mechanism steps which consist of carbonyl protonation, alcohol's nucleophilic attack, hemiacetal formation through deprotonation, protonation of alcohol, removal of water, alcohol's nucleophilic attack and deprotonation of water [35].

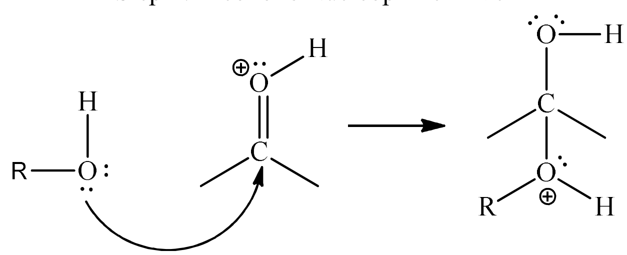
Table 1. Physicochemical properties of acetal

Property	Value	Reference
Molecular Weight	118.17 g/mol	
Density	0.831 g/cm^3	
Melting Point	-80-(-90) °C	
Boiling Point	103-104 °C	[36]
Vapor Pressure	20 mmHg	
Flash Point	-5 °C	
Solubility	Soluble in water	

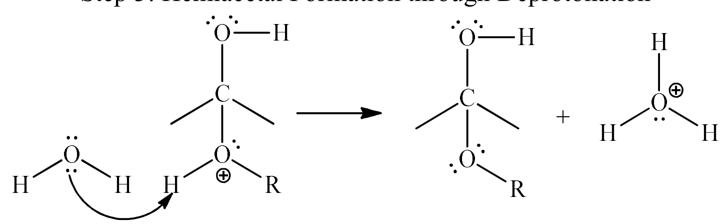
Step 1: Carbonyl Protonation



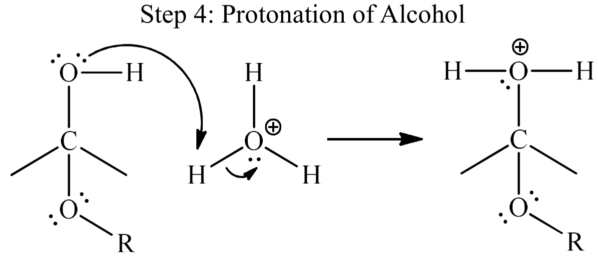
Step 2: Alcohol's Nucleophilic Attack



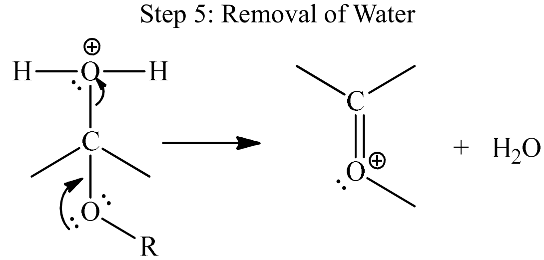
Step 3: Hemiacetal Formation through Deprotonation



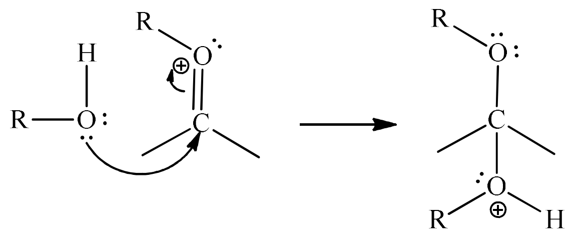
Step 4: Protonation of Alcohol



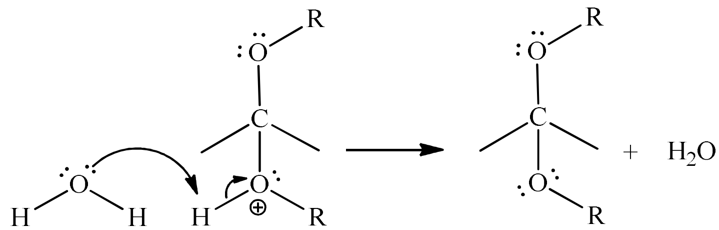
Step 5: Removal of Water



Step 6: Alcohol's Nucleophilic Attack



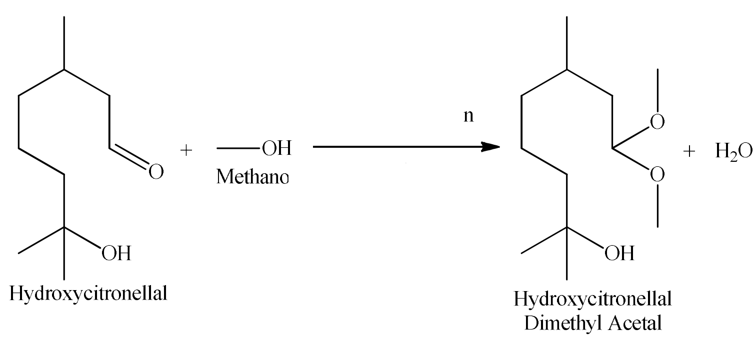
Step 7: Deprotonation of Water



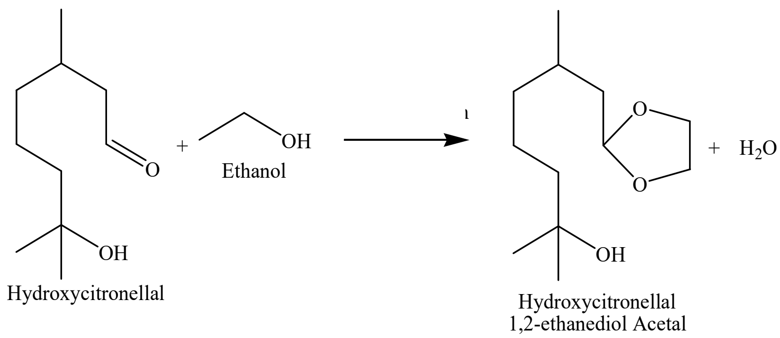
Scheme 2. Mechanism for Hemiacetal and Acetal Formation [35]

Synthesis of hydroxynellal acetal derovatives

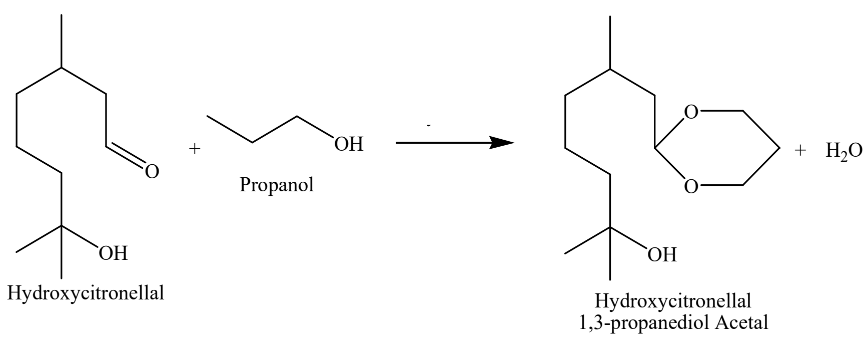
Some plants such as *Cymbopogon* species, to be more specified, *Cymbopogon winterianus* has been traditionally used to repel mosquitoes because it has mosquito repellent properties [37]. The plant can produces a yellow liquid of citronella oil through distillation process of dried Cymbopogon plants [27]. Citronella oil has been approved by United States Environmental Protection Agency (US EPA) to be applied on skin for insect repellent activities [13]. Recently, one of the citronella oil terpenes which are citronellal has been further studied by Zongde [25] by synthesizing hydroxycitronellal acetal derivatives to prolong its protection time . Schemes 3-5 show the synthesis reactions between hydroxycitronellal and its substituents. The overall reactions will be synthesized by using the same type of starting material which is hydroxycitronellal and by using the same methods.



Scheme 3. Synthesis of hydroxycitronellal dimethyl acetal [25]



Scheme 4. Synthesis of hydroxycitronellal 1,2-ethanediol acetal [25]



Scheme 5. Synthesis of hydroxycitronellal 1,3-propanediol acetal [25]

Catalysts usage during synthesis of acetal and acetal derivatives

Hydroxycitronellal is an aldehyde which has been synthesized from citronellal through hydrolysis process. Previously, citronellal acts as starting material, but the repellent properties itself has protection time less than 23 minutes [38] although citronellal has various of effective concentration from 0.05 to 25% (weight/volume) [27]. Then, hydroxycitronellal acts as starting material and has been reacted with a substituent which is methanol and benzene as a solvent [25]. The mixture has been mixed with sulfamic acid that acts as a catalyst. The presence of common acid catalysts such as hydrochloric acid, sulphuric acid, p-toluenesulfonic acid and trifluoroacetic acid [39] in the formation of ketals or acetals by treating aldehydes or ketones with alcohols are corrosive [40]. Alkynes, alkenes, silyl-protected alcohols and N-Boc-protected amines are the subtrates of acid-sensitive groups which are not compatible with acidic condition [41]. Pyridinium salt derivatives [42], dialkyltriazolium salts [43] and imidazolium salts [44] are aprotic salts series which are capable to act as Brønsted acids in chemoselectively acetalization [45]. Ammonium salts also can be employed to the acetalization or ketalization process between aromatic aldehydes or ketones and diols with pentyl methyl ether as solvent in Dean-Stark condition [46]. Mesoporous polymelamine-formaldehyde polymer can be used as catalyst in chemoselectively of aldehydes acetalization [47]. Graphitic-carbon nitride can catalyse the aldehydes or ketones acetalization process with alcohols compound to form acetals or ketal by using light in ambient conditions [48].However, Songkro [27] has found another alternative to control the release rate of desired product by using β-cyclodextrin as a catalyst for the synthesis and can increase the solubility in water [4]. This is because β-cyclodextrin forms an inclusion complex by forming hydroxycitronellal dimethyl acetal-β-cyclodextrin inclusion complex [27]. β-cyclodextrin is a better catalyst to be used in this reaction. Table 2 summarizes the types of catalysts which have been used for acetalization.

Solvent usage during synthesis of acetal and acetal derivatives

Benzene has been used as a solvent in the synthesis of hydroxycitronellal acetal derivatives. However, based on human and animal studies by the International Agency for Research on Cancer (IARC) since 1982, benzene has carcinogenic potential toward both studies [49]. Inhalation is the primary cause of the benzene exposure and the highest amount of the exposure which is 95%-99% can be found in cigarettes [50]. Benzene compound is associated with asthma effect among children [51]. Ferreira [35] has used carbon tetrachloride as one of the solvents to investigate iron (III) porphyrins catalytic activities for acetalization process and the solvent usage shows no product in the reaction because it is non-polar solvent. Besides, carbon tetrachloride also has been observed as chemical that can give liver injury due to its toxic metabolites [52]. Tanaka and co-researchers have found that the usage of dichloromethane as solvent for the regioselectivity ring-opening of benzylidene acetal can produce to 83% of percentage yield [53]. Ethyl acetate also has been used for both processes of preparation of dioxanesldithianes using hydrogen sulphate and deprotection of dioxanesldithianes using hydrogen sulphate [20]. Then, cyclohexane can be considered as an effective and efficient solvent. The usage of the solvent in both process of carbonyl compound as 1,3-dioxalanes protection using indium (III) chloride as catalyst and carbonyl compounds as dialkyl acetals protection using indium (III) chloride as catalyst can give more than 80% of percentage yield [54]. It can create an azeotropic mixture of cyclohexane and water and according to Le Chatelier's Principle, it will favour towards the product [55] if the ratio of the substituent more than starting material. However, the acetalization process does not take place between 2-methylpentanal and 2-methyl-2-propyl-1,3-propanediol at 1:1 ratio using cyclohexane, hexane, heptane and 1,4-dioxane as the solvents. The solubility between the solvents and 2-methyl-2-propyl-1,3-propanediol was low because their dielectric constant values are low [56]. Apart from that, water, glycerol [57] and polyethylene glycol [58] also can be a better option compared to other solvents because of its low toxicity and low risk of hazard [59]. Water can contribute to highest percentage yield of product from acetalization process. Table 3 lists the red solvents and their alternative green solvents for acetalization process.

Characterization

Fourier transform infra-red (FTIR) spectroscopy

The FTIR spectra have shown the absorption of specific chemical groups such as hydroxyl groups, carbonyl groups and alklyl groups [60] which are related to the synthesized acetal derivatives. The FTIR spectra will be recorded in the range of 3040-780 cm^{-1}. The stretching frequency of the C=C group in the aromatic shown at 1400 cm^{-1} and 1460 cm^{-1}. On the other hand, the stretching frequency of C-O in the compound has shown at 1100-1220 cm^{-1}. The peaks of C-H stretching vibration in the benzene ring of the acetal appeared at 759 cm^{-1}, 701 cm^{-1}, 3039 cm^{-1} and 3069 cm^{-1}[61]. Table 4 possess the IR frequency range and band assignment of acetal derivatives.

Proton nuclear magnetic resonance (^{1}H NMR) spectroscopy

The synthesized of hydroxycitronellal dimethyl acetal detected the resonance peak at 3.58 ppm which attributed to hydroxyl group in the acetal compound. On the other hand, result of the ^{1}H NMR showed signal at 4.19 ppm which attributed to methine group. Methyl group can be detected from the peak at 3.50 ppm. ^{1}H NMR chemical shift of hydroxycitronellal acetal derivatives is shown in Table 5.

CHNS elemental analysis

CHNS elemental analysis is a technique to identify the elements namely carbon, hydrogen, nitrogen and sulphur. The analyzed compound will undergo oxidative decomposition [62]. The compound also will undergo reduction of nitrogen and sulfur dioxide. The characteristic of thermal decomposition and the properties of the analyzed compounds that we have synthesized will affect the errors. There is potential of the under oxidation of the compound which will affect the determination of carbon and hydrogen. The speciation of nitrogen in synthesized compound will affect the decomposition of nitrogen-containing compound [62]. Table 6 show the percentage of the C and H elements.

Mosquito repellent activities

Mosquito repellent

There are variety ways to measure the spread of mosquito disease such as chemical measure, genetic measure, environmental measure and personal protection; mosquito repellents [4]. Chemical measure has been used larvicides and insecticides [71] to kill the larvae and adults. However, the use of the chemicals have contaminated the water source and this measure have not developed to control all mosquito species [63]. The non-biological pesticides have high toxicity which gave severe impact to our environment and wildlife [4]. Environmental measure also has been applied by monitoring or removing the unused tires, draining the ponds; mosquito habitats, putting the predator fish in the ponds and building the water flow system in the pools [6]. Unfortunately, this measure has many difficulties for its maintenance and requires a good cooperation between local people [4]. Genetic measure also has been used by manipulating the mosquitoes genetic, for instance, the lifespan of the mosquito becomes shorter to reduce the transmit rate of malaria [64] and the sterilized males has been released to mate with females but the females cannot fertilize eggs [65]. This measure requires high expense to produce males and only works on the islands because of the variability of genetics is high [4] and the insects are migrate from place to place. The usage of personal protection; mosquito repellents become our first line defense from mosquitoes because this measure has lowered the transmit of malaria above 80% [66]. This reason have brought awareness to use personal protection control [1] to prevent from getting mosquito bites [4]. The synthetic mosquito repellents which have been commercialized are N,N-diethyl-meta-toluamide (DEET) [9] and ethylbutylacetylaminopropionate (IR3535) [67] which are synthetic repellent and citronellal [68], [69] which is essential oil mosquito repellent.

N,N-diethyl-meta-toluamide (DEET)

DEET (Figure 6) has been considered as gold mosquito repellents standard [14] because of its effectiveness [70]. The efficacy of DEET at 15% solution is 7-8 hours of protection time against mosquitoes [71]. However, DEET has been highlighted to has high potential severe effects on human health as well as surrounding [1]. It can cause neurotoxic effects on human and other insects by inhibiting an specific enzyme key activities [72]. In addition, it also can cause effects of pro-angiogenic on human by inhibiting specific ion channels in mammalian cortical neurons [73].

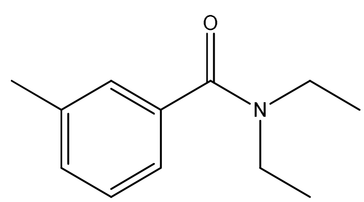


Figure 6. Chemical structure of DEET [1, 14, 70, 71, 72, 73]

Ethylbutylacetylaminopropionate (IR3535)

IR3535 (Figure 7) is one of the efficient repellents against mosquitoes. IR3535 has same effectiveness as DEET, also known as gold standard [1]. IR3535 has 7-10 hours protection times against Culex and Aedes mosquitoes and 3-4 hours protection time against Anopheles mosquitoes [67]. However, it has potential in dermal and oral toxicity [74] after the repellent has been tested on rats. It can cause eye irritation and skin irritation on human [1]. Then, IR3535 also can cause damage to synthetic material [75]. The positive point of IR3535 is this mosquito repellent may not has toxic potential towards life in water and it also not accumulates in our environment [76]. Figure 7 shows the chemical structure of IR3535.

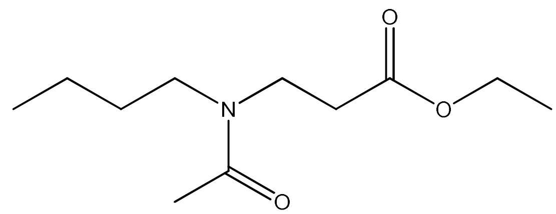


Figure 7. Chemical Structure of IR3535 [1, 67, 74, 75, 76]

Hydroxycitronellal acetal derivatives

Plant-based material have been used for thousand years by human as a personal protection against mosquitoes; a practice which is still widely uses in developing countries [77]. *Cymbopogon winterianus* has been extracted to produce citronellol, citronellal (Figure 8) and geraniol [78]. Citronella oil has been registered as mosquito repellent under United States Environmental Protection Agency (US EPA) [13], [37] because of its efficacy and it has low toxicity on test animal. Although, the gold-standard synthetic repellent DEET [14] can protect against various insect species, but it was reported that the repellent can give negative effect to human as mentioned earlier. Citronella-based repellents can repel in a certain period from mosquitoes. However, the oils rapidly leave the user unprotected because of the citronella itself is chemically has high rate of evaporation property [79]. Thus, Zongde [25] has modified the structure citronellal oil into hydroxycitronellal acetal derivatives (Figure 9) using acetalization process and Songkro [27] has formed inclusion complex [80] which will increase the number of molecules [81]. These efforts can enhance the protection time of the oil against mosquitoes.

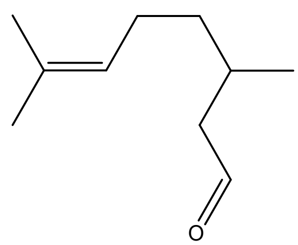


Figure 8. Chemical Structure of Citronellal [82]

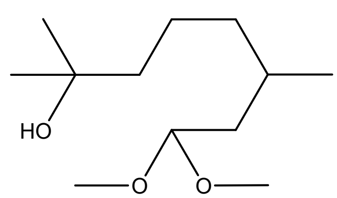


Figure 9. Chemical Structure of hydroxycitronellal dimethyl acetal [25]

Table 2. Catalysts for acetalization

Catalysts	References
Sulfamic acid	[25]
Hydrochloric acid	[39]
Sulphuric acid	
p-toluenesulfonic acid	
Trifluoroacetic acid	
Pyridinium salt derivatives	[42]
Dialkyltriazolium salts	[43]
Imidazolium salts	[44]
Ammonium salts	[46]
Mesoporous-polymelamine-formaldehyde polymer	[47]
Graphitic-C_3N_4	[48]
β-cyclodextrin	[27]

Table 3. Solvents for acetalization

Types of Solvent	Solvents Name	References
Red solvents	Benzene	[25]
	Carbon tetrachloride	[35]
	Chloroform	
Alternatives solvents	Cyclohexane	[54], [56]
	Hexane	[56]
	Heptane	
	1,4-dioxane	
	Dichloromethane	[53]
	Ethyl Acetate	[20]
Green solvents	Water	[59]
	Glycerol	[57]
	Polyethylene glycol	[58]

Table 4. IR frequency range and band assignment of acetal derivatives

Band Assignment	Wavenumber (cm^{-1})			Reference
	Hydroxycitronellal dimethyl acetal	Hydroxycitronellal 1,2-ethanediol acetal	Hydroxycitronellal 1,3-propanediol acetal	
v(C-O)	1056-1192	1052-1199	1076-1143	[25]
v(C-O-C)	1058-1194	1058-1201	1078-1250	
v(C-H)	1375-1464	2837-2939	1379-1647	
v(OH)	3212-3440	3257-3441	3259-3424	

Table 5. ^{1}H NMR chemical shift range of acetal derivatives

Compounds	Assignment	^{1}H NMR Chemical Shift Range, δ (ppm)	Reference
Hydroxycitronellal dimethyl acetal	δ_H (OH)	3.58-3.65	[25]
	δ_H (Methine)	1.65-4.19	
	δ_H (Methyl)	0.96-3.50	
	δ_H (Methylene)	1.25-1.44	
Hydroxycitronellal 1,2-ethanediol acetal	δ_H (OH)	3.58-3.65	
	δ_H (Methine)	1.65-4.19	
	δ_H (1,3-dioxalane)	4.05-4.89	
	δ_H (Methyl)	0.96-1.24	
	δ_H (Methylene)	1.25-1.40	
Hydroxycitronellal 1,3-propanediol acetal	δ_H (OH)	3.58-3.65	
	δ_H (Methine)	1.65-4.19	
	δ_H (1,3-dioxane)	1.88-4.69	
	δ_H (Methyl)	0.96-1.24	
	δ_H (Methylene)	1.25-1.55	

Table 6. Composition of carbon and hydrogen element in acetal derivatives

Compounds	Element Composition (%)		Reference
	C	H	
Hydroxycitronellal dimethyl acetal	66.06	11.93	[62]
Hydroxycitronellal 1,2-ethanediol acetal	66.67	11.11	
Hydroxycitronellal1,3-propanediol acetal	67.83	11.30	

Method of repellency test using human assay

The neutral soap will be used to wash the forearm and hand of a human subject. The forearm and hand will be thoroughly rinsed and dried for 10 min before apply synthesized compound. The hand will be wear a glove to protect against bites [83]. The forearm will be covered using a paper sleeve with a 25 mm circle to expose the skin. 3 mL product will be applied to the skin. The other forearm will be protected with a same paper sleeve without applying any products to the skin as a control. 20 mosquitoes will be placed in 20 × 20 × 20 cm cages. The cage will have a cotton stockinet on the front, clear glass at the back and top, an aluminum sheet bottom and screen on the sides. The test must be 27 °C temperature. Test will be conducted by placing the forearm with the repellent into a test cage for 5 minutes [84]. After 5 minutes of repellent application the stopwatch will be started. Every 30 minutes will be recorded as protection time until the test subject received a mosquito bite. Protection time will be recorded as the period time between repellent application and the observation period until the forearm obtain a bite. If no bites in 90 min, test will be stopped and protection time will be recorded as 90 minutes. It will be considered as a bite if a mosquito attempt to insert its stylets [83]. For the rare case, if there is no mosquito bite on the without repellent application arm during the observation, the trial will be stopped and will be repeated with new mosquito batch. This situation is to make sure that no bites is due to the repellent compound. Every synthesized compound will be used three times on the subject [10]. Each of the product will be tested once a day. Since, there are three different acetal derivatives that will be obtained, so the repellence test will be taken 9 days to complete it. Each of the repellency test will be conducted at night.

Method of repellency test using animal assay

The soap will be used to wash the abdomen of 4 mice and dried the mice for 20 minutes. The fur of mice's abdomen has been shaved in square shape of 2.5 cm x 2 cm. Hydroxycitronellal oil has been applied to first mice on its skin, which acts as controlled mice. Then, the remaining mice's have been applied hydroxycitronellal dimethyl acetal, hydroxycitronellal 1,2-ethandiol acetal and hydroxycitronellal 1,3-propanediol acetal. Then, they have prepared a cylindrical applicator with the diameter 5.5 cm and height of 12 cm with a square opening area of 2 cm x 2 cm at the lower end [25]. The applicator has been filled with 30 mosquitoes. The test has been repeated three times to obtain an average protection time of mice against mosquitoes.

Protection time of mice against mosquitoes

According to result, the first mice which has been applied to hydroxycitronellal oil has the shortest protection time. The last mice which have been applied with hydroxycitronellal 1,3-propanediol acetal has the longest protection time. Table 7 shows the repellence times of synthesized hydroxycitronellal derivatives which are hydroxycitronellal dimethyl acetal, hydroxycitronellal 1,2-ethanediol acetal and hydroxycitronellal 1,3-propanediol acetal.

Table 7. The repellence time of the compounds against mosquitoes

Compounds	Repellence Times (min) Number of Trial			Reference
	1	2	3	
Hydroxycitronellal	10	8	9	[10, 25]
Hydroxycitronellal dimethyl acetal	20	18	29	
Hydroxycitronellal 1,2-ethanediol acetal	30	28	40	
Hydroxycitronellal 1,3-propanediol acetal	60	58	57	

Protection time of human against mosquitoes

According to the result, the first human hand which has been applied to hydroxycitronellal oil has the shortest protection time. The last human hand which has been applied with hydroxycitronellal 1,3-propanediol acetal has the longest protection time. Table 8 lists the repellence times of synthesized hydroxycitronellal derivatives which are hydroxycitronellal dimethyl acetal, hydroxycitronellal 1,2-ethanediol acetal and hydroxycitronellal 1,3-propanediol acetal.

Table 8. The repellence time of the compounds against mosquitoes

Compounds	Repellence Times (min) Number of Trial			Reference
	1	2	3	
Hydroxycitronellal	10	8	9	[10, 25]
Hydroxycitronellal dimethyl acetal	20	18	29	
Hydroxycitronellal 1,2-ethanediol acetal	30	28	40	
Hydroxycitronellal 1,3-propanediol acetal	60	58	57	

Conclusion

DEET, IR3535 and citronellal are initially used for mosquito repellent because of the potential protection time and release rate. However, DEET and IR3535 recently have been reported to have high potential effect towards human health and surroundings. Citronellal oil, plant-based oil has similar efficacy as mosquito repellent compared to the commercial repellents. The green oil undergoes hydrolysis process to produce hydroxycitronellal oil and recently hydroxycitronellal oil undergo acetalization process to produce its derivatives. The modification of functional groups of green citronellal oil has been take place to improve the protection time and efficacy. During the synthesis process, acid catalysts can improve in protection time. However, by using green catalyst which is β-cyclodextrin, it can form inclusion complex. The complex improves the release rate mosquito repellent. The usage of solvent in acetalization can improve to percentage yield of our desired product. Benzene, carbon tetrachloride, chloroform, toluene, acetone and xylene are listed in red solvents. This is due to one of the solvents which is benzene has carcinogenic potential towards human and animal through primary exposure of benzene which is through inhalation. There are many alternatives solvents which can be used for this reaction such as water, glycerol and polyethylene glycol. The alternatives solvents are not just green solvents but it can contribute to the reaction to obtain products with better percentage yield. Green synthesis of mosquito repellent can be undergoing by wisely selecting potential plant-based starting material, non-hazardous solvent and green catalyst. Apart from that, there are two types of assays to examine our mosquito repellent products which are human assay and animal assay. Acetal derivatives of hydroxycitronellal oils have promising protection time. The derivatives have promising release rate and volatility which affected by their molecular weight and inter-molecular bonding.

Acknowledgment

The authors would like to thank Faculty of Science and Technology, Universiti Sains Islam Malaysia, for all the support given to complete this review.

References

1. Abd-Ella, A., Stankiewicz, M., Mikulska, K., Nowak, W., Pennetier, C., Goulu, M. and Lapied, B. (2015). The repellent DEET potentiates carbamate effects via insect muscarinic receptor interactions: An alternative strategy to control insect vector-borne diseases. *PLoS ONE*, 10(5): 1-20.
2. Abdullah Khan, M., Teixeira, I. F., Li, M. M. J., Koito, Y. and Tsang, S. C. E. (2016). Graphitic carbon nitride catalysed photoacetalization of aldehydes/ketones under ambient conditions. *Chemical Communications*, 52(13): 2772-2775.
3. Ali Ashter, S. (2016). 3 - mechanisms of polymer degradation. In *Introduction to Bioplastics Engineering* (pp. 31–59).
4. Amraoui, F., Pain, A., Piorkowski, G., Vazeille, M., Couto-Lima, D., de Lamballerie, X., … and Failloux, A. B. (2018). Experimental adaptation of the yellow fever virus to the mosquito *Aedes albopictus* and potential risk of urban epidemics in Brazil, South America. *Scientific Reports*, 8(1): 4-11.
5. Azzena, U., Carraro, M., Mamuye, A. D., Murgia, I., Pisano, L. and Zedde, G. (2015). Cyclopentyl methyl ether-NH_4X: A novel solvent/catalyst system for low impact acetalization reactions. *Green Chemistry*, 17(6): 3281-3284.
6. Barnard, D. R. and Xue, R. De. (2004). Laboratory evaluation of mosquito repellents against *Aedes albopictus, Culex nigripalpus,* and *Ochlerotatus triseriatus* (Diptera: Culicidae). *Journal of Medical Entomology*, 41(4): 726-730.
7. Cal, K. and Centkowska, K. (2008). Use of cyclodextrins in topical formulations: Practical aspects. *European Journal of Pharmaceutics* and *Biopharmaceutics*, 68(3): 467-478.
8. Capeletti, M. R., Balzano, L., De La Puente, G., Laborde, M. and Sedran, U. (2000). Synthesis of acetal (1,1-diethoxyethane) from ethanol and acetaldehyde over acidic catalysts. *Applied Catalysis A: General*, 198(1–2): 8-11.
9. Chen, L., Nohair, B. and Kaliaguine, S. (2015). Glycerol acetalization with formaldehyde using water-tolerant solid acids. *Elsevier B.V.*, (10): 1-38.
10. Chen, W. L., Wang, L. Y. and Li, Y. J. (2020). C-H functionalization of amino alcohols by osmium tetroxide/NMO or TPAP/NMO: Protecting group-free synthesis of indolizidines (–)-223AB and 3-Epi-(–)-223AB. *European Journal of Organic Chemistry*, 2020(1): 103-107.
11. Choi-sledeski, Y. M. and Wermuth, C. G. (2015). Designing prodrugs and bioprecursors. *The Practice of Medicinal Chemistry*, 2015: 657-696.
12. Clarensia, V., Kurniawan, J. and Lo, D. (2021). The changes in density, flavor compounds, and sensory description of vanilla extract after expiration. *IOP Conference Series: Earth Environmental Science*, 794: 1-8.

13. Climent, M. J., Corma, A. and Velty, A. (2004). Synthesis of hyacinth, vanilla, and blossom orange fragrances: the benefit of using zeolites and delaminated zeolites as catalysts. *Applied Catalysis A: General*, 263(2): 155-161.
14. Corazza, M., Borghi, A., Zampino, M. R. and Virgili, A. (2004). Allergic contact dermatitis due to an insect repellent : double sensitization to picaridin and methyl glucose dioleate. *Acta Dermato-Venereologica*, 1(1): 264-265.
15. Corby-Harris, V., Drexler, A., de Jong, L. W., Antonova, Y., Pakpour, N., Ziegler, R. and Riehle, M. A. (2010). Activation of akt signaling reduces the prevalence and intensity of malaria parasite infection and lifespan in *Anopheles stephensi* mosquitoes. *PLoS Pathogens*, 6(7): 1-10.
16. Diaz, J. H. (2016). Chemical and plant-based insect repellents: efficacy, safety, and toxicity. *Wilderness and Environmental Medicine*, 27(1): 153-163.
17. Dong, J. L., Yu, L. S. H. and Xie, J. W. (2018). A simple and versatile method for the formation of acetals/ketals using trace conventional acids. *ACS Omega*, 3(5): 4974-4985.
18. dos Reis, E. F., Campos, F. S., Lage, A. P., Leite, R. C., Heneine, L. G., Vasconcelos, W. L., Mansur, H. S. (2006). Synthesis and characterization of poly (vinyl alcohol) hydrogels and hybrids for RMPB70 protein adsorption. *Materials Research*, 9(2): 185-191.
19. Drapeau, J. (2017). Insect repellents based on para-menthane-3,8-diol. *University of Regensburg*, 1(1): 1-194.
20. Eden, W. T., Alighiri, D., Supardi, K. I. and Cahyono, E. (2020). The mosquito repellent activity of the active component of air freshener gel from Java citronella oil (*Cymbopogon Winterianus*). *Journal of Parasitology Research*, 1(1): 1-5.
21. Erlanger, T. E., Keiser, J. and Utzinger, J. (2008). Effect of dengue vector control interventions on entomological parameters in developing countries : A systematic review and meta-analysis. *Medical and Veterinary Entomology*, 22(1): 203-221.
22. Fadeeva, V. P., Tikhova, V. D. and Nikulicheva, O. N. (2008). Elemental analysis of organic compounds with the use of automated CHNS analyzers. *Journal of Analytical Chemistry*, 63(11): 1094-1106.
23. Fradin, M. and Day, J. (2002). Comparative efficacy of insect repellents against mosquitoes. *AAP Grand Rounds*, 8(4): 42-43.
24. Gautam, S. (2020). A call to (green) arms : Synthesis of acetals and cyclic acetals with and without solvents - a comparison. *International Journal of Scientific Development and Research*, 5(2): 416-423.
25. Gillij, Y. G., Gleiser, R. M. and Zygadlo, J. A. (2008). Mosquito repellent activity of essential oils of aromatic plants growing in argentina. *Bioresource Technology*, 99(7): 2507-2515.
26. Goodyer, L. I., Croft, A. M., Frances, S. P., Hill, N., Moore, S. J., Onyango, S. P. and Debboun, M. (2010). Expert review of the evidence base for arthropod bite avoidance. *Journal of Travel Medicine*, 17(3): 182-192.
27. Grabowski, J., Granda, J. M. and Jurczak, J. (2018). Preparation of acetals from aldehydes and alcohols under basic conditions. *Organic and Biomolecular Chemistry*, 16(17): 3114-3120.
28. Grison, C., Carrasco, D., Pelissier, F. and Moderc, A. (2020). Reflexion on bio-sourced mosquito repellents: nature, activity, and preparation. *Frontiers in Ecology and Evolution*, 8(8): 1-14.
29. Gupta, N., Sonu, Kad, G. L. and Singh, J. (2007). Acidic ionic liquid $[B_{mim}]HSO_4$: An efficient catalyst for acetalization and thioacetalization of carbonyl compounds and their subsequent deprotection. *Catalysis Communications*, 8(9): 1323-1328.
30. Hosseini, M. S. and Masteri-Farahani, M. (2020). Fabrication of new magnetite based sulfonic-phosphotungstic dual-acid catalyst for catalytic acetalization of benzaldehyde with ethylene glycol. *Reaction Kinetics, Mechanisms and Catalysis*, 130(2): 979-991.
31. Hsieh, W., Chang, C. and Gao, Y. (2006). Controlled release properties of chitosan encapsulated volatile citronella oil microcapsules by thermal treatments. *Colloids and Surface B: Biointerfaces*, 53(1): 209-214.

32. Johnson, A. A. and Riehle, M. A. (2015). Resveratrol fails to extend life span in the mosquito anopheles stephensi. *Rejuvenation Research*, 18(5): 473-478.
33. Kaetan, G., Ferreira, B., Carvalho, C. and Nakagaki, S. (2019). Studies of the catalytic activity of iron (III) porphyrins for the protection of carbonyl groups in homogeneous media. *Catalysts*, 9(4): 1-14.
34. Kaihara, S., Matsumura, S. and Fisher, J. P. (2007). Synthesis and properties of poly [poly (ethylene glycol)-co-cyclic acetal] based hydrogels. *Macromolecules*, 40(21): 7625-7632.
35. Katz, T. M., Miller, J. H. and Hebert, A. A. (2008). Insect repellents: Historical perspectives and new developments. *Journal of American Academy of Dermatology*, 58(5): 865-871.
36. Kubisa, P. and Vairon, J. P. (2012). Ring-opening polymerization of cyclic acetals. In *Polymer Science: A Comprehensive Reference,* 4: pp. 183-211.
37. Kumar, R., Kumar, D. and Chakraborti, A. K. (2007). Perchloric acid adsorbed on silica gel ($HClO_4$-SiO_2) as an inexpensive, extremely efficient, and reusable dual catalyst system for acetal/ketal formation and their deprotection to aldehydes/ketones. *Synthesis*, 1(2): 299-303.
38. Legeay, S., Clere, N., Hilairet, G., Do, Q. T., Bernard, P., Quignard, J. F. and Faure, S. (2016). The insect repellent n,n-diethyl-m-toluamide (DEET) induces angiogenesis via allosteric modulation of the M3 muscarinic receptor in endothelial cells. *Scientific Reports*, 6(1): 1-13.
39. Lenard, E. J., Botteselle, G. V, Azambuja, F. De, Perin, G. and Jacob, R. G. (2007). Citronellal as key compound in organic synthesis. *Tetrahedron*, 63(803): 6671-6712.
40. Li, X., He, W., Chen, Y., Yang, G., Wan, H., Zhang, L., … and Tao, W. (2017). Discovery of SHR9352: A highly potent g protein-biased μ -opioid receptor agonist. *ACS Omega*, 2(12): 9261-9267.
41. Lindbohm, M. L., Sallmén, M., Kyyrönen, P., Kauppinen, T. and Pukkala, E. (2009). Risk of liver cancer and exposure to organic solvents and gasoline vapors among finnish workers. *International Journal of Cancer*, 124(12): 2954-2959.
42. Lu, P. C. W., Shahbaz, S. and Winn, L. M. (2020). Benzene and its effects on cell signaling pathways related to hematopoiesis and leukemia. *Journal of Applied Toxicology*, 40(8): 1018-1032.
43. Lupi, E., Hatz, C. and Schlagenhauf, P. (2013). The efficacy of repellents against aedes, anopheles, culex and ixodes Spp. - A literature review. *Travel Medicine and Infectious Disease*, 11(6): 374-411.
44. Maia, M. F. and Moore, S. J. (2011). Plant-based insect repellents: A review of their efficacy, development and testing. *Malaria Journal*, 10: 1-15.
45. Manwill, P. K., Kalsi, M., Wu, S., Martinez-Rodriguez, E. J., Cheng, X., Piermarini, P. M. and Rakotondraibe, H. L. (2020). Semi-synthetic cinnamodial analogues: structural insights into the insecticidal and antifeedant activities of drimane sesquiterpenes against the mosquito *Aedes aegypti. PLoS Neglected Tropical Diseases*, 14(2): 1-21.
46. Marina, C. F., Bond, J. G., Hern, K., Valle, J., Ulloa, A., Fern, I. and Liedo, P. (2021). Population dynamics of *Aedes aegypti* and *Aedes albopictus* in two rural villages in Southern Mexico : Baseline data for an evaluation of the sterile insect technique. *Insects*, 12(58): 1-18.
47. Moore, S. J., Hill, N. and Ruiz, C. (2007). Field evaluation of traditionally used plant-based insect repellents and fumigants against the malaria vector anopheles darlingi in Riberalta, Bolivian Amazon. (Bloland 2001): 624-630.
48. Morrison, A. C., Minnick, S. L., Rocha, C., Forshey, B. M., Stoddard, S. T., Getis, A. and Kochel, T. J. (2010). Epidemiology of dengue virus in iquitos, Peru 1999 To 2005: Interepidemic and epidemic patterns of transmission. *PLoS Neglected Tropical Diseases*, 4(5): e670.
49. Moss, G., Smith, P. A. S. and Tavernier, D. (1995). Glossary of class names of organic compounds and reactive based on structure (IUPAC Recommendations 1995). *Pure and Applied Chemistry*, 67: 1307-1375.

50. Myles, L., Gathergood, N. and Connon, S. J. (2013). The catalytic versatility of low toxicity dialkyltriazolium salts: in situ modification facilitates diametrically opposed catalysis modes in one pot. *Chemical Communications*, 49(46): 5316-5318.
51. Myles, L., Gore, R. G., Gathergood, N. and Connon, S. J. (2013). A new generation of aprotic yet brønsted acidic imidazolium salts: low toxicity, high recyclability and greatly improved activity. *Green Chemistry*, 15(10): 2740-2746.
52. Myles, L., Gore, R., Špulák, M., Gathergood, N. and Connon, S. J. (2010). Highly recyclable, imidazolium derived ionic liquids of low antimicrobial and antifungal toxicity: a new strategy for acid catalysis. *Green Chemistry*, 12(7): 1157-1162.
53. Nentwig, G. (2003). Use of repellents as prophylactic agents. *Parasitology Research*, 90(1): 40-48.
54. Nerio, L. S., Olivero-Verbel, J. and Stashenko, E. (2010). Repellent activity of essential oils: A review. *Bioresource Technology*, 101(1): 372-378.
55. Panke, S. and Wubbolts, M. (2005). Advances in biocatalytic synthesis of pharmaceutical intermediates. *Current Opinion in Chemical Biology*, 9(2): 188-194.
56. Park, B. S., Choi, W. S., Kim, J. H., Kim, K. H. and Lee, S. E. (2005). Monoterpenes from thyme (*Thymus vulgaris*) as potential mosquito repellents. *Journal of the American Mosquito Control Association*, 21(1): 80-83.
57. Patel, R. N. (2008). Synthesis of chiral pharmaceutical intermediates by biocatalysis. *Coordination Chemistry Reviews*, 252(5-7): 659-701.
58. Peng, Z., He, M., Zhou, L., Wu, X., Wang, L., Li, N. and Deng, S. (2022). Mosquito repellents: Efficacy tests of commercial skin-applied products in China. *Molecules*, 27(17): 1-13.
59. Perestrelo, R., Silva, C., & Câmara, J. S. (2019). Madeira Wine Volatile Profile. A Platform To Establish Madeira Wine Aroma Descriptors. *Molecules*, *24*(17), 3028.
60. Procuranti, B., & Connon, S. J. (2008). Unexpected catalysis: Aprotic pyridinium ions as active and recyclable brønsted acid catalysts in protic media. *Organic Letters*, 10(21): 4935-4938.
61. Purcaro, G., Moret, S. and Conte, L. S. (2015). Polycyclic aromatic hydrocarbons. In *Encyclopedia of Food and Health*.
62. Qian, S., Liu, X., Emel'Yanenko, V. N., Sikorski, P., Kammakakam, I., Flowers, B. S. and Bara, J. E. (2020). Synthesis and properties of 1,2,3-triethoxypropane: a glycerol-derived green solvent candidate. *Industrial and Engineering Chemistry Research*, 1(1): 1-11.
63. Sastri, V. R. (2014). 7 - Engineering thermoplastics: Acrylics, polycarbonates, polyurethanes, polyacetals, polyesters, and polyamides. In plastics in medical devices *(Second Edition)*: pp. 121-172.
64. Ranu, B. C., Jana, R. and Samanta, S. (2004). A simple, efficient and general procedure for acetalization of carbonyl compounds and deprotection of acetals under the catalysis of indium (III) chloride. *Advanced Synthesis and Catalysis*, 346(4): 446-450.
65. Reinhold, J. M., Lazzari, C. R. and Lahondère, C. (2018). Effects of the environmental temperature on *Aedes aegypti* and *Aedes albopictus* mosquitoes: A review. *Insects*, *9*(4): 1-17.
66. Rowland, M., Downey, G., Rab, A., Freeman, T., Mohammad, N., Rehman, H. and Fayaz, M. (2004). DEET mosquito repellent provides personal protection against malaria: A household randomized trial in an afghan refugee camp in Pakistan. *Tropical Medicine and International Health*, 9(3): 335-342.
67. Sakulku, U., Nuchuchua, O., Uawongyart, N., Puttipipatkhachorn, S., Soottitantawat, A. and Ruktanonchai, U. (2009). Characterization and mosquito repellent activity of citronella oil nanoemulsion. *International Journal of Pharmaceutics*, 372(1-2): 105-111.
68. Scalia, S., Tursilli, R., Bianchi, A., Nostro, P. Lo, Bocci, E., Ridi, F. and Baglioni, P. (2006). Incorporation of the sunscreen agent, octyl methoxycinnamate in a cellulosic fabric grafted with β-cyclodextrin. *International Journal of Pharmaceutics*, 308(1-2): 155-159.

69. Sekerová, L., Spáčilová, M., Vyskočilová, E., Krupka, J. and Červený, L. (2019). Acid catalyzed acetalization of aldehydes with diols resulting into the formation of fragrant cyclic acetals. *Reaction Kinetics, Mechanisms and Catalysis*, 127(2): 727-740.
70. Sheng, D., Xu, F., Yu, Q., Fang, T., Xia, J., Li, S. and Wang, X. (2015). A study of structural differences between liver cancer cells and normal liver cells using FTIR spectroscopy. *Journal of Molecular Structure*, 1099(1): 18-23.
71. Songkro, S., Hayook, N., Jaisawang, J., Maneenuan, D., Chuchome, T. and Kaewnopparat, N. (2012). Investigation of inclusion complexes of citronella oil, citronellal and citronellol with β-cyclodextrin for mosquito repellent. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 72(3–4): 339-355.
72. Sparks, J. T., Botsko, G., Swale, D. R., Boland, L. M., Patel, S. S. and Dickens, J. C. (2018). Membrane proteins mediating reception and transduction in chemosensory neurons in mosquitoes. *Frontiers in Physiology*, 9(1309), 1-14.
73. Stephen D., Dini M., Chow-Y. L. (2018). Advances in the biology and management of modern bed bugs. (1st edition). United Kingdom: John Wiley & Sons Ltd.
74. Tan, M. X., Gu, L., Li, N., Ying, J. Y. and Zhang, Y. (2013). Mesoporous poly-melamine-formaldehyde (MPMF)-a highly efficient catalyst for chemoselective acetalization of aldehydes. *Green Chemistry*, 15(5): 1127-1132.
75. Tanaka, N., Ogawa, I., Yoshigase, S. and Nokami, J. (2008). Regioselective ring opening of benzylidene acetal protecting group(s) of hexopyranoside derivatives by DIBAL-H. *Carbohydrate Research*, 343(15): 2675–2679.
76. Teschke, R. (2018). Liver injury by carbon tetrachloride intoxication in 16 patients treated with forced ventilation to accelerate toxin removal via the lungs : a clinical report. *Toxics*, 6(25): 1-32.
77. Trifoi, A. R., Agachi, P. Ş. And Pap, T. (2016). Glycerol acetals and ketals as possible diesel additives. a review of their synthesis protocols. *Renewable and Sustainable Energy Reviews*, 62: 804-814.
78. Von Elert, E., Preuss, K. and Fink, P. (2016). Infodisruption of inducible anti-predator defenses through commercial insect repellents? *Environmental Pollution*, 210(1): 18-26.
79. Ward, R. D. (2008). Parasites & vectors review of “medical entomology for students”. *BioMed Central*, 1(12): 1-2.
80. Webb, C. E. and Hess, I. M. R. (2016). A review of recommendations on the safe and effective use of topical mosquito repellents. *Public Health Research and Practice*, 26(5): 8-11.
81. World Health Organization. (2009). Guidelines for efficacy testing of mosquito repellents for human. Access from https://apps.who.int/iris/handle/10665/70072.
82. Yu, L., Lin, C., Liao, C., Zeng, X., Chen, X., Zhu, Z. and Chen, L. (2020). Green chemistry: Efficient acetalization of aldehydes with alcohols using the acid red 52 photocatalyst. *Environmental Chemistry Letters*, 18(4): 1353-1359.
83. Zhang, Y., Wang, Z., Xu, X., Gao, J., Xu, D., Zhang, L. and Wang, Y. (2020). Entrainers selection and vapour-liquid equilibrium measurements for separating azeotropic mixtures (ethanol+n-hexane/ cyclohexane) by extractive distillation. *Journal of Chemical Thermodynamics*, 144(1): 106070.
84. Zongde, W., Jinzhu, C., Qian, S. Z., Zhi-wide, J. and Outstanding, S. D. (2010). Synthesis of hydroxycitronellal and acetals repellent activity against mosquitoes. *Acta Entomologica Sinica*, 53(11): 1241-1247.