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RESEARCH AS A RESULT OF INTERNATIONAL COOPERATION: ONPU – USDA-ARS

TERPENOIDS AND THEIR ESTERS AS REPELLENTS AGENTS

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Repellent activity of monoterpenoid esters (1-6) with neurotransmitter amino acids (GABA and glycine) was investigated against Aedes aegypti by using a “cloth-patch” assay and compared to reference standard N,N-diethyl-3-methylbenzamide (DEET). Carvacrol ester of GABA (2, MED of 0.031 ± 0.008 mg/cm²) exhibited the highest repellency in tested six monoterpenoid esters in comparison to the standard repellent DEET (MED of 0.009 ± 0.002 mg/cm²). In the present study, we report repellent efficacy of prolonged GABA and glycine esters of menthol, carvacrol, guaiacol (1-6) and compared to their monoterpene moiety.

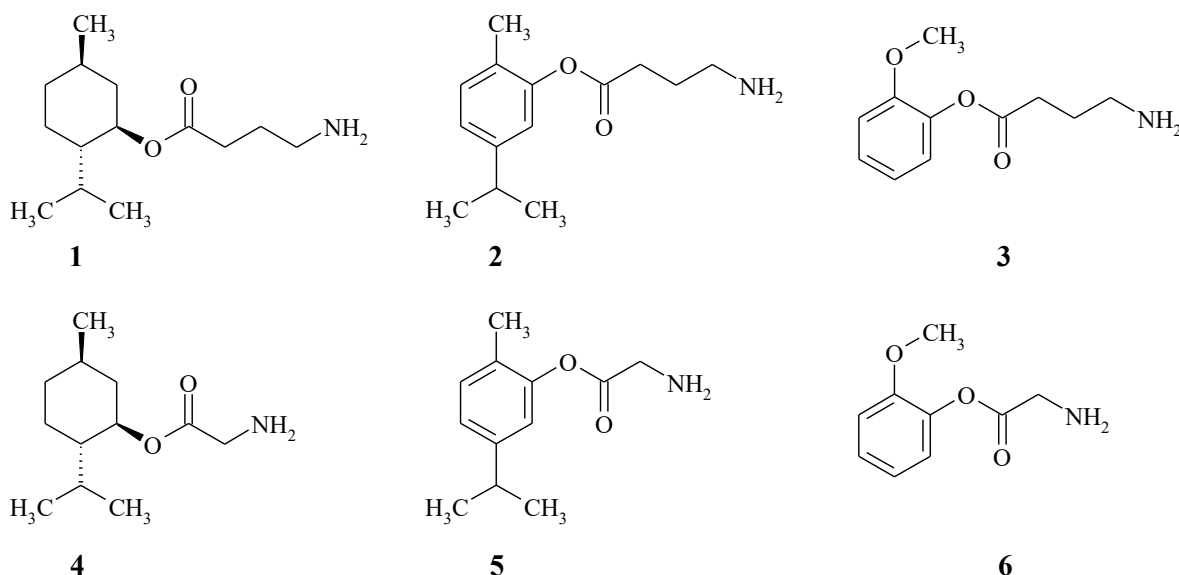
Keywords: repellents, mosquito, monoterpenoids, GABA, glycine.

Cooperation: the study has been conducted in collaboration with the Center for Medical, Agricultural and Veterinary Entomology (USDA-ARS) in Gainesville (Florida, USA) and the Subtropical Horticulture Research Station, Miami (Florida, USA).

Extermination of harmful insects and protecting humans and animals from them is a priority for scientists around the world. The most pressing problem is the protection against mosquito bites and the preservation of harvests. Mosquito *Aedes aegypti* (L.) is the main carrier of viruses that cause dengue fever, hemorrhagic fever of dengue and yellow fever in the tropical and subtropical region of the world. Recently, the World Health Organization (WHO) acknowledged that *Aedes*-borne Zika virus caused an international public health emergency. Today, pest control technology pays particular

attention to the development of “green” methods and there are several products on the market that are different from DEET. Essential oils for medicinal plants have been extensively studied to repel or destroy insects. Most botanical repellents contain citronella, eucalyptus, geraniol and/or cedar oil as an active ingredient. In this regard, the actual task is to find effective means of protection based on natural substances.

Our international scientific group investigated the repellent efficacy of three monoterpenoids (menthol, carvacrol and guaiacol) and their esters combined with amino acids (gamma-aminobutyric acid – GABA and glycine).



Monoterpenoids esters of GABA and glycine have been synthesized at the Odessa National Polytechnic University; mosquitoes used in all bioassays were female *Aedes aegypti* from the colony maintained at the Center for Medical, Agricultural and Veterinary Entomology (USDA-ARS) in Gainesville, FL; repellent efficacy was determined as the minimum effective dosage (MED) of a compound against *Aedes aegypti* at the Subtropical Horticulture Research Station, Miami, FL.



In our research, DEET, known as a highly efficacious repellent was the positive control (MED value of 0.009 ± 0.002 mg/cm²). The investigation of insecticidal activity of synthesized compounds against *Aedes aegypti* demonstrated that most of the terpenoid esters produced MED value that ranged from 0.125 - 0.469 mg/cm²; this range implicates these compounds as weaker repellents compared to DEET. The most toxic derivative

tested against *Aedes aegypti* was carvacrol ester **2** with a repellent MED of 0.031 mg/cm². Carvacrol acylation with GABA residues leads to a reduction in repellent activity compared with pure carvacrol (MED = 0.013 ± 0.005 mg/cm²) implicating a significant role of the free OH group in terpenoids structure. A comparison of MED values for pure menthol (0.094 ± 0.000 mg/cm²) and guaiacol (0.109 ± 0.041 mg/cm²) to MEDs of their corresponding esters (0.312 mg/cm² for ester **4** and 0.125 mg/cm² for ester **6**), the effect of the hydroxyl group is also necessary for the repellent activity.

Table: Minimum effective dosage (MED) of tested esters against *Aedes aegypti*

Compound	MED, mg/cm ² ± SEM	MW	RP*
1	0.375 ± 0.000	277.5	41.667
2	0.031 ± 0.008	271.5	3.444
3	0.469 ± 0.282	245.5	52.111
4	0.312 ± 0.063	249.5	34.667
5	0.125 ± 0.031	243.5	13.889
6	0.125 ± 0.031	217.5	13.889
Menthol	0.094 ± 0.000	156	8.545
Carvacrol	0.013 ± 0.005	150	2.167
Guaiacol	0.109 ± 0.041	124	9.909
DEET	0.009 ± 0.002	191	-

*RP – ratio of compound MED to DEET MED for a particular experiment.

Here, we have shown the possibility of developing contact repellents based on a combination of terpenoid esters and neurotransmitter amino acids. However, their potential utility as spatial repellents will be a subject of examination in the next phase of our research since these derivatives undergo hydrolysis with the gradual release of initial terpenoids provided prolonged insecticidal action.

Thus, we evaluated the repellent activity of monoterpenoid esters combined with GABA and glycine against *Ae. aegypti*. Among the derivatives, the carvacrol ester of GABA was the most active repellent with a MED value of 0.031 ± 0.008 mg/cm². For practical use of terpenoid derivatives as long lasting repellents, further research confirming their prolonged action is needed.