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Protective effect of terpenoids and their derivatives on alcohol withdrawal syndrome

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Background. At the core of alcohol withdrawal syndrome is the existence of spontaneous behavioral disturbances that are produced by alcohol removal and suppressed by alcohol replacement. At the molecular level, alcohol has been reported to enhance GABA-activated currents in several cell types expressing different combinations of GABA(A) receptor subunits. Additionally, alcohol is able to influence the other pharmacological targets such as glycine, NMDA and serotonin receptors. At the same time, recent studies have reported that cyclic monoterpenes such as menthol, carvacrol and others have actions within the CNS and act as potent positive allosteric modulators of GABA(A) receptors whereas some terpenes are also antagonists of cortical glycine and GABA(A) receptors. Thus, investigation of terpenoids along with their derivatives containing GABA and glycine residues is an expedient approach for symptoms relief caused by alcohol abuse.

Objective. To elucidate protective ability of terpenoids and their derivatives (esters and hydrazones) against alcohol withdrawal syndrome by determining their anticonvulsant profile.

Materials and methods. In order to treat alcohol withdrawal, the following terpenoids and their derivatives have been used: menthol, thymol, car-

vacrol, eugenol, borneol, guaiacol and their esters with GABA and glycine; menthone, carvone, verbenone, camphor, pulegone, thujone and their hydrazones with GABA and glycine. The experiment was carried out with outbreed male white mice (18−22 g) distributed into 38 groups of five animals each, treated orally by: ethanol 96% 1 g/kg; ethanol solutions of all aforementioned compounds based on 50 mg/kg of each terpenoid – their esters and hydrazones were administered in equimolar amounts; vehicle – for control group. The anticonvulsant activity of pure ethanol as well as mixtures of alcohol with each terpenoid (or its derivative) was evaluated in model of acute generalized seizures induced by intravenous infusion of 1% pentylenetetrazole solution (PTZ) with the determination of PTZ minimum effective doses (MED) inducing clonic-tonic convulsions (CTC) and tonic extension (TE) in test animals. PTZ doses for inducing clonic-tonic convulsions (DCTC) and tonic extension (DTE) were calculated relative to control; pharmacological effect of compounds was estimated from 0.5 to 24 hours. All results are expressed as mean ± standard error mean (SEM). Statistical significance was determined by Student's *t*-test at $P < 0.05$ that was considered as significant compared to control group.

Results. As an example of terpenoids' effect on alcohol withdrawal seizures, the results of menthone co-administration with ethanol are given. According to obtained data, alcohol administration led to the occurrence of pro-convulsive phase at short time periods – 0.5 h and 3 h as evidenced by decreasing of DCTC and DTE values compared with control. In contrast, simultaneous administration of alcohol and menthone manifested by the disappearance of the abovementioned effect with further display of terpene anticonvulsant activity. For example, DCTC and DTE values at 3 h after orally administered ethanol were found to be 50% and 53%, respectively, while adding of menthone doubled these indicators. Interestingly, moderate antiseizure action was registered at long time period (18 h and 24 h) in mice treated with pure alcohol with average DCTC and DTE values of 130%.

Conclusion. Our experimental data demonstrate that orally administered terpenoids and their derivatives (esters and hydrazones) have protective activity against ethanol withdrawal seizures. Bearing in mind that GABA(A) receptors have been proposed to be main targets of action for alcohol, terpene derivatives containing GABA residues might be used for management of alcohol withdrawal syndrome.