Transdermal delivery of novel terpenoid esters in pain management

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Background: There is strong evidence that TRPA1 and TRPV1 play a key role in nociception since the blockade of the abovementioned channels leads to reductions in pain sensation. Terpenes and their derivatives comprise a large group of TRP modulators possessing analgesic action. Glycine receptors GlyT1, GlyT2, and GlyRs are also involved in inhibition of nociceptive signaling. Recent studies have provided strong evidences that GABAB receptors are also localized in the periphery; surprising in this context is the finding of GABA localization at the terminal endings of corneocytes' nociceptors. Thus, the combination of TRP-channel modulators and compounds that bind to GABA/glycine receptors is expedient for development of novel drugs possessing a wide range of pharmacological activity.

Objective: The investigation of the analgesic action of esters based on terpenoids and neurotransmitter amino acids (GABA and glycine).

Methods: In order to elucidate the analgesic effect pharmacological models of thermal and chemical stimuli have been used. In our research, pain in experimental animals was caused by thermal stimuli in the "hot plate" test and by chemical stimuli via subplantar injection of formalin, capsaicin, and allyl isothiocyanate (AITC) - all of these pharmacological models are associated with the activation of TRP channels. The analgesic activity of compounds was compared with reference drug benzocaine (BZC), which was also found to activate TRPA1/TRPV1 channels.

Results: Terpenoid esters were studied as potential analgesic agents under topical application. The highest local anesthetic action was demonstrated by menthol and borneol derivatives which increased pain threshold 2-3 times in model of thermo- and 3-4 times in model of chemical-induced pain compared to the reference drug - benzocaine.

Conclusion: We have synthesized esters based on mono- and bicyclic terpenoids (L-menthol, thymol, carvacrol, guaiacol, borneol, and eugenol) with a neurotransmitter acids - GABA and glycine. Analgesic activity of obtained compounds was investigated by pharmacological models of thermal and chemical stimuli in mice after their transdermal delivery. Herein, we propose the mechanism of competitive binding between terpenoid esters and TRPA1/TRPV1 agonists as an explanation of the significant analgesic effect of terpene esters.

Conflicts of Interest: The authors declare no conflict of interest.