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Cannabinoids and Terpenes as Potential Modulators of Efflux Transporters for Overcoming Drug Resistance in Epilepsy

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Abstract : The blood-brain barrier (BBB) serves as a protective shield, preventing the entry of harmful substances into the central nervous system. On the other hand, it also restricts the transport of neuroactive drugs, such as antiepileptics, which mitigate epileptic seizures. Drug-resistant epilepsy is often associated with the overexpression of efflux transporters, including P-glycoprotein (P-gp) or multidrug resistance protein 1 (MRP1), on the BBB. The aim of this work is to find P-gp and MRP1 inhibitors derived from phytocannabinoids and terpenes. The work evaluates whether these compounds interact directly with P-gp or MRP1 by rhodamine 123 or fluorescein efflux assay. The effect of phytocannabinoids on the gene expression of these transporters is also studied using qPCR and Western blot. These transporters are found in BBB cells; however, we decided to use the human ovarian cancer cell line (A2780ADR) due to its overproduction of P-gp and malignant glioma cell line (U87) due to its overproduction of MRP1. The results showed that while terpenes suppressed the activity of efflux transporters, phytocannabinoids tended to decrease their expression. Terpenes demonstrated an average inhibition of 65%, surpassing phytocannabinoids, which exhibited an average inhibition of approximately 30%. Particularly noteworthy was the modulating effect of (-)-α-bisabolol with the highest activity among the compounds tested. Based on these findings, phytocannabinoids and terpenes emerge as promising natural candidates for addressing drug resistance linked to efflux transporters. Acknowledgment: The project was funded by the Grant No 22-20860S of The Czech Science Foundation.
Keywords : drug-resistant epilepsy, efflux transporters, multidrug resistance protein 1, P-glycoprotein, phytocannabinoids, terpens
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