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Flavonoid compounds as reversing agents of the P-glycoprotein-mediated multidrug resistance: An *in vitro* evaluation with focus on antiepileptic drugs

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ABSTRACT

The pharmacoresistance to antiepileptic drugs (AEDs) remains a major unsolved therapeutic need. The overexpression of multidrug transporters, as the P-glycoprotein (P-gp), at the level of the blood-brain barrier of epileptic patients has been suggested as a key mechanism underlying the refractory epilepsy. Thus, efforts have been made to search for therapeutically useful P-gp inhibitors. Herein, the strategy of flavonoid/AED combined therapy was exploited as a possible approach to overcome the P-gp-mediated pharmacoresistance. For this purpose, several *in vitro* studies were performed using Madin-Darby canine kidney II (MDCK II) cells and those transfected with the human multidrug resistance-1 (*MDR1*) gene, overexpressing the P-gp (MDCK-MDR1). Overall, the results showed that baicalein, (−)-epigallocatechin gallate, kaempferol, quercetin and silymarin, at 200 μM, produced a marked increase on the intracellular accumulation of rhodamine 123 in MDCK-MDR1 cells, potentially through inhibiting the P-gp activity. In addition, with the exception of lamotrigine, all other AEDs tested (phenytoin, carbamazepine and oxcarbazepine) and their active metabolites (carbamazepine-10,11-epoxide and licarbazepine) demonstrated to be P-gp substrates. Furthermore, the most promising flavonoids as P-gp inhibitors promoted a significant increase on the intracellular accumulation of the AEDs (excluding lamotrigine) and their active metabolites in MDCK-MDR1 cells, evidencing to be important drug candidates to reverse the AED-resistance. Thus, the co-administration of AEDs with baicalein, (−)-epigallocatechin gallate, kaempferol, quercetin and silymarin should continue to be explored as adjuvant therapy for refractory epilepsy.

List of chemical compounds studied in this article:

Baicalein (PubChem CID: 5,281,605); Carbamazepine (PubChem CID: 2554); Carbamazepine 10,11-epoxide (PubChem CID: 2555); (−)-Epigallocatechin gallate (PubChem CID: 65064); Kaempferol (PubChem CID: 5280863); Lamotrigine (PubChem CID: 3878); Licarbazepine (PubChem CID: 114709); Oxcarbazepine (PubChem CID: 34312); Phenytoin (PubChem CID: 1775); Silymarin (PubChem CID: 7073228); Quercetin (PubChem CID: 5280343); Verapamil (PubChem CID: 2520).

1. Introduction

Despite the clinical availability of more than twenty antiepileptic drugs (AEDs) with different pharmacokinetic profiles, mechanisms of action and potential for drug interactions, the development of drug-resistant epilepsy remains as a major unresolved problem, affecting 30–40% of patients (Baulac et al., 2015; Franco, French, & Perucca, 2016; Ventola, 2014). Although several pathomechanisms have been advocated to explain the drug resistance to AEDs, two major hypotheses have gained emphasis: the target hypothesis and the multidrug transporter hypothesis (Löscher, Klitgaard, Twyman, & Schmidt, 2013; Rogawski, 2013; Wang, Wang, Liu, & Ma, 2016). The former postulates that AEDs lose efficacy due to changes in the structure/functionality of their target ion channels and neurotransmitter receptors; while the multidrug transporter hypothesis suggests an overexpression of multidrug efflux transporters such as P-glycoprotein (P-gp) in brain capillary endothelial cells, restricting AEDs penetration into the brain tissue of non-responsive epileptic patients (Ferreira, Pousinho, Fortuna, Falcão, & Alves, 2015; Gidal, 2014; Xiong, Mao, & Liu, 2015). This hypothesis has been supported by important clinical findings that demonstrated a greater expression of P-gp in patients with recurrent seizures (drug-resistant patients) than in those who have been seizure-free

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