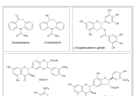

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Influence of the dual combination of silymarin and (-)-epigallocatechin gallate, natural dietary flavonoids, on the pharmacokinetics of oxcarbazepine in rats

Ana Ferreira[a, b], Márcio Rodrigues[a, c], Alexandre Marques[a], Amílcar Falcão[b, d], Gilberto Alves[a, b],

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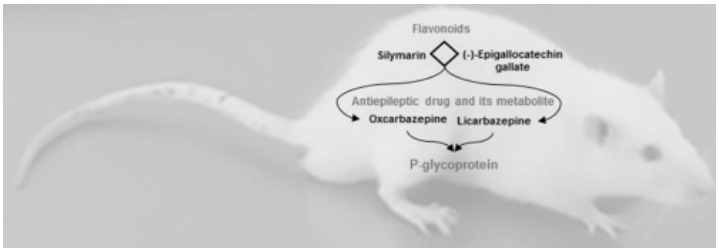
Highlights

- Natural dietary flavonoids silymarin and (-)-epigallocatechin gallate as *in vivo* P-gp inhibitors.
- Flavonoids as reversing agents of the pharmacoresistance in epilepsy.
- Pre-administration of flavonoid combinations significantly increased the C_{max} of oxcarbazepine.

Abstract

Considering the potential of flavonoids in reversing the P-glycoprotein (P-gp)–mediated multidrug resistance, this work aimed to assess the combined effects of silymarin and (-)-epigallocatechin gallate (EPG) on the pharmacokinetics of the P-gp substrates oxcarbazepine (OXC) and licarbazepine (LIC). Rats were pre-treated intraperitoneally with silymarin (25 mg/kg), EPG (25 mg/kg), silymarin/EPG (12.5/12.5 mg/kg; 6.25/18.75 mg/kg; 18.75/6.25 mg/kg) or verapamil (25 mg/kg, reference P-gp inhibitor) before the intraperitoneal administration of OXC (50 mg/kg). Pre-treatment with dual silymarin/EPG combinations originated peak plasma concentrations of OXC and LIC (pharmacologically active metabolite of OXC) similar to those achieved in the presence of verapamil (positive control). Moreover, the effects promoted by silymarin/EPG combinations on the magnitude of systemic drug exposure to OXC and LIC were also reflected in the corresponding drug levels attained in the brain (biophase). These findings evidence the synergistic effect of silymarin and EPG in enhancing the degree of systemic exposure to OXC and LIC in rats, which occurred in a comparable extent to that observed with verapamil. Hence, our findings support the combination of flavonoid-type P-gp inhibitors and P-gp substrate antiepileptic drugs as a potential therapeutic strategy for the management of pharmacoresistant epilepsy.

Graphical abstract



Keywords

(-)-Epigallocatechin gallate; Licarbazepine; Oxcarbazepine; P-glycoprotein; Pharmacokinetics; Silymarin

Abbreviations

AEDs, antiepileptic drugs; AUC, area under the concentration-time curve; AUC_{0-t}, AUC from time zero to the last sampling time; $AUC_{0-\infty}$, AUC from time zero to infinite; C_{last}, last quantifiable concentration; C_{max}, peak concentration; CV, coefficient of variation; CYP, cytochrome P450; DAD, diode array detector; DMSO, dimethyl sulfoxide; HPLC, high-performance liquid chromatography; i.p., intraperitoneal; k_{el}, apparent terminal rate constant; LIC, licarbazepine; LLOQ, lower limit of quantification; MRT, mean residence time; OXC, oxcarbazepine; P-gp, P-glycoprotein; QC, quality control; SEM, standard error of the mean; $t_{1/2el}$, apparent terminal elimination half-life; t_{max}, time to reach C_{max}

Corresponding author. Faculty of Health Sciences, CICS-UBI – Health Sciences Research Centre, University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal.