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RESPONSIBLE EDITORS
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ETN and DZN. ETN, at 10 μM and 100 μM, inhibited ($p<0.01$) testosterone 6-beta hydroxylase activity (76% and 81%, respectively) in cattle liver microsomes. Similar results were obtained in presence of equimolar concentrations of DZN (74% and 93% at 10 μM and 100 μM, respectively; $p<0.01$). Both ETN and DZN would potentially interfere with the pattern of the hepatic metabolism of relevant CYP3A substrates pharmacologically relevant in bovine medicine, such as tiamulin, macrolide antibiotics and the ionophore monensin.

84. (448) **MEROPENEN INHIBITS THE CYTOCHROME P450 (CYP) 3A-DEPENDENT BIOTRANSFORMATION OF THE IMMUNOSUPPRESSIVE TACROLIMUS IN HUMAN LIVER MICROSOMES.**

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Tacrolimus (TAC), a immunosuppressive drug used in solid organ transplantation, is metabolized by CYP3A4 and 3A5. The simultaneous administration of TAC and meropenem (MEP) in pediatric kidney transplant patients may led to a significant increase in plasma concentrations of TAC. We hypothesized that this negative pharmacokinetic interaction is due to the inhibition of the CYP3A4-mediated biotransformation of TAC by MEP, particularly in those individuals lacking the expression of CYP3A5. The aim of this study was to evaluate *in vitro* the potential metabolic interaction between TAC and MEP. Human liver microsomes were prepared with discard liver samples obtained from healthy donors (n=2) and individuals subjected to tumor resection (n=2). The specific CYP3A-dependent enzyme activity, testosterone 6-beta hydroxylase, was assayed in the absence (control) and in presence of TAC (5 and 20 μM), MEP (10 μM) and the combinations of TAC and MEP. TAC, incubated at 5 and 20 μM, inhibited ($p<0.05$) the CYP3A-mediated 6-beta hydroxylation of testosterone (18±13% and 51±16%, respectively). This finding may confirm the high affinity of CYP3A4 for TAC. MEP, at 10 μM, did not affect this enzyme reaction. After co-incubations of TAC and MEP, testosterone 6-beta hydroxylase activities resembled those observed when TAC was incubated alone. In control assays, rates of TAC metabolism were 30±20 and 120±40 pmol/min.mg of microsomal protein, respectively. MEP, at 10 μM, significantly inhibited ($p<0.05$) the hepatic biotransformation of TAC; rates (pmol/min.mg) of TAC metabolism (at 5 and 20 μM) were 20±10 (43±24% inhibition) and 70±50 (49±23% inhibition), respectively. These preliminary results show a metabolic interaction between TAC and MRP on CYP3A-dependent metabolism in human liver. The enhancement of the systemic availability of TAC observed *in vivo* in the co-administration with MEP would be due to the inhibition of the CYP3A4-dependent biotransformation of the immunosuppressive drug.

Farmacognosia - Farmacobotánica

85. (091) **ANTIANGIOGENIC ACTIVITY OF THE ALKALOID SKIMMIANINE ISOLATED FROM *ZANTHOXYLUM COCO*.**

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The term angiogenesis refers to the development of new blood vessels from the preexisting vasculature. Under physiological conditions, this process is strictly regulated being focal and self-limited in time. Nevertheless, disbalances between the biochemical signals that regulate angiogenesis may occur, resulting in a chronic neovascularization that takes part in a large number of diseases including neoplastic transformation, rheumatoid arthritis, psoriasis, and different ocular conditions. In this context, the development of new agents capable of downregulating pathological angiogenesis become relevant in the field of drug discovery.

The flora from Argentina stands out among the different sources of new bioactive molecules. In previous studies conducted by our research team, the ethanol extract of *Zanthoxylum coco* showed a remarkable antiangiogenic effect. Therefore, this species was submitted to the bioassay guided isolation of its active principle. This process involved the alternation of different chromatographic techniques with the evaluation of the antiangiogenic activity in terms of the tube formation assay. One compound identified by diverse spectroscopic techniques as the alkaloid skimmianine was isolated. This molecule significantly inhibited tube formation even at 12.5 mg/mL. HPLC analysis showed that this compound is one of the major constituents of the ethanol extract of *Z. coco*. No toxic effect against peripheral blood mononuclear cells, used as model of normal cells, was observed. Additionally, the compound did not affect the integrity of the erythrocyte membrane. Pharmacokinetic and drug-likeness parameters were evaluated by SwissADMET online tool.

The obtained results support the potential of the flora from Argentina as a source of new small molecules capable of downregulating neovascularization and position this naturally occurring alkaloid as a promising lead for the development of new analogs with improved antiangiogenic activity.

86. (194) **INHIBITION OF LIPID PEROXIDATION BY *CANNABIS SATIVA* AND *LARREA DIVARICATA* EXTRACTS AND THEIR COMBINATION**

Malén Saint Martin, Ignacio Peralta, Fresia Melina Silva Sofrás, Laura Cogoi, Catalina van Baren, María Rosario Alonso, Claudia Anesini

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Oxidative stress, through lipid peroxidation, affects central nervous system altering cognitive functioning during epilepsy. *Cannabis sativa* L. (Cannabaceae) is a medicinal plant used as anticonvulsant, being cannabidiol (CBD) its main anticonvulsant agent. *Larrea divaricata* Cav. (Zygophylliaceae) is an autochthonous plant with antioxidant activity. The aim of this work was to study the synergistic effect of an ethanolic extract of *C. sativa* (CSR) and an aqueous extract of *L. divaricata* (LE) on inhibition of lipid peroxidation to improve the therapeutic outcomes. The participation of CBD and nordihydroguaiaretic acid (NDGA) was evaluated.

CBD and NGDA were identified and quantified by HPLC-UV. Antioxidant activity was determined in an egg yolk phospholipid peroxidation model. A combination index (CI) was calculated to investigate the interaction between extracts. Results were expressed as inhibitory concentration 50 (IC50) or as mean g% p/p ± SEM of two or three assays made in triplicate.

Quantification of CBD: 23.1 g% p/p. Quantification of NDGA: 1.56 g% p/p. Inhibition of lipid peroxidation: IC50 drugs alone: CSR: 30.5±3.0 μg/ml; LE: 630.95 ± 63 μg/ml; CBD: 10.2±1 μg/ml. IC50 of better combinations: CSR + LE 500 μg/ml: 2.45±0.1 μg/ml ($p< 0.0001$); CBD+ LE 500 μg/ml: 2.18 ± 0.2 μg/ml ($p< 0.0001$). CI of better combinations: CSR 10 μg/ml/LE 500 μg/ml: 0.16 (strong synergism); CSR 3 μg/ml/LE 500 μg/ml: 0.36 (significative synergism).

Conclusions: CSR and LE presented inhibitory activity. CBD was involved in CSR activity. NDGA showed a very low activity. The association of extracts showed strong, significative or week synergism