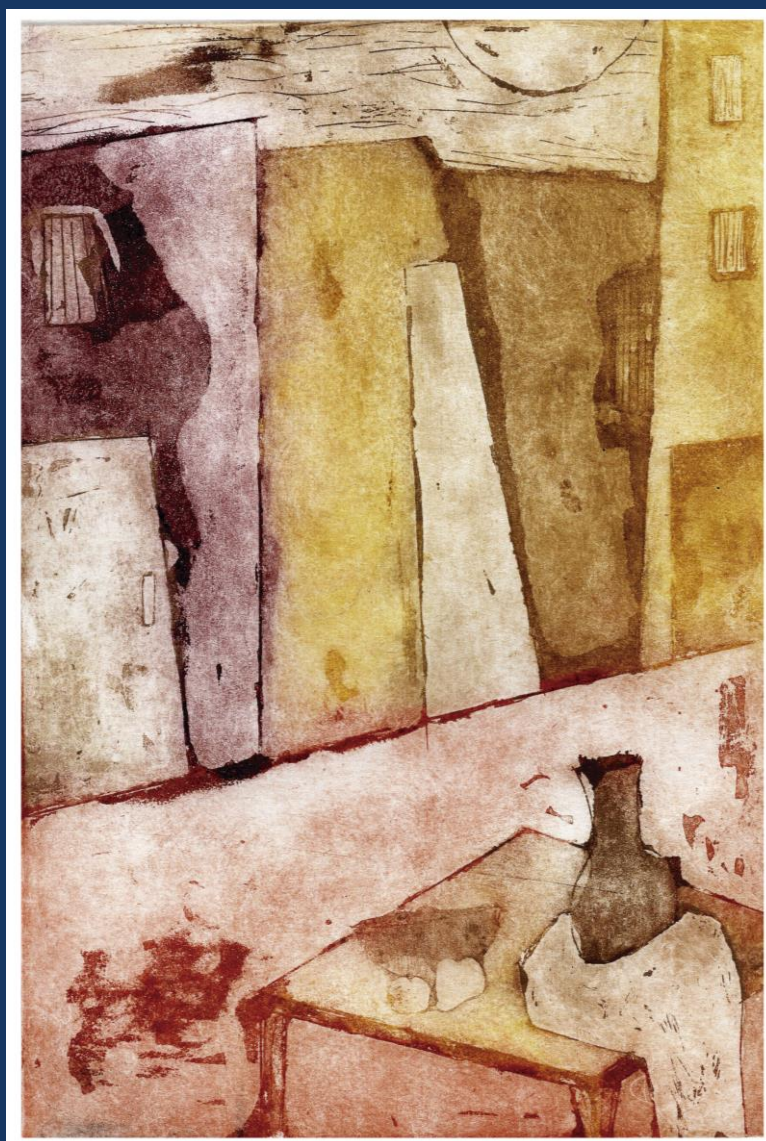


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Atardecer en la tarde
Antonella Ricagni

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**Dra. Mónica Costas
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Dr. Pablo Azurmendi**

Abstract/Resumen: Previously, our group demonstrated that *Ligaria cuneifolia* (Lc) crude extract increased blood viscosity and decreased plasma cholesterol levels in rats. In the present study, we analyzed the effect of PLc on plasmatic lipid profile in adult male Wistar rats hyperlipemic. Rats aged 70 days were fed with: standard diet (Control, C; n= 5), standard diet added with 40 % bovine meat juice during 28 days (HFD; n= 10). At the end of this time, the rats were injected i.p. each 24hr either with physiological solution (HFD, n=5, and also the C rats) or PLc 3mg/100g body weight HFD only (HFD+PLc; n= 5) during 7 days. At day 8 after treatment, rats were anaesthetized i.p. with Ketamine/Xylazine (100mg/kg and 3mg/kg, respectively) to obtain blood samples by cardiac puncture. Plasma assays: Cho (enzymatic method with cholesterol oxidase esterase) and TG (enzymatic methods) Plasma (mean \pm SE): Cho (mg%): C: 138.8 \pm 14.8 HFD: 203.3 \pm 21.5*; HFD+PLc: 119.5 \pm 28.5#; TG: C: 170.7 \pm 18.5 HFD: 274.7 \pm 30.7*; HFD+PLc: 190.50 \pm 21.65# (*p<0.05 vs. C; #p<0.05 vs. HFD). Additionally, we evaluated the total plasmatic free fatty acids (FFA) (Derivatized plasma samples were then analyzed by GC-MS) and plasmatic levels of some polyunsaturated fatty acids (PUFAs), expressed as % of Control, mean \pm SE. FFA: HFD: 882.12 \pm 306.27; HFD+PLc: 114.36 \pm 15.72# Linolenic Acid C18:2: HFD: 59.0 \pm 18.1; HFD+PLc: 82.6 \pm 10.8. Arachidonic Acid C20:4: HFD: 61.7 \pm 5.7; HFD+PLc: 104.7 \pm 20.7 and Docosahexanoic Acid C22:6: HFD: 55.8 \pm 10.7; HFD+PLc: 122.6 \pm 14.2# (#p<0.05 vs. HFD). Our results showed that the treatment with PLc has a lipid-lowering effect in rats fed with HFD. Interestingly, we found that PLc treatment was able to restore the altered HFD-derived plasma levels of some PUFAs that are direct or indirectly associated with an obesity-related modified lipid profile. In conclusion, we have obtained a fraction of the crude extract of Lc, which lowers the total Co and TG in plasma and restore plasma free fatty acid profile after HFD.

Farmacología/ Pharmacology III

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0173 - DRUG COMBINATION ANALYSIS OF COMPOUNDS WITH POTENTIAL SYNERGISTIC EFFECTS IN A PRECLINICAL MODEL OF DISSEMINATED RETINOBLASTOMA

Santiago ZUGBI (1) | Ursula WINTER(1) | Rosario ASCHERO(2) | Claudia SAMPOR(3) | Mariana SGROI(4) | Angel CARCABOSO M(5) | Guillermo CHANTADA(6) | Paula SCHAIQUEVICH(1)

UNIDAD DE TRATAMIENTOS INNOVADORES, SERVICIO MEDICINA DE PRECISIÓN, HOSPITAL DE PEDIATRÍA GARRAHAN (1); SERVICIO DE PATOLOGÍA, HOSPITAL DE PEDIATRÍA GARRAHAN (2); SERVICIO DE HEMATO-ONCOLOGÍA, HOSPITAL DE PEDIATRÍA GARRAHAN (3); SERVICIO DE OFTALMOLOGÍA, HOSPITAL DE PEDIATRÍA GARRAHAN (4); DEPARTAMENTO DE HEMATOLOGÍA Y ONCOLOGÍA PEDIÁTRICA, HOSPITAL SANT JOAN DE DEU (5); SERVICIO DE MEDICINA DE PRECISIÓN, HOSPITAL DE PEDIATRÍA GARRAHAN (6)

Abstract/Resumen: Patients with metastatic retinoblastoma receive an empirical and aggressive chemotherapy treatment but they still have a fatal outcome. Considering this malignancy like an unmet medical need, new therapies or alternative drugs are necessary. We were previously successful in identifying FDA approved drugs with cytotoxicity effect in a cell line derived from tumor dissemination in the lymph node using High-Throughput Screening. Now, we aimed to identify and evaluate drug combinations with a synergistic effect between active drugs previously selected using a homemade decision algorithm. We evaluated carboplatin-CB, vincristine-VC, panobinostat-PN and bortezomib-BT in a 3x2 concentration matrix at the IC10, IC25 and IC50 (drug concentration that inhibits 10, 25 or 50 % of cell proliferation) to determine the most promising combinations. To confirm the activity of the selected combinations, we evaluated

the dose-response curves of the combination and compared the IC50s to those calculated for individual drugs according to the combination index (CompuSyn). Mean (range) IC50s for CB, PN, BT, and VC was 95.6 μ M (94.2-97.6), 67.2 nM (74.2-47.7), 5.2 nM (5.2-3.2), and 62.6 nM (56.7-68.5), respectively. The IC50s for CB and PN combined with PN at the IC25 and BT at the IC50 were 70 μ M and 8.2 mM, respectively. Both combinations presented a combination index <1 meaning a synergistic effect. In this study we managed to develop a rational design of drug selection to evaluate cytotoxic activity in preclinical models and identified two drug combinations with synergistic effects in a primary cell line derived from a patient with metastatic retinoblastoma. Synergistic effect was observed between CB-PN and PN-BT in vitro. These results are the first step for an upcoming evaluation in an animal tumor model.

0189 - P-GP MODULATING EFFECT OF THE PENTACYCLIC TRITERPENOID BETULIN, ISOLATED FROM LIGARIA CUNEIFOLIA, IN MULTIDRUG RESISTANT LEUKEMIC CELLS.

Jerónimo LAIOLO | Mariana Belen JORAY | María Cecilia CARPINELLA

INSTITUTO DE INVESTIGACIONES EN RECURSOS NATURALES Y SUSTENTABILIDAD JOSE SANCHEZ LABRADOR S.J.

Abstract/Resumen: Multidrug resistant (MDR) constitutes nowadays one of the major obstacle in cancer therapy, being the efflux of drugs by P-glycoprotein (P-gp) a predominant factor. Plants are recognized as a rich source of metabolites with structural diversity being an invaluable starting point for drug discovery. With the aim of finding promising compounds to modulate MDR phenotype mediated by P-gp, 120 native and naturalized plants collected in the hills of Córdoba, Argentina, were screened on K562 human myelogenous leukemia cell line and its MDR counterpart Lucena 1. *Ligaria cuneifolia* was one of the most active and thus it was subjected to bioguided isolation to separate the active principle responsible for its activity. This process yielded the triterpenoid betulin (1). Intracellular doxorubicin (DOX) accumulation was determined, at non-cytotoxic concentrations determined by MTT, using flow cytometry. Fluorescence intensity ratio (FIR) was calculated as the ratio between the fluorescence intensity of each cell line treated and the fluorescence intensity of its respective solvent control. The activity was confirmed by the MTT reversal assay. Compound 1 increased the accumulation of DOX at a minimum effective concentration (MEC) of 1.56 μ M (FIR 1.09 \pm 0.04) and increased DOX cytotoxicity by a factor of 3.83 \pm 0.26 at 12.5 μ M and 1.29 \pm 0.08 at 0.39 μ M showing no differences with respect to the same concentrations of verapamil, used as positive control (p \geq 0.05). Compound 1 showed no effect at the MEC on K562 cells. This is the first report regarding compound 1 as an inhibitor of the efflux mediated by P-gp. This triterpenoid could arise as scaffold to obtain novel P-gp inhibitors to use in combination with anticancer drugs for the improvement of leukemia therapies.

0190 - STUDY OF THE ANTIANGIOGENIC EFFECT OF A TERTHIOPHENE ISOLATED FROM TAGETES MINUTA.

María Candelaria LLORENS DE LOS RÍOS(1) | Priscila Ailin LANZA CASTRONUOVO(2) | Cecilia Luján BARBIERI(2) | Macarena FUNES CHABAN(3) | Domingo Mariano VERA(2) | Gastón SORIA(1) | María Cecilia CARPINELLA(3) | Mariana Belen JORAY (3)

CIBICI-CONICET. FACULTAD DE CIENCIAS QUÍMICAS. UNIVERSIDAD NACIONAL DE CÓRDOBA. (1); INBIOTEC-CONICET, FACULTAD DE CIENCIAS EXACTAS Y NATURALES. UNIVERSIDAD NACIONAL DE MAR DEL PLATA. (2); IRNASUS-CONICET. FACULTAD DE CIENCIAS QUÍMICAS. UNIVERSIDAD CATÓLICA DE CÓRDOBA. (3)

Abstract/Resumen: Angiogenesis is an essential mechanism involved in biological processes such as reproduction, development and wound healing. Imbalances between the factors that regulate angiogenesis have been linked to different diseases that affect human health. Despite the great progress achieved in antiangiogenic therapy, its limited efficacy, severe adverse effects and the development of resistance demands the continuous development of novel therapeutic agents to overcome these obstacles. In this context plant-derived metabolites continue to play a highly significant role in drug discovery. From a screening performed in our laboratory, the ethanol extract of *Tagetes minuta* arose as a potent antiangiogenic agent. This effect was evaluated by the tube formation assay using bovine aortic endothelial cells (BAEC). Through bio-guided chemical fractionation three compounds identified as: 5'-methyl-5-(4-hydroxybut-1-ynyl)-2,2'-bithiophene (1), 5-(4-hydroxybut-1-ynyl)-2,2'-bithiophene (2) and alfa-terthienylmethanol (3) were obtained. Among these, compound 3 showed a potent antiangiogenic activity (IC50 = 2.69 µM). The influence of 3 over cell proliferation and cell invasion induced by the vascular endothelial growth factor (VEGF) was evaluated. While no effect was observed in the MTT proliferation assays, 3D transwell experiments demonstrated that compound 3 efficiently blocked cell invasion. Additionally, molecular docking experiments showed that 3 overlaps with the tyrosine kinase inhibitor sorafenib (a potent antioangiogenic agent) at the catalytic cleft of VEGF receptor 2 interacting with key aminoacids such as Glu885, Phe1047 and Cys919, extending over Val916 into the adjacent allosteric hydrophobic back pocket resembling a type II inhibition. These studies contribute to position 3 as a potential candidate to be used in antiangiogenic therapy itself or as a lead compound for the development of analogues with improved activity.

0375 - COMPARATIVE XENOBIOTIC BIOTRANSFORMATION IN PRECISION-CUT LIVER SLICES FROM SWINE AND CATTLE

María Victoria MIRÓ | Paula VIVIANI | Juan HERRERA | Laura MATÉ | Carlos LANUSSE | Adrian LIFSCHITZ | Guillermo VIRKEL

CIVETAN (CONICET-CICPBA-UNCPBA), FACULTAD DE CIENCIAS VETERINARIAS, UNCPBA, TANDIL

Abstract/Resumen: Species differences in the pattern of metabolism of foreign compounds is a key issue for veterinary practitioners. Comparative studies on the in vitro hepatic metabolism of xenobiotics among different farm animals requires the use of consistent and robust methodologies. The aim of the current work was to validate the technique of precision-cut liver slices (LSs) for comparative studies on xenobiotic metabolism in swine and cattle. Swine (n= 3) and bovine (n= 6) liver samples were obtained from local abattoirs. LSs (around 20 mg wet weight) were produced by operating a Brendel-Vitron™ tissue slicer filled with oxygenated ice-cold Krebs buffer. LSs were cultured (up to 6 h) in Williams' Medium E at 37 °C under a humidified atmosphere (95% O₂: 5% CO₂). Tissue viability was assessed by histopathology and the measurement of intracellular reduced (GSH) and oxidized (GSSG) glutathione. The assayed enzyme activities were: benzydamine N-oxidase (BZ N-ox, flavin-containing monooxygenase), ethoxyresorufin O-deethylase (EROD, cytochrome P450 1A1) and methoxyresorufin O-demethylase (MROD, cytochrome P450 1A2). The S-oxidation of the anthelmintic drugs albendazole (ABZ) and fenbendazole (FBZ) was also assessed. HPLC analysis was performed and the rates of appearance of the metabolites in the incubation medium were calculated. Similar BZ N-ox and EROD activities were observed in both species. Conversely, MROD was 2.6-fold higher (p<0.05) in swine (12 ± 9 pmol/h) compared to cattle (4.6 ± 2.5 pmol/h). The S-oxidation of ABZ was 1.5-fold higher (p<0.05) in swine (3.3 ± 0.7 nmol/h) compared to cattle (2.2 ± 0.5 nmol/h), but the opposite occurred for FBZ S-oxidation. In both species, as observed in other in vitro systems like liver microsomes, ABZ S-oxidation resulted 5-fold (cattle) and 13-fold (swine) higher (p<0.05) compared to FBZ S-oxidation. The work described here

shows that LSs are a useful tool to obtain relevant information on species-specific differences in xenobiotic metabolism.

0493 - GA-RXODE METHOD, A NEW PROCEDURE WITH SEVERAL USES IN PHARMACOMETRICS

Mikhail MOROZOV | Eduardo NUSKE | Héctor Alejandro SERRA

PRIMERA CÁTEDRA DE FARMACOLOGÍA, FACULTAD DE MEDICINA, UBA

Abstract/Resumen: Background: In the "Big Data era" it seems paradoxical that few drugs have a complete and available set of pharmacometric data. Combining two R written routines, "Genetics Algorithms" (GA) and "Running simulations from Ordinary Differential Equations based models" (RxODE), we have developed a procedure to improve those data from the available ones. The aim of present work was to describe and validate GA-RxODE method, an informatic instrument running in any computer, capable to optimize raw data in general. We have applied the method on pharmacokinetic (PK) raw data of clarithromycin sustained release formulation study and validated it by population PK modelling in SAEMIX, an R written non-linear mixed effects algorithm. Applying GA-RxODE we have obtained a final construct called token data or sim(ulated)-data. From reconstructed sim-data concentration-time curves of clarithromycin we have generated several population PK models: Complete Model (CM) including the original number of determinations (11) as the clarithromycin study, and Partial Models (PMs) containing 4 to 10 determinations. We have expressed the values as median (interquartile range) and used one- or two-way ANOVA to analyze them. The uncorrected-to-zero correlation between variances (raw concentration and the corresponding sim-data) exhibited a slope of 0.6026 ± 0.087; r²= 0.842; p<0.001, indicating sim-data maintained the original structure with less variability. In addition, C_{max} analysis, CM= 1.91 (1.54-2.28) mg/l vs PM with only 4 values= 1.73 (1.41-2.04) mg/l, was non-significant indicating a good agreement between models. Conclusions: By optimizing raw data, maintaining their structure and reducing their variability, the derived sim-data can be suitable to any further PK analysis. Furthermore, the procedure can be considered valid because the CM was non-different from PMs. This places GA-RxODE method as a proper tool to be applied in Pharmacometrics.

0635 - POPULATION PHARMACOKINETIC MODELING OF PYRIMETHAMINE (PYR) DURING THE TREATMENT OF CONGENITAL TOXOPLASMOSIS IN PEDIATRICS.

Ulises FLEITAS (1) | Maria Elena MARSON(1) | Jaime ALTICHEH(1) | Carlos PEREZ(2) | Anabela PROSPITTI(3) | Guillermo MOSCATELLI(2) | Samanta MORONI(4) | Guido MASTRANTONIO(1) | Facundo GARCIA BOURNISSEN(2)

FACULTAD DE CIENCIAS EXACTAS, UNLP - UPL, CICPBA - CONICET (1); HOSPITAL DE NIÑOS RICARDO GUTIERREZ-CONICET (2); UPL-COMISION DE INVESTIGACIONES CIENTÍFICAS DE LA PROVINCIA DE BUENOS AIRES (3); HOSPITAL DE NIÑOS "RICARDO GUTIERREZ" (4)

Abstract/Resumen: Infection with *Toxoplasma gondii*, is one of the most widespread zoonoses in the world. Particularly risky is congenital form (CT) with a global risk of transmission by this route of about 40 %, reaching 90 % in the last month of pregnancy. Children with CT receive treatment, usually PYR and sulfadiazine, to prevent morbidity. The current therapy in pediatric patients is protocolized, but due to the absence of pediatric formulations the drugs are prepared in the hospital pharmacy in the form of syrup and at the moment, pharmacological parameters of these drugs have not been corroborated in patients, especially PYR. The objective of this study was to evaluate the pharmacokinetics of PYR in the treatment of pediatric toxoplasmosis, from a population approach