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and even antagonism depending on the concentrations associated. Results allow in a future their association at some concentrations to increase antioxidant effects.

87. (321) **POLYPHENOLS FROM ANDEAN POTATO INDUCE CITOTOXICITY IN GLIOBLASTOMA CELLS BY MODIFING THE REDOX STATUS**

Vazquez M., Filiberti V., Andreu A.B, Silveyra M.X.
Instituto de Investigaciones Biológicas, IIB-CONICET-UNMdP.

Andean potatoes (*Solanum tuberosum* ssp. *andigena*) are a good source of dietary polyphenols, such as chlorogenic acid and anthocyanins. This study aimed to analyze the cytotoxic activity of polyphenols from Andean potato var. Santa María on glioblastoma cells. In order to test this, we first assayed the cell viability by incubating different concentrations of polyphenol extracts with human glioblastoma LN-229 cells. We observed that polyphenols induced changes in the morphology of the cells and reduced the viability in a concentration-dependent manner. Then, we calculated the CC_{50} (50% cytotoxic concentration) of total polyphenols extract and proceeded to investigate how the cells dye. First, we treated the cells with the CC_{50} for 4 hr and measured the intracellular reactive oxygen species (ROS) using the probe H_2DCFDA. At the beginning of treatment, the ROS levels decreased compared to control, but after 2 hr, they increased, suggesting that the polyphenols altered the redox homeostasis in glioblastoma cells. To analyze what happens in the mitochondria, we determined the potential mitochondrial membrane with Rhodamine 123. After 3 hr of treatment, we observed a significant decrease, confirming that polyphenols would induce a dysfunction in the mitochondria that contributes to increased ROS levels. Finally, we performed a DAPI staining of cells' nuclei and visualized them with fluorescence microscopy, observing significant alterations in treated cells such as bright nuclear condensation and, in some cases, fragmented nucleus. However, we checked the genomic DNA fragmentation in agarose gel, and we determined that polyphenols produced a slight reduction in genomic DNA size with a lack of oligonucleosomal fragments, suggesting the activation of a mechanism of death caspase-independent. These findings demonstrated that polyphenols from Andean potato var. Santa María would be a good source of bioactive compounds with anti-glioblastoma activity that impacts human health.

88. (339) **HISTOPATHOLOGICAL EVALUATION OF THE EFFECT OF CARROT FIBER ON THE STOMACH OF RATS**.

Maria Rosana Ramirez[1,2], Valeria Cerevin[2], Juan Carlos Yori[1,3]
[1]CONICET-[2]Instituto Universitario de Ciencias de la Salud, Facultad de Medicina, Fundación H.A. Barceló, sede Santo Tome, Corrientes, [3]Facultad de Ingeniería Química-UNL. Santa Fe.

Dietary fiber intake elicits a wide range of physiologic effects, not just locally in gastrointestinal tract, but systemically. These changes can then alter the physiology of the body's other nutrient management and detoxification organs, such as the liver and kidneys. Nevertheless, establishing the source of origin, type, and dose of dietary fiber inclusion is importance to obtain the above-noted benefits. A study was conducted to investigate the effect of carrot fiber isolated on stomach histomorphology, in rats. The fibers were obtained from discards from carrot production. Twelve conventional Wistar rats were fed fibre-free or fibre supplemented diets (90 days), and their stomach were examined by optical microscopic. Fixed tissue samples were processed, and embedded in paraffin. Sections of 5 - 6 µm thick, were cut using a rotary microtome. Slides were routinely stained with Hematoxilyn & Eosin. Postmortem alterations such as gland dilatations with epithelial elongation and dysplasia in the mucosa of the stomach were observed, in supplemented rats. These results indicate that carrot fiber may have an effect on rat stomach, which may have health implications.

FARMACOLOGÍA

89. (187) **REPLACING GLUCOSE MEDIA WITH GALACTOSE TO EVALUATE MITOCHONDRIAL TOXICITY OF IMIQUIMOD.**

Rodrigo Rocco[1,2], Rosa Wainstok[1], Adriana Cochón[2]*, Silvina Gazzaniga[2]*.
[1] IQUIBICEN, Instituto de Química Biológica de la Facultad de Ciencias Exactas y Naturales, CONICET-Universidad de Buenos Aires, [2] Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires. (*) contribución equitativa

The off-label use of imiquimod (IQ) for hemangioma treatment has shown clinical benefits. We have previously reported a selective direct IQ-cytotoxic effect on transformed H5V endothelial cells (EC) (hemangioma model) vs normal 1G11 EC. We observed a severe imbalance in antioxidant defense and apoptosis in H5V but not in 1G11. To further address this issue, we studied the possibility of IQ being a mitochondrial toxicant. H5V and 1G11 cells were treated with IQ (0-50 μg/mL) for 2, 4, 12 or 24 h and analyzed for reactive oxygen species (ROS) with $DCFH_2$-DA probe and mitochondrial stress by MitoTracker™ Red CMXRos fluorescence. Viability assays were performed using the standard culture medium with 5.5 mM glucose (regular) or media containing 25 mM glucose (high) or 25 mM galactose (depleted). IQ treatment increased ROS level in H5V after 2 h (35-60%; $p<0.05$) but in 1G11 only at 4 h (50%; $p<0.05$). Mitochondrial membrane potential in H5V cells was affected after 4 and 12 h treatment, revealed by a decreased in MitoTracker fluorescence (≈50%; $p<0.05$). In contrast, 1G11 cells were unaffected and only presented a significant 30%-decrease in fluorescence after 12 h with 50 μg/mL IQ ($p<0.05$). Cells grown in a high glucose medium can adapt to a glycolytic phenotype. By assessing the effect of IQ in this medium, both cell lines became significantly less affected than with the regular culture medium. On the contrary, by forcing cells to respiration with galactose instead of glucose-containing medium, IQ treatment enhanced cell death in both cell lines, being fully cytotoxic for H5V ($p<0.05$) but leaving ≈32% 1G11 cells still alive at the highest IQ concentrations.
These results provide more evidences about the higher susceptibility of transformed EC to IQ, where an early ROS production and mitochondrial dysfunction drove H5V cells to death. By shifting cells towards diminished respiration in absence of glucose, we proved IQ acts as a mitochondrial toxicant in both EC lines.

90. (249) **BEHAVIORAL AND MOLECULAR BASES OF THE ANTHELMINTIC ACTIVITY OF ESSENTIAL OILS EXPLORED IN THE NEMATODE *CAENORHABDITIS ELEGANS***

Guillermina Hernando, Ornella Turani and Cecilia Bouzat
Instituto de Investigaciones Bioquímicas de Bahía Blanca, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, 8000 Bahía Blanca, Argentina.

Control of helminth infections in both human and veterinary medicine currently relies mainly on chemotherapy, but acquisition of resistance is an increasing problem that leads to the urgent need of discovery of novel drugs. *C. elegans* has demonstrated to be a model system for the discovery of new anthelmintics and for characterizing their mechanisms of action and resistance. Essential oils (EOs) are natural products produced by aromatic plants. We perform paralysis assays of wild-type and mutant *C. elegans* strain to identify EOs with potential anthelmintic activities, reveal the active components, their target sites, and mechanisms of action. We found that EOs belonging to different orders produce rapid paralysis of *C. elegans* with EC50 values between 0.02-2 % EOs. All EOs tested also inhibited egg hatching, a property related to anthelmintic ability. Thus, EOs mediate both rapid and long-term anthelmintic effects. We examined anthelmintic properties of terpenoids and phenylpropenes and determined that all compounds tested produce both paralysis and egg-hatching inhibition. By testing mutant worms, we identified the muscle L-AChR and GABA receptors as EOs and trans-cinnamaldehyde (TC, phenylpropene) targets. Thus, by mod-

ulating two receptors with key roles in worm motility, these EOs emerge as novel sources of anthelmintic compounds. To unequivocally confirm that these receptors are targets of TC and to describe the mechanism by which they affect these receptors, we performed whole-cell and single-channel recordings from *C. elegans* muscle cells. Electrophysiological recordings at the single-channel level revealed that TC reduces L-AChR channel activity without affecting channel properties. The results are compatible with the action of these drugs as allosteric inhibitors. It is hoped that this work can update the recent progress on natural nematicide discoveries and provide new ideas for the design and mechanism of action studies of anthelmintics.

91. (284) **DEVELOPMENT AND ASSESSMENT OF THE COENCAPSULATION OF CARVEDILOL AND CURCUMIN IN A NANOMICELLAR DISPERSION SYSTEM IN AN EXPERIMENTAL MODEL OF HYPERTENSION.**

Yanina Santander Plantamura[1,2], Miguel Ángel Allo[1,2], Jennifer Riedel[2,3], Pedro Fuentes[2,3], Marcela Moretton[2,3], Diego Chiappetta[2,3], Christian Höcht[1,2], Susana Gorzalczany[1,2]

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Carvedilol is a third-generation ß-blocker with pleiotropic effects, including antioxidant, anti-inflammatory and anti-apoptotic effects. Curcumin is a phenolic compound belonging to turmeric, with a beneficial effect on blood pressure. The objective of the present work was the development and assessment of the pharmacokinetic (PK) and pharmacodynamic (PD) profile of the coencapsulation of carvedilol and curcumin in nanomicellar dispersions of Soluplus in spontaneously hypertensive rats (SHR).

Nanomicellar dispersions of 10% w/v Soluplus containing carvedilol 3 mg/ml, curcumin 2 mg/ml , or both were prepared using the solvent evaporation technique. Plasma pharmacokinetics and hemodynamic response after oral administration of carvedilol 9 mg/kg, curcumin 6 mg/kg or carvedilol/curcumin 9/6 mg/kg were assessed in 20 male SHR rats after carotid artery cannulation.

Results: Plasma curcumin levels were comparable after coadministration of carvedilol/curcumin or curcumin only. Coencapsulation did not modify the PK profile of carvedilol. Curcumin oral administration did not induce changes in blood pressure and heart rate. Coencapsulation resulted in a greater MAP reduction when compared with carvedilol (-28,5±4,0 % vs –12,1±3,1%, $p<0.05$). HR reduction was comparable after oral administration of carvedilol or coencapsulation.

Conclusions: Coencapsulation of curcumin with carvedilol in nanomicellar dispersions potentiates the antihypertensive effect of carvedilol without modifying the bradycardic responser nor the pharmacokinetic profile. These results suggest that coencapsulation of carvedilol and curcumin represents a potential pharmacodynamic synergistic combination for the management of arterial hypertension.

92. (305) **MOD-1 RECEPTOR AS A NOVEL DRUG TARGET FOR ANTHELMINTIC THERAPY**

Noelia Rodriguez Araujo, Guillermina Hernando, Jeremías Corradi and Cecilia Bouzat.

Instituto de Investigaciones Bioquímicas de Bahía Blanca, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, Bahía Blanca, Argentina.

Caenorhabditis elegans (Nematoda) contains a homomeric 5HT-gated chloride channel, MOD-1, that belongs to the Cys-loop receptor family and modulates locomotor behavior. Although it binds 5-HT, MOD-1 is not present in vertebrates, and it therefore emerges as a possible anthelmintic target. We deciphered MOD-1 pharmacological properties and searched for novel modulators with potential anthelmintic activity by performing patch-clamp recordings from mammalian cells heterologously expressing MOD-1 and locomotor activity assays in *C. elegans*. Whole-cell recordings showed that MOD-1 desensitizes slowly and recovers from desensitization with a time constant of about 1 s. Compared to the vertebrate 5-HT_3A receptor, dose-response curves were similar for 5-HT but very different for the orthosteric agonists tryptamine and 2-Me-5HT. The anthelmintic drugs ivermectin (IVM), levamisole, and piperazine (PZE), which are agonists of other Cys-loop receptors, did not activate MOD-1. However, IVM produced a slight and irreversible inhibition and PZE produced a profound and reversible inhibition of MOD-1 currents elicited by 5-HT. The analysis indicated that PZE is a non-competitive antagonist of MOD-1, revealing a novel function of this drug. To relate the molecular effects to behavioral actions of these compounds, we performed locomotor activity assays in *C. elegans*. We found that 5-HT produces rapid and reversible paralysis of wild-type (WT) worms while MOD-1 mutants are partially resistant under similar conditions, thus indicating that MOD-1 is the main 5-HT target in this type of assays. Additional assays using drug combinations in WT and mutant strains confirmed the inhibition of MOD-1 activity by IVM and PZE. The elucidation of the molecular pharmacology of MOD-1 enhances our knowledge of function and drug selectivity of Cys-loop receptors and contributes to determine its potential as a novel target for anthelmintic therapy.

93. (390) **RATIONAL SEARCH FOR G PROTEIN-COUPLED RECEPTOR KINASE 5 INHIBITORS UTILIZING DOKING-BASED VIRTUAL SCREENING**

Emiliana Echeverría[1], Sonia Ripoll[1], Maia Cabrera[2], Pablo Lorenzano-Menna[2], Natalia Fernández[1].

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G protein-coupled receptor (GPCR) kinase 5 proved to be overexpressed in failing hearts causing increased desensitization of beta-adrenergic receptors (βARs), deficit in cardiac contractility and failure progression. It has two main domains: Regulator of G protein Signaling (RGS) homology domain (RH), and protein kinase domain (KD). The mechanism of GPCRs phosphorylation by GRK5 requires the disruption of an ionic lock in RH/KD interface, leading to a more stable complex with the GPCR that enhances catalytic properties of the kinase.

To obtain GRK5 inhibitors we performed a docking-based virtual screening (VS) using pdb ID 4TND to search within Enamine Advanced Collection for compounds able to bind to RH/KD interface, intending to strengthen ionic lock and avoid the catalytically competent conformation to be reached. We obtained a list of hits ordered by docking energy, ranging from -10.4 to -9.7. Using Protein Ligand Interaction Profiler tool, we evaluated non-covalent interactions between GRK5 and predicted docking poses, and observed several hydrophobic interactions and hydrogen bonds joining residues from RH and KD. Also, interesting interactions such as salt bridges, halogen bonds and π-cation were found. Accordingly, we chose 15 compounds to be purchased and evaluated in biological activity assays, for what we setted up FRET-based determinations to quantify real-time intracellular cAMP. HEKT Epac-SH187 cells co-transfected with GRK5 and β1AR or β2AR were stimulated with 10μM isoproterenol (Iso) and AUC (area under curve) values of 10min response were determined in FlexStation3 at 37°C. AUCs were reduced from 244.4±24 to 112.5±7.4 for β1AR and from 138.7±10 to 64.73±3.45 for β2AR ($p<0.05$) by GRK5 overexpression (confirmed by Western Blot).

Both computer aided identification of potential GRK5 ligands and obtention of a methodology for screening these compounds will allow us to identify candidate inhibitors of GRK5 in the search of new cardioprotective drugs.

94. (476) **BIOACTIVITY OF ALPHA-HALOACRYLATES OF METYL BETA-SUBSTITUTED SYNTHETIZED *DE NOVO* IN AN *IN VITRO* MODEL OF MAST CELL DEGRANULATION**