PANEL COMMUNICATIONS
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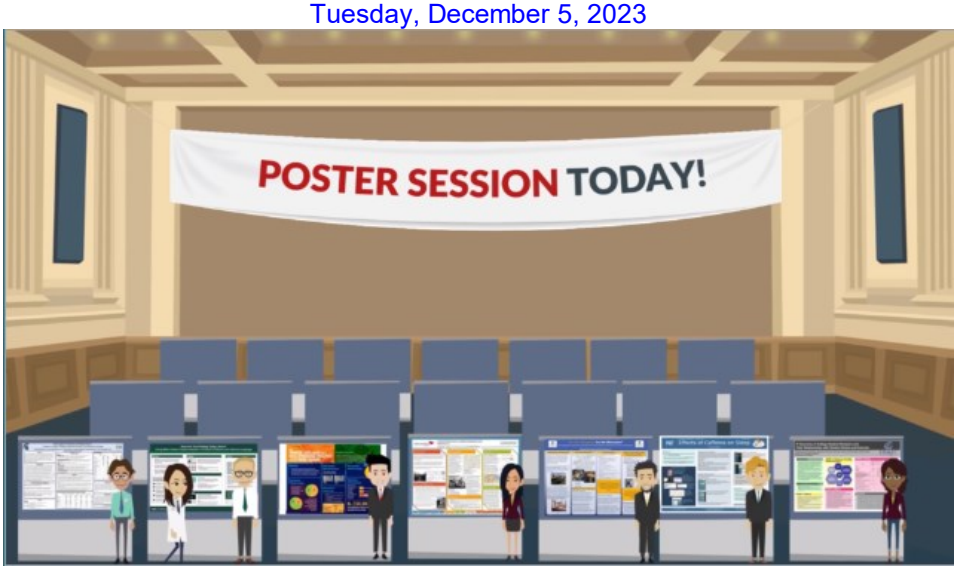

1.

ASOCIACIÓN ENTRE LA VARIANTE RS11231809 EN OAT4 Y EL INICIO DE LA NEUTROPENIA CON RECUENTO ABSOLUTO DE NEUTRÓFILOS DE 0 EN PACIENTES PEDIÁTRICOS CON LLA EN TRATAMIENTO CON QUIMIOTERAPIA. Association between the rs11231809 variant in OAT4 and the onset of neutropenia with absolute neutrophil count of 0 in pediatric patients with all under treatment with chemotherapy.

Childhood Acute Lymphoblastic Leukemia (ALL) is the most common type of cancer in children under 15 years of age. The main treatment is cytotoxic chemotherapy, which with the best treatments has brought survival to around 80%. However, it has the disadvantage of its high rate of toxicities, which result in increased morbidity. One of the most common toxicities is neutropenia. The variability in the onset of neutropenia could be explained by genetics.
Objective: To associate the presence of the rs11231809 variant in the OAT4 protein involved in the pharmacokinetics of antineoplastic drugs, with neutropenia defined as an absolute neutrophil count of 0.
Methodology: A mixed cohort was carried out in patients diagnosed with ALL from 2012 to 2023 at HLCM, HRR and HEGC hospitals during their induction therapy (IA protocol), they were asked for an oral swab sample from which the DNA. The analyzes were carried out with real time – PCR with Taqman probes. The onset of neutropenia was obtained from the blood counts and clinical records. The difference between the genotypes was evaluated through a survival analysis with the log-rank test and Cox regression to determine the strength of association with the Hazard Ratio (HR) and its 95% Confidence Interval (95%CI).
Results: 188 patients with ALL were recruited, of which the average age at diagnosis was 5.1 +- 3.3 and 56% (105) were men. The TT genotype had a frequency of 49.6% (57), the AA genotype 6.1% (7) and the AT heterozygous 44.4% (51). The recessive phenotype (TT) is a risk factor for the early onset of rank 0 neutropenia (log-rank p = 0.01) with an HR=2.4 (95% CI: 1.1 – 5.0).
Conclusion: The genotype of the rs11231809 variant is associated with the onset of neutropenia. These results can be used to individualize the treatment and follow-up of patients with ALL.

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2.

CARACTERIZACIÓN CLÍNICA Y SOCIODEMOGRÁFICA DEL USO DE QUETIAPINA DURANTE 2022 EN PACIENTES DE ATENCIÓN PRIMARIA DE SALUD DE VALDIVIA: ANÁLISIS CON DATOS DEL MUNDO REAL. Clinical and sociodemographic characterization of quetiapine use during 2022 in primary healthcare patients of valdivia's desam: real world data (rwd) analysis.

Off-label prescription of drugs approved by regulatory agencies represents a significant public health problem. This practice creates conflict between the scientific community, the pharmaceutical industry, healthcare policies, and medical practitioners. Quetiapine, an atypical antipsychotic primarily used off-label, makes a good case study to analyze the determinant factors of its prescription. This analysis can contribute to lay foundations for its better prescription. The current massification of digital tools and databases in primary healthcare centers provides trustworthy data on key variables that allows pharmaco-epidemiological research. Methodology: Using RWD from primary healthcare centers, provided by Departamento de Salud Municipal de Valdivia, we obtained data on prescriptions of drugs and associated supplies carried out during 2022. We performed a statistical analysis using STATA and Microsoft Excel 365 to identify the factors associated to quetiapine prescription. We focused on sociodemographic variables, prescription diagnosis, concomitant diagnosis -mental health and non-transmissible chronic illnesses-, as well as comedication. Results: The total sample includes 42.661 patients, of which 1.675 were quetiapine users with a total of 9.892 prescriptions. 82,23% of quetiapine prescriptions were off-

label (representing 75,28% of all quetiapine users). The sociodemographic analysis demonstrated a strong association of off-label quetiapine prescription with dementia (OR 5.1, 95% CI 4.9 to 5.4) and insomnia (OR 2.7, 95% CI 2.6 -2.8) diagnosis. The second highest was the association of quetiapine prescription to treat the approved diagnosis of bipolar disorder (OR 2.2, 95% CI 1.6- 2.8) and major depressive disorder (OR 1.4, 95% CI 1.0 - 1.2). No significant associations were found between quetiapine prescription and sociodemographic variables such as age, sex or ethnicity. The most common comedications were hypolipidemic, analgesic, antihypertensive, antidepressant, hypnotic, and hypoglycemic drugs.

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3.

EFECTO DE LA ADMINISTRACIÓN EXOGENA DE OXITOCINA SOBRE LA PERFORMANCE EN EJERCICIO Y CONTROL CARDIOVAGAL DURANTE HIPOXIA HIPOBÁRICA EN RATAS. Effects of exogenous oxytocin on exercise performance and cardiovagal control during hypobaric hypoxia in rats.

Exogenous oxytocin (OXY) administration has been shown to enhance parasympathetic drive. Previous research has demonstrated that vagal control is pivotal in exercise performance. In our earlier work, we found that during hypobaric hypoxia (HH), there is an impairment of baroreflex-dependent parasympathetic control, which coincides with a deterioration in exercise performance. Therefore, the administration of OXY can improve baroreflex-dependent parasympathetic control, thereby enhancing exercise performance during HH. This study aimed to investigate the impact of OXY administration on exercise performance and cardiovagal control in rats during HH. Male adult Wistar Kyoto rats (n=8, 276+-5g) were randomly assigned to Vehicle (Veh, n=4) and OXY groups (n=4). Veh (NaCl 0.9%, 100uL, i.p.) and OXY (0.433ug/kg, 100uL, i.p.) were administrated for 14 days. Before and after Veh and OXY, the animals underwent an incremental exercise performance test (J) during normobaric normoxia (NN, pO2:156mmHg) and HH (pO2:100mmHg). After 14 days, baroreflex (bolus technique) was assessed during NN and HH, and ventilatory response HH was determined. Before Veh or OXY administration, the two groups had no significant difference in exercise performance during HH. However, the OXY group demonstrated a similar work done between NN and HH (382.2+-60.2 vs. 281.5+-105.6 J, respectively), a response not observed in the Veh group (353.7+-104.5 vs. 73.2+-1.4 J, respectively). The Veh group showed a baroreflex reset (blood pressure 50: delta26.8+-8.9 mmHg) and an increment of bradycardic response (parasympathetic indicator) (delta54.9+-24.3 beats/min) during HH, which was reversed with OXY administration (blood pressure 50: delta-37.0+-8.8 mmHg; bradycardic response: delta-54.6+-20.8 beats/min). Both groups showed similar ventilatory responses to HH (delta60% minute ventilation). Our results strongly indicate that the administration of exogenous OXY significantly improved the vagal response to HH and was associated with an enhanced exercise response during HH.

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4.

CARACTERIZACIÓN POBLACIONAL DE MUTACIONES RELEVANTES PARA LA ANEMIA FALCIFORME Y SU TRATAMIENTO: UN PASO HACIA LA PERSONALIZACIÓN DE LA ENFERMEDAD. Population characterization of mutations for sickle cell anemia and its treatment: one step towards personalized medicine for the disease.

Sickle cell anaemia (SCA) is the most common genetic disease in the world. In countries with massive public health programs with early detection, this disease is not considered lethal. However, delayed diagnosis and treatment can generate various complications for patients' health. Several specific haplotypes or single-base polymorphic variants (SNPs) associated with SCA prognosis have been established in the literature. In the present work, we analyze population frequencies and correlations of several SNPs related to the prognosis of SCA (i.e., basal fetal haemoglobin levels, response to hydroxyurea treatment, and response to other drugs used in the SCA treatment, taken from validated databases. The results extend those from previous reports and show that the profile of most of the SNPs studied present statistically significant differential distributions among general ethnic groups, pointing to the need to carry out massive early testing of relevant SNPs for SCA in patients diagnosed with this disease. It is concluded that the application of a broad mutation detection program will lead to a more personalized and efficient response in the treatment of SCA. Keywords: Sickle cell anemia, Single base polymorphisms, Fetal hemoglobin, Ethnic groups, Bioinformatics.

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5.

CONCURSO DRA. MARÍA EUGENIA LETELIER

PRIMER INFORME SOBRE LA SÍNTESIS DE COMPLEJOS DE PD(II) EFECTO DE UN EXTRACTO POLIFENÓLICO DE *UGNI MOLINAE* SOBRE LA NEURODEGENERACIÓN DESCRITA EN UN MODELO DE ENFERMEDAD DE HUNTINGTON. Effect of a polyphenolic extract from *Ugni molinae*, on neurodegeneration described in a Huntington`s disease model.

Huntington's disease (HD) is an autosomal–dominant inherited neurological disorder caused by an unstable trinucleotide CAG repeat expansion at the N-terminus of gene encoding the huntingtin protein (Htt). The mutation results in the production of abnormal aggregation of Htt (mHtt) which promotes neuronal dysfunction and death of medium spiny neurons in the striatum, resulting in altered motor control and cognitive function. Effective treatments for HD are still pending. Previously, our group identified the presence of polyphenols in leaves from the Chilean-native berry Ugni molinae, whose extracts showed a potent anti-aggregation activity in models of Alzheimer´s disease. We evaluated the efficacy of 8 fruit extracts from different genotypes of U. molinae on reducing protein aggregation using

cellular models of HD. One extract, ETE 19-1, significantly reduced polyglutamine aggregation levels. Materials & Methods: R6/2 HD mouse model was treated with ETE-19-1 by Gavage daily for one month. We evaluated motor capacity by Rotarod test, protein aggregation and inflammation in the gut and brain tissue. Results: Our results in HD preclinical models treated with ETE 19-1 shows that improves motor function, reduces protein aggregates and neuroinflammation in striatum, and provide additional relief to the intestinal damage present in R6/2 mice. Conclusion: Bioactive components in extracts from U. molinae berries have positive effects on HD. This demonstrates the potential effect of native berries to treat neurodegenerative diseases associated with protein aggregates.

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6.
CARACTERIZACIÓN DE LA EXPRESIÓN DE GPR110 Y GPR158 EN MÉDULA ESPINAL ADULTA. Characterization of GPR110 and GPR158 expression in adult spinal cord.

G-protein receptor 110 (GPR110) belongs to the adhesion G-protein coupled receptors (GPCRs) family and is the target of the lipidic mediator N-docosahexaenoylethanolamine (synaptamide), whose activation stimulates synaptogenesis. On the other hand, G-protein coupled receptor 158 (GPR158) is a metabotropic receptor activated by glycine. Although it is known that these receptors are highly expressed in brain, their expression in spinal cord remains unclear. Moreover, whether these receptors could be exploited as novel pharmacological targets has been not investigated. To initiate the assessment of the potential relevance of these receptors in pain processing, we analyzed the GPR110 and GPR158 mRNA using RT-qPCR from spinal cord from adult mice. In addition, cultured spinal neurons were examined using similar methodologies. The protein expression in these systems was evaluated by Western Blot and immunostaining. Our preliminary data show that GPR110 and GPR158 transcripts are detectable in adult spinal cord tissue and in cultured spinal neurons. Western Blot assays confirm that these receptors are expressed in spinal cord from adult mice. Furthermore, spinal cord immunostaining suggests that GPR110 is localized in preferentially in neurons. Taken together, our findings suggest that GPR110 and GPR158 are expressed in spinal cord. Since both receptors have been recently deorphanized, we believe that its spinal expression is an interesting starting point for the identification and characterization of synthetic ligands with therapeutic potential as future analgesics.

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7.
KLK4 Y KLK12 COMO MODULADORES POTENCIALES DEL DESARROLLO Y PROGRESIÓN DEL CÁNCER DE MAMA KLK4 and KLK12 as potential modulators of the development and progresion of breast cancer.

Breast cancer is one of the most common cancers in Chile and worldwide. Although great advances account for the progression of this pathology, the role of kallikrein-related peptidases (KLKs) is less studied. In this sense, it is of outmost importance to study their role in cell adhesion, migration, metastasis, and angiogenesis in the context of breast cancer (BC). KLK12 (2 y 10 ng/ml x 24 h) was found to modulate an important survival pathway for BC cells visualized by high levels of insulin growth factor (IGF) and its associated binding proteins (IGFBP3 and 7) in conditioned medium (CM). Constitutive pathways involved with cellular proliferation, like epidermal growth factor receptor (EGFR) and mammalian target of rapamycin (mTOR), were increased by KLK4 and KLK12 (10 ng/ml x 24 h). We also observed a cross-link between the secretion of these KLKs since MCF7 BC cells stimulated with KLK12 or KLK4 (10 ng/ml x 24 h) presented high levels of both KLKs in CM. In addition, BC cells stimulated with KLK4 (10 ng/ml) were associated with a negative regulation of cytokeratin-18 levels and an increase in TGF beta 1 secretion, which might indicate the ability of KLK4 to lead BC cells to a more invasive state and metastasis. KLK4 and KLK12 (10 ng/ml x 24 h) also increased the adhesion of MCF7 cells to a synthetic matrix. Furthermore, KLK12 (10 ng/ml) increased the secretion of angiogenic factors in CM, such as vascular endothelial growth factor and platelet-derived growth factor A/B, which emphasize the key role of KLK4 and KLK12 in the development and progression of breast cancer.

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8.
ACTIVIDAD ANTIPROTOZOARIA Y PERFIL QUÍMICO DE ESPECIES DE BACCHARIS CONTRA TRYPANOSOMA CRUZI. Anti-protozoal activity and chemical profile of Baccharis species against Trypanosoma cruzi.

The protozoan Trypanosoma cruzi responsible for Chagas' disease affects between 6 and 7 million people worldwide, especially in Latin America. Currently, Chagas' disease chemotherapy is limited to benznidazole and nifurtimox, drugs effective only in the acute phase of the infection. Natural products have provided interesting secondary metabolites with potential roles against protozoan neglected diseases. The genus Baccharis is endemic in South America, becoming a source of bioactive substances. The present study analyzes the trypanocidal effect of Baccharis species extracts and their chemical profile by LC MS- MS. Hexane, ethyl acetate, hydroethanolic and aqueous extracts of B. tola, B. linearis, B. paniculata and B. vernalis were prepared. The hexane and ethyl acetate extracts of each

specie reported a higher percentage of cell death against T. cruzi, compared to the hydroethanolic and aqueous extracts. All Baccharis extracts induced concentration-dependent effects against T. cruzi Trypomastigote and the viability of mammalian cells is lower for B. vernalis extracts. However, this motivated us to study an intracellular infection model for Baccharis species at different concentrations. The chemical profiles provided a preliminary identification of the main compounds for each species. Among these compounds, we identified flavonoids, coumarins and terpenes. This is the first report of trypanocidal activity for these species, contributing to the search for new agents against T. cruzi and bioprospecting study for this genus.

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9.
ACTIVIDAD CITOTÓXICA, INHIBICIÓN DE TOPOISIOMERASA I Y II DE NUEVOS SESQUITERPEN-ARIL DERIVADOS. Cytotoxic activity, Topoisomerase I and II inhibithion of new sesquiterpen-aryl derivatives.

Drimane metabolites obtained from the Drimys winteride tree known as "canelo de Magallanes" have interesting bioactive properties, for example against cancer.[1] Human DNA Topoisomerase enzymes (TOP 1/2) are crucial in cancer and their inhibition induces cell apoptosis, being pharmacological targets for clinical use. [2] In turn, the drimane derivative, albaconol, is an effective inhibitor of TOP2.[3] In the present study, the synthesis of 15 new neoalbaconol analogs of aryl drimane structure with a bridging bond with different degrees of oxidation was carried out from the metabolite drimenol obtained from Drimys w. The antiproliferative activity of the synthesized compounds was evaluated in MCF-7(breast cancer) cell lines, using MCF-10 as a control. The best candidates synthesized possess antitumor activity in the range of 20-50µM. The compounds that presented the best cytotoxicity and selectivity index (SI) values were evaluated for their ability to inhibit topoisomerase I and II as well as caspase 3 and 7 activation. Therefore, considering these results, compounds with aryl-drimane structure are promising compounds in the search for new antitumor agents.

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10.
EL ÁCIDO NORDIHIDROGUAIARÉTICO COMO POTENCIAL TERAPIA COMBINADA PARA EL CÁNCER DE PULMÓN DE CÉLULAS NO PEQUEÑAS (NSCLC). Nordihydroguaiaretic acid (NDGA) as a potential combined therapy for non-small cell lung cancer (NSCLC).

Lung cancer (LC) has the highest rates of mortality worldwide and non-small cell lung cancer (NSCLC) represent 80% of all lung cancer cases diagnosed. Despite the efforts to improve therapies to LC, the survival of patients remains low. In this context, natural products represent an attractive source of new drugs to fight against LC and other cancer. Nordihydroguaiaretic acid (NDGA) is the main metabolite of Larrea tridentata, an abundant plant in dessert Areas of Mexico and United States. The lignan NDGA has been shown to have different properties including antioxidant, antiviral, antifungal, antibacterial, antiaging and anticancer. In the present study we demonstrated the antitumoral capacity of NDGA against non-small cell lung cancer (NSCLC) cells. The treatment with NDGA causes decreased in cell proliferation and cell death measured by resazurin reduction assay, bromodeoxyuridine (BrdU) incorporation, colony formation and propidium iodide assay. In consequence, we investigated the effect of this compound combined with the most used chemotherapeutics for LC; carboplatin, gemcitabine and taxol and we found that the combination of this drugs with NDGA impact synergically on the cell viability of non-small cell lung cancer cells H1975, H1299 and A549.

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11.
CARACTERIZACIÓN MOLECULAR Y FUNCIONAL DEL RECEPTOR DE GLICINA EN LÍNEAS DE MACRÓFAGOS. Molecular and functional characterization of glycine receptors in macrophages cell lines.

Macrophages, the surveillance cells of the innate branch of the immunity system, play a critical role in the regulation of diverse physiological processes, from tissue regeneration to the development of inflammatory responses. In a functional point of view, depending on the tissue-specific micro-environmental stimulus, they can be derived in macrophages type M1 (pro-inflammatory) or type M2 (anti-inflammatory). For this purpose, they express a wide variety of functional receptors in the plasmatic membrane, where recently the role played by members of the superfamily of ligand-activated pentameric ion channels (pLGIC), has gained a significant relevance. Even though several experimental data have been reported the expression of the glycine receptor (GlyR), which play an inhibitory role in the central nervous system, in different macrophages populations (e.g. Kupffer cells, alveolar and splenic macrophages), the physiological role in these cells is still unknown. In the present work we characterize the expression and function of GlyRs using the RAW264.7 macrophage line as a cellular model using immune-staining, molecular and electrophysiological

techniques. In addition, we tested the expression of GlyRs under activation conditions using endotoxin (LPS) treatment. Our immunocytochemical experimental results show that the RAW264.7 macrophage expresses GlyRs at the level of the plasma membrane and presenting cell polarity under the stimulation of LPS. Further, we also detected the expression of the alpha2 and alpha3 subunits by RT-qPCR without the expression of alpha1 or beta subunits. Overall, our experimental data increase the knowledge about the role of the GlyRs, a receptor typically inherent to the central nervous system, in the activation of the immune response mediated by macrophages.

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12.

LA QUERCETINA PREVIENE LA RESISTENCIA A LA ENZALUTAMIDA EN CÉLULAS DE CÁNCER DE PRÓSTATA RESISTENTES A LA CASTRACIÓN. Quercetin prevent enzalutamide resistance in castration-resistant prostate cancer cells.

Castration-Resistant Prostate Cancer (CRPC) is treated in the first instance with enzalutamide. The main characteristic of CRPC is the progression even in the absence of androgens and, in some cases, despite the use of drugs such as enzalutamide. An important pathway for the progression of CRPC is PI3K/AKT, which increases the expression of AR and AR-V7, two important components of CRCP and enzalutamide resistance. Quercetin is a secondary metabolite with antioxidant activity and antiproliferative effects in different cancers. In a previous investigation, we demonstrated that Trolox, an antioxidant, prevents enzalutamide resistance in CRPC cells by decreasing ROS. Thus, we propose quercetin could prevent Enzalutamide resistance by AKT inactivation and decreasing AR and AR-v7 expression and activation. Increasing doses of quercetin were used on C4-2B, and 22RV1 (CRPC cell lines), and the activation of AKT was analyzed through Ser473 phosphorylation by western blot. Furthermore, AR and AR-V7 were analyzed by western blot, and cell proliferation assays were performed. Our results showed that quercetin inhibits cell proliferation and prevents the activation of the AKT, decreasing the AR and AR-v7 expression and activation. Moreover, a co-treatment with enzalutamide and quercetin increased the cytostatic effect of enzalutamide on C4-2B cells.

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13.

CONCURSO DRA. MARÍA EUGENIA LETELIER

EFECTO ANSIOLITICO DE LOS DERIVADOS HEMISINTETICOS HALOGENADOS DE CITISINA AISLADOS DESDE SOPHORA SECUNDIFLORA EN UN MODELO DE PEZ CEBRA. Anxiolytic effect of hemisynthetic halogenated derivatives of Cytisine isolated from Sophora secundiflora in a Zebrafish model.

Anxiety is a serious mental disorder, and recent statistics have determined that 35.12% of the global population had an anxiety disorder during the COVID-19 pandemic. A mechanism associated with anxiolytic effects is related to nicotinic acetylcholine receptor (nAChR) agonists, principally acting on the a4b2 nAChR subtype. nAChRs are present in different animal models, including murine and teleostans ones. Zebrafish has become an ideal animal model due to its high human genetic similarities (70%), giving it high versatility in different Áreas of study, among them in behavioral studies related to anxiety. The novel tank diving test (NTT) is one of the many paradigms used for studies on new drugs related to their anxiolytic effect. In this work, an adult zebrafish was used to determine the behavioral effects of 3- and 5-halocytisine derivatives from cytisine isolated from Sophora secundiflora seeds, using the NTT at different doses. Our results show that substitution at position 3 by chlorine or bromine decreases the time spent by the fish at the bottom compared to the control. However, the 3-chloro derivative at higher doses increases the bottom dwelling time. In contrast, substitution at the 5 position increases bottom dwelling at all concentrations showing no anxiolytic effects in this model. Unexpected results were observed with the 5-chlorocytisine derivative, which at a concentration of 10 mg/L produced a significant decrease in bottom dwelling and showed high times of freezing. In conclusion, the 3-chloro and 3-bromo derivatives show an anxiolytic effect, the 3-chlorocytisine derivative being more potent than the 3- bromo derivative, with the lowest time at the bottom of the tank at 1mg/L. On the other hand, chlorine, and bromine at position 5 produce an opposite effect.

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14.

EL MODULADOR DEL RECEPTOR DE GLICINA 2,6-DTBP RECUPERA LA CONDUCTANCIA UNITARIA REDUCIDA POR FOSFORILACIÓN MEDIADA POR PKA, EN LA VARIANTE ALFA 3K DEL RECEPTOR DE GLICINA. The glycine receptor modulator 2,6-DTBP, recovery the unitary conductance, reduced by PKA-mediated phosphorylation, in the glycine receptor alpha 3K variant.

The glycine receptor (GlyR) is an inhibitory ion channel, member of the superfamily of pentameric ligand-gated ion channels (pLGICs), which play a critical role in the control of neural excitability. To date 4 alpha subunit and 1 beta subunit have been described. Each subunit is composed by an extracellular domain (ECD), a transmembrane domain (TMD) and an intracellular domain (ICD). The different alpha subunits are diversely expressed through the nervous system. In the specific context of the alpha 3 containing GlyRs, they are expressed mainly in the lamina II of the spinal cord, where play a crucial role in the sensorial processing. The alpha 3 subunit present two variants product of an alternative splicing that eliminates the exon 8 of the GRL3 gene resulting in an alpha3K, which lack 15 residues of the ICD compared with the alpha3L variant. In previous work from our lab,

we demonstrated that the function of alpha3L containing GlyRs can be modulated by phosphorylation events. In the present work, we extended theses analysis to the alpha3K variant. By using electrophysiological recordings we observed that activation of the PKA through a photoactivatable adenylyl cyclase (bPAC) or the introduction of a phosphomimetic mutation (S346E) in the alpha3K variant produced a significant reduction in the unitary conductance, without change in the membrane distribution or in the macroscopic glycine-activated currents. Interestingly, this attenuation of unitary currents can be reverted by the co-application of 2,6-DTBP, a positive allosteric modulator of GlyRs. Taken together, ours experimental results provide new insights in the molecular requirements involves in the modulation of alpha3 containing GlyR by PKA-mediated phosphorylation.

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15.

CONTROL DE LA CONDUCTANCIA UNITARIA DEL RECEPTOR DEL ÁCIDO GAMA-AMINOBUTÍRICO TIPO A POR RESIDUOS INTRACELULARES: IMPLICANCIAS EN LA REGULACIÓN DEL CANAL POR FOSFORILACIÓN. Control of unitary conductance of the gamma-aminobutyric acid type A receptors by intracellular residues: implications in the regulation of the channel by phosphorylation.

The gamma-aminobutyric acid type A receptors (GABAARs) belong to the family of pentameric ligand-gated ion channels (pLGICs). The functional pentamer is formed by the arrangement of five subunits surrounding a central chloride-permeable pore. Each subunit is composed by an extracellular domain (ECD), a transmembrane domain (TMD) and a large intracellular domain (ICD). The function of the GABAARs can be modulated by several protein kinases targeting serine residues located in the ICD. Even though several experimental data had shown that phosphorylation reduced the maximum currents in the GABAARs, the molecular mechanism underlying this effect is still controversial. One of the most plausible explanation for this phenomena is the reduction in the unitary conductance of the channel. To test whether the introduction of a negative charge in the ICD impacts on the unitary conductance of the GABAAR composed by alpha 1 and beta 2 subunits, we performed whole-cell and single-channel electrophysiological recordings in GABAARs carrying the phosphomimetic mutation S410E in the beta 2 subunit. Interestingly, the phosphomimetic mutation reduced the unitary conductance of the channel but displayed no impact at the macroscopic level. In addition, we tested a non phosphorylatable mutation (S410A) which showed a behavior similar to a non-phosphorylated channel. Overall, our results suggest that the inhibition of the GABAARs function by phosphorylation events could be explained by a significant reduction in the unitary conductance.

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16.

EFECTOS DE LA ACTIVACIÓN E INHIBICIÓN DE LA PROTEINA QUINASA DEPENDIENTE DE CICLINA 5 (CDK5) EN LOS RECEPTORES DE GLICINA. Effects of activation and inhibition of cyclin-dependent protein kinase 5 (CDK5) on glycine receptors.

Cyclin-dependent kinase 5 (Cdk5) phosphorylates serine and threonine residues. Its activity is mainly dependent on the expression of its activator protein, p35. Previous studies have reported that Cdk5 modulate the activity of neuronal ion channels by direct phosphorylation. However, the role of Cdk5 in the modulation of inhibitory ion channels has not yet been explored. In this context, glycine receptors (GlyRs) are pentameric ion channels permeable to chloride, that contributes to the control of neuronal excitability. Here, we explored whether Cdk5 activity modulate the expression of GlyRs. Sequence analyzes identified consensus phosphorylation sites for Cdk5 on 3 GlyR subunits (α1, α2, β) within the TM3-TM4 intracellular domain. Interestingly, the β subunits display a canonical consensus sequence for Cdk5 phosphorylation (391TPVH394). Confocal microscopy analyzes show that transfection of the α1-GlyR subunit together with p35 into HEK293 cells has no significant effect on receptor expression. On the contrary, similar assays showed that the expression of p35 enhanced the expression of α1β-GlyRs. This increase in the GlyR expression was blocked by roscovitine, a chemical Cdk5 inhibitor. Additional experiments in cultured spinal cultures show that infection with a virus that promote p35 expression results in a decrease in GlyRs compared to the GFP-expressing virus. On the other hand, pharmacological inhibition of Cdk5 did not significantly alter GlyR signals. Taken together, our findings show that Cdk5 activation may modulate GlyR expression likely thorough the phosphorylation of β subunits.

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17.
CARACTERIZACIÓN QUÍMICA DEL POLISACÁRIDO SOLUBLE DEL ALGA ULVA SPP. PARA SU POSTERIOR EVALUACIÓN DE SU POTENCIAL ACTIVIDAD COMO ADYUVANTE DE VACUNAS. Chemical characterization of the soluble polysaccharide from the alga ulva spp. for further evaluation of its potential activity as a vaccine adjuvant.

There is currently no evidence of the chemical characterization of the sulfated polysaccharide ulvan extracted from Ulva spp. algae from the Valparaiso region. The chemical structure of ulvan gives it the ability to stimulate the secretion of cytokines and nitric oxide, which may prevent an overexpression of inflammation, an improvement in the potency of the immune response against pathogens without producing immunotoxicity, giving it an interesting projection as a possible vaccine adjuvant. The objective of this work is to chemically characterize the ulvan polysaccharide extracted from Ulva spp. algae and to evaluate its immunostimulatory properties in a human macrophage cell model. To date, the ulvan has been characterized by spectrophotometric and FTIR methods. Subsequently, it will be injected by GC-MS and, in parallel, the cytotoxicity of the polysaccharide will be evaluated in cell cultures in vitro and its immunostimulant activity through the secretion of cytokines, nitric oxide and surface markers. Results to date indicate that the ulvan extracted from the Valparaiso region has 47% total sugars, 25% uronic acids and 10% sulfate, which coincides with characterizations performed for other Ulva species. As for the FTIR measurement, the stretching and vibrational bands show the functional groups associated with sugars (3340.3 cm-1 of uronic acids, 2943.4 cm-1 of rhamnose, 1647.2 cm-1 of glucuronic acid) and sulfate groups (1244.2 cm-1 and 847.3 cm-1), confirming the chemical structure of the ulvan. These results are positive projections for in vitro evaluation in human macrophage cell models. It is projected that this research will provide baseline information to deliver new strategies for use in research at the cellular level and as a potential vaccine adjuvant.

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18.
SÍNTESIS, CARACTERIZACIÓN Y EVALUACIÓN DE LA ACTIVIDAD ANTIDEPRESIVA DE LA FLUOXETINA DIMETILADA EN RATAS SPRAGUE-DAWLEY MACHO ADULTAS. Synthesis, characterization and evaluation of the antidepressant activity of dimethylated Fluoxetine in adult male Sprague-Dawley rats.

Selective serotonin reuptake inhibitors (SSRI's) have been shown to act on non-neuronal peripheral targets, including bacteria. In the gut lumen, there are bacteria sensitive to SSRI's like fluoxetine (Flx), suggesting that part of its effect could be through the microbiota-gut-brain axis. To test this, it is necessary to have an SSRI that does not cross the intestinal barrier nor the blood brain barrier (BBB). Aim: To synthesize a quaternary amine derivative of Flx, and to evaluate its permeability on the BBB. Methods: Methylated Flx (Flx+) was obtained using methyl iodide in an alkaline media. Its characterization was carried out using 1H-NMR and 14C-NMR. As a proxy to BBB permeability, forced swim tests (FST) was used in adult male Sprague-Dawley rats using intraperitoneal (ip) injections of Flx and Flx+ at 20mg/kg each. Control rats only received vehicle. Results: 1H-NMR and 14C-NMR show that additions of methyl groups to Flx shifts both spectra to the predicted integrals, thus confirming the synthesis of Flx+. In the FST, rats that were given Flx had a less immobility behaviours in comparison to control animals, while rats given Flx+ had immobility times comparable to control rats. Conclusion and discussion: Adding methyl groups to the amine of Flx generates the corresponding quaternary amine, which does not have an effect on the central nervous system when administered ip. This result confirms that adding a positive charge to a compound known to cross the BBB, generates a drug that might have peripheral but not central effects.

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19.
DISEÑO DE BETA-CETO ESTERES CON ACTIVIDAD ANTIBACTERIANA. Design of beta-Keto Esters with Antibacterial Activity.

This work proposes the design of beta-keto esters as antibacterial compounds. The design was based on the structure of the autoinducer of bacterial quorum sensing, N-(3-oxo-hexanoyl)-l homoserine lactone (3-oxo-C6-HSL). Eight beta-keto ester analogues were synthesised with good yields and were spectroscopically characterised, showing that the compounds were only present in their beta-keto ester tautomer form. We carried out a computational analysis of the reactivity and ADME (absorption, distribution, metabolism, and excretion) properties of the compounds as well as molecular docking and molecular dynamics calculations with the LasR and LuxS quorum-sensing (QS) proteins, which are involved in bacterial resistance to antibiotics. The results show that all the compounds exhibit reliable ADME properties and that only compound 7 can present electrophile toxicity. The theoretical reactivity study shows that compounds 6 and 8 present a differential local reactivity regarding the rest of the series. Compound 8 presents the most promising potential in terms of its ability to interact with the LasR and LuxS QS proteins efficiently according to its molecular docking and molecular dynamics calculations. An initial in vitro antimicrobial screening was performed against the human pathogenic bacteria Pseudomonas aeruginosa and Staphylococcus aureus as well as the phytopathogenic bacteria Pseudomonas syringae and Agrobacterium tumefaciens. Compounds 6 and 8 exhibit the most promising results in the in vitro antimicrobial screening against the panel of bacteria studied.

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20.

EVIDENCIAS DE LA EXISTENCIA DE INTERACCIONES NACHR(A4)-DAT EN EL CEREBRO DE RATA. RELEVANCIA PARA LA NEUROGÉNESIS ADULTA. Evidences for the existence of nAchR(a4)-DAT interactions in the rat brain. Relevance for Adult Neurogenesis.

In the brain, nicotinic acetylcholine receptors (nAChRs) are widely expressed at both pre- and post-synaptic levels, playing a crucial role in various functions like learning, memory, reward, motor control, pain relief, mood regulation, and anxiety. Notably, nicotine's impact on nAChRs influences neurotransmitter systems (dopamine, GABA, glutamate, serotonin, acetylcholine), which require precise mechanisms for proper function. Activation of nAChRs at synaptic endings releases dopamine and modulates DAT function, contributing to dopamine regulation. We explore nAChR-DAT interactions in rat brains through in situ PLA methods. Our analysis on fixed rat brain sections confirms nAChR-DAT interactions in striatum, nucleus accumbens, septum, and subventricular zone. Highest interactions are observed in SVZ and septum, lowest in nAcbSh. Analysis of nAChR-DAT interactions by means of in situ PLA in primary striatal cell cultures (CPU cells) also validate nAChR-DAT complexes. Acute nicotine (500 nM) treatment of CPU cells doesn't significantly alter nAChR-DAT complex formation. Overall, our study reveals nAChR-DAT complexes' existence, distribution and densities in the rat brains. Also confirms nicotine's limited impact on their affinities, expression, and densities (at least in CPU cells).

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21.

EFECTO DE L-BUTIONINA-(S,R)-SULFOXIMINA (BSO) E IMIDAZOL CETONA ERASTINA (IKE) EN EL TRATAMIENTO CON ABIRATERONA EN CÉLULAS DE CÁNCER DE PRÓSTATA HUMANO RESISTENTE A LA CASTRACIÓN. Effect of L-Buthionine-(S,R)-Sulfoximine (BSO) and Imidazole Ketone Erastin (IKE) on Abiraterone Treatment in Castration-Resistant Human Prostate Cancer Cells.

Castration-resistant prostate cancer (CRPC) is typically treated with Abiraterone. Nevertheless, the effectiveness of this treatment is hindered by the overexpression of the androgen receptor (AR) and alterations in oxidative stress, primarily due to changes in the levels of reactive oxygen species (ROS) and the presence of glutathione (GSH). GSH acts as a protective antioxidant in tumor cells, which helps them resist the impact of cancer treatments. To enhance the sensitivity of these therapies, GSH synthesis inhibitors such as L-buthionine-(S,R)-sulfoximine (BSO) and imidazole ketone erastin (IKE) have been investigated. However, whether BSO or IKE can sensitize CRPC cells to Abiraterone treatment remains to be confirmed. Based on this premise, our hypothesis is that BSO and IKE can increase the sensitivity of CRPC cells to Abiraterone treatment. To test this hypothesis, our overarching goal was to analyze the impact of BSO and IKE on Abiraterone treatment in human CRPC cells. We used cell viability assays and examined AR-dependent progression markers (AR, AR-V7, and PSA), as well as key enzymes involved in androgenesis (CYP17A1). These analyses were carried out using RT-qPCR and Western Blot techniques in C4-2B and 22RV1, CRPC cell lines. Our results showed that the co-treatment of BSO/ABI and IKE/ABI reduced cell viability in both CRPC models. Furthermore, combined BSO/ABI and IKE/ABI treatment decreased the expression of classical markers associated with resistance to second-generation antiandrogens, which could explain the increased sensitivity to abiraterone treatment.

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22.

ACIDO LINOLEICO ATENÚA EL ESTRÉS OXIDATIVO Y LA RESPUESTA INFLAMATORIA INDUCIDA POR LA RADIACIÓN UVB EN QUERATINOCITOS. Linoleic Acid Attenuates Oxidative Stress and The Inflammatory Response Induced by UVB Radiation In Keratinocytes.

Overexposure to ultraviolet B (UV-B) radiation can lead to cancer and reduce the skin's functionality as a protective barrier. Upon exposure to UV-B radiation, keratinocytes produce excessive amounts of reactive oxygen species (ROS), altering the oxidant/antioxidant balance and significantly increasing the inflammatory response. Linoleic acid (LA) is a fatty acid member of the ω-6 family and one of the skin's most abundant fatty acids. Although the importance of linoleic acid for the proper functioning of the skin has been established, the role that this fatty acid plays in the oxidative stress and inflammatory response induced by UVB radiation is still unknown. In this study, we investigated the effects and mechanism of LA on the production of reactive oxygen species and COX-2 induced by UVB radiation in Human immortalized keratinocytes (HaCaT) cells. Cells were exposed to UV-B at an intensity of 45 mJ/cm2 and treated with 25 or 50 μM LA for 6 h. The GCLC (Glutamate-Cysteine Ligase Catalytic Subunit), GSS (Glutathione Synthetase), and COX-2 levels were measured using RT-QPCR and western blot. Glutathione levels were quantified using a commercial kit, and PGE2 concentration was quantified by ELISA assay. The results show that LA decreases UVB-induced ROS production and increases the content of antioxidant factors, such as glutathione, GCLC, and GSS. Furthermore, LA abrogated UVB-induced NF-κB activation and COX-2 expression, as well as PGE2 synthesis. In conclusion, our findings present evidence of LA's antioxidant and anti-inflammatory mechanisms, suggesting a protective role of keratinocytes against the aggression of UV-B radiation.

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23.
EFECTO ANTIINFLAMATORIO DEL OMEGA-3. Anti-inflammatory effect of Omega-3.

The inflammatory response is designed to help fight and clear infections, eliminate harmful chemicals, and repair damaged tissues and organ systems. Although this process, in general, is protective, failure to resolve inflammation and return the target tissue to normal can lead to disease, including the development of cancer, cardiovascular, neurodegenerative, musculoskeletal, and inflammatory bowel diseases, among other pathologies. Thus, the present study seeks to make a preliminary evaluation of the anti-inflammatory activity of omega-3 fatty acids, specifically DHA, for the subsequent development of pharmaceutical or nutraceutical products that can be used, either for the treatment or prevention of diseases with an inflammatory basis. The research we are carrying out focuses on determining the anti-inflammatory effects of DHA on cells, both human and animal. The results of the study show, in evaluations of hemolysis by heat and with hypertonic saline solution, protection of the erythrocyte membrane, basic experiments to evaluate inflammation. Based on these results, clonogenic and invasion assays were performed on A2780 and Hose cells (ovarian cancer and non-tumor ovarian control cells) AGS and GES-1 (gastric adenocarcinoma and non-tumor gastric control), demonstrating an anti-inflammatory and anti-cancer. Based on these results, the pathways by which these effects are generated will continue to be evaluated.

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24.
CAMBIOS EN ACTIVIDAD CITOTÓXICA DE EPICATEQUINAS Y DERIVADOS ASOCIADAS A MODIFICACIONES TIOLICAS. Change on cytotoxic activity of epicatechins derivates with thiol modifications.

Las epicatequinas (EC) y sus derivados corresponden a las principales familias de polifenoles presentes en el té verde. Diversas propiedades farmacológicas asociadas al de té verde son producto la presencia de estos compuestos, entre ellas destaca su efecto citotóxico. Sin embargo, los resultados de los estudios que dan cuenta de estas actividades varían dependiendo de si se trata de ensayos in vitro o in vivo, ya que, las EC tienen una biodisponibilidad limitada. Se ha estudiado diversas estrategias para mejorar la biodisponibilidad de las EC, entre ellas, el uso de nucleófilos tiolícos sobre carbocationes de epicatequina derivadas de procianidinas naturales extraídas de cáscara de palta. En este trabajo, las modificaciones tiólicas enfocadas en aumentar la lipolificidad de las epicatequinas naturales permitieron la obtención de un stock de 6 nuevas moléculas. A partir de las 6 EC modificadas se consideró las de mayor interés, para sintetizar teaflavinas con modificaciones tiolicas. Las potenciales propiedades anticancerígenas de estas moléculas fueron evaluadas empleando el método de sulforodamina B en la línea celular de cáncer colorrectal CACO-2 y en la línea celular de fibroblastos no tumoral HDF. A las concentraciones ensayadas se presenció un efecto citotóxico dependiente de la polaridad de la modificación realizada. En particular, los aductos formados con nucleófilos derivados de benzeno-tiol, muestran un alto potencial citotóxico, y el aducto formado con etanditiol exhibe citotoxicidad selectiva contra células cancerígenas, lo que hace necesario profundizar a futuro en su estudio para esclarecer su comportamiento in vivo y el mecanismo por el cual estarían ejerciendo muerte celular.

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25.
EFECTO DE RESOLVINA D1 SOBRE LA SENESCENCIA DE FIBROBLASTOS CARDÍACOS DE RATA ADULTA INDUCIDA POR LPS. Effect of Resolvin D1 on LPS-Induced Senescence of Adult Rat Cardiac Fibroblasts.

Cellular senescence is a hallmark feature of aging that contributes to the progression of cardiovascular disease. Cardiac tissue has a high cellular organization where cardiac fibroblasts (CF) are sentinel cells that respond to numerous stimuli, including LPS, a ligand capable of specifically activating Toll-like receptor 4 (TLR-4); where its activation has been linked to the induction of senescence by inducing a potent proinflammatory response. Previous research from our laboratory has described that Resolvin D1 (Rv-D1) decreases the inflammatory response through various mechanisms. Therefore, it is important to determine if RvD1 is also able to prevent the LPS-induced CF senescent. Objective: Evaluate if the pre-treatment with Rv-D1 attenuates the LPS-induced senescence of adult rat CF. Methodology: Isolated CFs from adult rats were treated with LPS for 3 and 7 days to induce cellular senescence. Different senescence markers were evaluated, including SA-β-galactosidase activity and cell cycle progression protein levels (p53, p-Rb) by western blot. In addition, the preventive effect of RvD1 in LPS-induced senescence CF was measured at the times and markers described above. Results: Treatment with LPS increased SA-β-galactosidase activity after 3 and 7 days. Similarly, p53 protein levels increased on both days, while Rb phosphorylation decreased, proving that LPS induces CF senescence. The pre-treatment with Rv-D1 decreases the SA-β-galactosidase activity and p53 protein levels as well as, Rv-D1 prevents the decrease of Rb phosphorylation at 3 days induced by LPS. Conclusion: The pre-treatment with Rv-D1 prevents LPS-induced senescence in adult rat CF.

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26.
LOS EXTRACTOS DE COPAO REDUCEN LA PROLIFERACIÓN EN LAS CÉLULAS CANCEROSAS PERO NO EN LAS CÉLULAS NORMALES. Copao Extracts Reduce Proliferation On Cancer but Not On Normal Cells.

Chronic diseases such as cancer and its treatment are one of the most studied fields worldwide. However, the drugs developed present undesirable secondary effects and an aggressive response to the patient. In this way, it is believed that functional foods can prevent these effects. Among these natural products, the fruits of cacti present important biological activities including antioxidant and anti-inflammatory activities. Among the

cacti, Copao, an endemic species from the north of our country, has antioxidant and anti-inflammatory characteristics that make it interesting as a possible treatment for cancer disease. The aim of this work is to evaluate the effects of Copao extracts on the proliferation and survival of cancer cells, incubating AGS and CACO cells with different doses of aqueous and ethanolic extracts from Copao's pulp and peel, using Cisplatin as antineoplastic control. Incubation with aqueous but not ethanolic extracts reduced the proliferation and survival of cancer but not normal cells, suggesting that aqueous Copao extracts have selective antineoplastic properties that could be used in the treatment of Cancer.

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27.
EFECTO DE LA LIPOPROTEÍNA OXIDADA DE BAJA DENSIDAD SOBRE LA EXPRESIÓN DE MARCADORES DE PROGRESIÓN TUMORIAL EN CÉLULAS DE GLIOBLASTOMA. Effect of Oxidized Low-Density Lipoprotein on the Expression of Tumor Progression Markers in Glioblastoma Cells.

In prostate, breast, and colorectal cancers, the internalization of oxidized low-density lipoproteins (LDLox), mediated by scavenger receptors such as LOX-1 and CD36, increases various parameters of tumor progression, including angiogenesis, invasion, and proliferation. However, this has not been studied in glioblastoma (GBM), a highly aggressive brain cancer. Accordingly, we analyzed the expression of scavenger receptors in GBM cells and orthotopic xenografts, as well as the effect of LDLox treatment on the expression of tumor progression markers in GBM cells in vitro. Methodology: Western blot, immunofluorescence, and immunohistochemistry were used for the expression analysis of scavenger receptors LOX-1 and CD36 in U87-GM cells and orthotopic xenografts. LDLox internalization was evaluated using BODIPY dye in U87-MG cells. Finally, the expression of tumor progression markers was assessed in LDLox-treated cells. Results: Through Western blot, immunocytochemistry, and immunohistochemistry, we found a higher expression of the LOX-1 receptor compared to CD36 in U87-GM cells and orthotopic xenografts. Moreover, Lipid internalization is increased in oxLDL-treated cells compared to control. Finally, the expression of tumor progression markers such as Ki67, Slug, VEGF, SNAI1, Rac-1, and vimentin increased in LDLox-treated cells. Conclusion: We concluded that LDLox internalization could occur through LOX-1 in U87-GM cells and that treatment with LDLox increased the expression of tumor progression markers. Therefore, LOX-1 could be considered a potential therapeutic target for glioblastoma.

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28.
PROPIEDADES ANTIOXIDANTES Y ACTIVIDAD INHIBIDORA ENZIMÁTICA DE *AZARA SERRATA* ÚTIL CONTRA ENFERMEDADES CRÓNICAS NO TRANSMISIBLES. Antioxidant properties and enzymatic inhibitory activity of *Azara serrata* useful against chronic non-communicable diseases.

The World Health Organization has emphasized the importance of consuming small fruits for the prevention of chronic health problems, including diabetes, cardiovascular diseases, cancer, and obesity which are named chronic non-communicable diseases (NCDs). *Azara serrata* is a shrub endemic to Chile from the Salicaceae family and produces an underutilized blue-gray berry growing wild in southern Chile. In this work several glycosilated anthocyanins were detected and quantified using UHPLC coupled to UV detection and mass spectrometry (LC-PDA-MS) in the anthocyanin rich extract prepared using an optimized anthocyanin extraction protocol from this berry. The extract proved to be active in the inhibition of several enzymes linked to NCDs, such as acetylcholinesterase, tyrosinase, amilase, lipase, and glucosidase. The results were comparable to the superfruit berry maqui (*Aristotelia chilensis*). Furthermore, the extract concentrated in anthocyanins showed good antioxidant activity evidenced by the bleaching of the radicals DPPH and ABTS, ferric reducing antioxidant power (FRAP) and oxygen radical absorbance capacity (ORAC). The results can probe that neglected endemic small berries can be a source of healthy phytochemicals. These Chilean berries can be functional food and their extracts candidates for their use as functional ingredients and naturally healthy products.

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29.
ASOCIACIÓN ENTRE LA VARIANTE RS776746 EN LA PROTEÍNA CYP3A5 Y EL INICIO DE LA NEUTROPENIA CON RECUENTO ABSOLUTO DE NEUTRÓFILOS (RAN) MENOR A 1500 EN PACIENTES PEDIÁTRICOS CON LLA EN TRATAMIENTO CON QUIMIOTERAPIA. Association Between the Rs776746 Variant In Cyp3a5 Protein And The Onset Of Neutropenia With Absolute Neutrophil Count (ANC) Less Than 1,500 In Pediatric All Patients Undergoing Chemotherapy Treatment.

Childhood Acute Lymphoblastic Leukemia (ALL) is the most common type of cancer in children under 15 years of age. The main treatment is cytotoxic chemotherapy, which over the years has brought survival to around 80%. However, it has the disadvantage of its high rate of toxicities, which results in increased morbidity. One of the most common toxicities is neutropenia. The variability in the onset of neutropenia could be explained by genetics. Objective: To associate the presence of the rs776746 variant in the CYP3A5 protein involved in the pharmacokinetics of antineoplastic drugs, with neutropenia defined as an absolute neutrophil count less than 1,500. Methodology: A mixed cohort was carried out in patients diagnosed with ALL from 2012 to 2023 in the pediatric hospitals Dr. Roberto del Río, Luis Calvo Mackenna and Exequiel González Cortés during their induction therapy (IA protocol), they were asked for a buccal swab sample from which DNA was extracted. The analyzes were carried out with real time – PCR with Taqman probes. The onset of neutropenia was obtained from the blood counts and clinical records. The difference between the genotypes was evaluated through a survival analysis with the log-rank test and Cox regression to

determine the strength of association with the Hazard Ratio (HR) and its 95% Confidence Interval (95%CI).
Results: 188 patients with ALL were recruited, of which the average age at diagnosis was 5.1 +- 3.3 and 44.1% (83) were women. The CC genotype had a frequency of 91.8% (112), the TT genotype 5.7% (7) and the heterozygous 2.5% (3). The dominant phenotype (TT+TC) is a risk factor for the early onset of neutropenia ANC <1500 (log-rank p = 0.02) with an HR=2.5 95%CI: 1.1 – 5.9.
Conclusion: The genotype of the rs776746 variant is associated with the onset of neutropenia. These results can be used to personalize the treatment and monitoring of patients with ALL.

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30.
EFECTO DE EXTRACTOS DE COLLIGUAJA ODORIFERA MOLINA SOBRE LA VIABILIDAD CELULAR DE LÍNEAS CELULARES DE CÁNCER MAMARIO DEPENDIENTES E INDEPENDIENTES DE ESTRÓGENOS. *Colliguaja Odorifera Molina* Extracts Effects On The Viability Of Estrogen Dependent And Independent Breast Cancer Cell Lines.

Colliguaja odorifera Molina es una planta endémica que en Chile se encuentra desde la IV a la VII Región. Su uso tradicional se sustenta en propiedades antiinflamatorias, antibacterianas y analgésicas. Además, se ha reportado actividad anticáncer en células de leucemia linfocítica murina. Por otra parte, ensayos previos demostraron mediante HPLC, su alto contenido en quercetina, molécula asociada a efectos anticancerígenos. De esta manera surge el objetivo de esta investigación que es establecer el efecto de extractos hidroacetónicos, hidrometanólicos e hidrolizados acetónicos sobre células MCF-7 y MDA-MB231 de cáncer de mama dependientes e independientes de estrógenos, respectivamente. Para lograr este objetivo, la planta fue identificada botánicamente para luego, generar los respectivos extractos; hidrometanólico (metanol : agua 80:20); hidroacetónico (acetona:agua 60:40) y uno hidrolizado a partir del extracto hidroacetónico. La viabilidad de las células expuestas a los extractos fue determinada mediante el ensayo resazurin. Para el extracto hidroacetónico la máxima inhibición de la viabilidad fue 62,4% sobre la línea MCF-7, con IC50 de 10,1 µg/mL, y una selectividad de 6,7 con respecto a fibroblastos. Para el extracto hidrometanólico, la máxima inhibición fue 53,4% sobre la línea MCF-7, la IC50 fue 12 µg/mL, con una selectividad de 14,6, respecto a fibroblastos. Para el extracto acetónico hidrolizado, la máxima inhibición fue 55,1% sobre la línea MCF-7, la IC50 fue 55,5 µg/mL, con una selectividad de 2,4 respecto a fibroblastos. Por su parte, la línea celular MDA MB-231 resultó más resistente a la inhibición por los tres extractos. Sólo se pudo calcular IC50 para el extracto hidroacetónico, que fue 43,6 µg/mL con una selectividad de 1,5. En conclusión, el extracto hidrometanólico es el más promisorio bajo las condiciones evaluadas.

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31.
EFECTO ANTIINFLAMATORIO Y NEUROPROTECTOR DE FRACCIONES BIOACTIVAS DEL SHILAJIT ANDINO. Neuroprotective and Anti-Inflammatory Effect of Bioactive Fractions Of Andean Shilajit.

Alzheimer's disease is the form of dementia with the highest incidence worldwide and with an accelerated growth rate in people over 50 years, mainly in women. The main aim of this work is to find a natural product capable of reducing neuroinflammation and human tau protein aggregation, the main hallmarks of AD. Andean Shilajit is a brown exudation, a mixture of humic and fulvic organic substances, metabolites and minerals present in the Andes of Chile. Polar, apolar, and neutral fractions were isolated from the Andean Shilajit, enriched in different metabolites from which the fractions with the highest biological activity were selected. Low concentrations of the bioactive fractions F9 and F15 reduce the aggregation of human recombinant tau protein (rhtau40), and protect from rhtau40-induced death in undifferentiated and differentiated SHSY5Y human neuroblastoma cell cultures. F9 and F15 treatments showed anti-inflammatory effect, reduced TNF-α-induced cell death in SHSY5Y, activation of human microglia line HCM3 and decreased expression of inflammatory markers. Orally administered F9 and F15 protected 12-week-old c57BL6 mice from lipopolysaccharide (LPS 100ng/mL)-induced memory impairment. Treatment with a daily dose of F15 (100mg/mL p.o.) protected from impairment of working, spatial and novel-recognition memory, while F9 (100mg/mL p.o.) slightly protected the spatial learning process. Andean Shilajit (100mg/mL p.o.) did not significantly improve mouse memory. In addition, it was observed that F9 and F15 treatments significantly reduced depressive symptoms associated with LPS-induced neuroinflammation. This evidence suggests that a balanced therapeutic dosage of metabolites of the F15 fraction with anti-aggregatory activity of the tau protein and anti-inflammatory activity could produce a modifying effect on AD and, at the same time, depressive symptoms associated with diseases with an inflammatory clinical picture.

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32.
DISEÑO COMPUTACIONAL DE POTENCIALES INHIBIDORES DUALES PARA LOS RECEPTORES TUBULINA Y PD-L1. Computational design of potential dual inhibitors for Tubulin and PD-L1 receptors.

Tubulin plays a pivotal role in cellular processes such as cell division, intracellular transport, and maintenance of cell shape. As a critical constituent of microtubules, tubulin provides structural support to cells and facilitates crucial processes like mitosis and cell migration. Given its essential role in cell division, targeting tubulin has been a longstanding strategy for cancer treatment. On the other hand, PD-L1 is an immune checkpoint protein that plays a key function in regulating the immune response. Under normal physiological conditions, PD-L1 binds to its receptor, programmed cell death protein 1 (PD-1), on the surface of immune cells, thereby downregulating immune activation and preventing excessive immune responses. However, cancer cells exploit the PD-L1/PD-1 pathway to evade immune surveillance and suppress antitumor immune responses. The search for dual inhibitors targeting both tubulin and PD-L1 proteins in cancer therapy holds great promise for overcoming the limitations of single-

target therapies and achieving synergistic effects, leading to enhanced efficacy. In this study, deep learning methods, virtual screening, classical molecular dynamics, and binding energy estimations were employed for the exploration of new compounds with potential affinity to the colchicine site of tubulin protein and the PD-L1 receptor. Here, 7 compounds were identified that share interaction properties similar to TP5 (a ligand reported as active by both receptors), as well as a potential improved affinity revealed through MMGBSA calculations. These results are expected to serve as the starting point for the generation and design of new compounds with potential anticancer action.

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33.
NIVELES PLASMATICOS DE CLOZAPINA Y NORCLOZAPINA EN UNA INSTITUCIÓN PSIQUIATRICA DE REFERENCIA NACIONAL. Plasma Levels of Clozapine and Norclozapine in A National Reference Psychiatric Institution.

Clozapine, a first-line antipsychotic drug for the management of treatment-resistant Schizophrenia, has a metabolism influenced by age, sex, smoking habit, and drug interaction with other medications. In Chile, the information available from local patients is limited. The aim of the present study is to evaluate, in the population treated at the Dr. José Horwitz Psychiatric Institute (IPS), the plasma levels of clozapine and norclozapine in relation to the prescribed dose and factors that influence pharmacokinetics. This retrospective observational study was carried out with information from 333 clozapine users, over 15 years of age, who were treated at the IPS between April 2022 and March 2023. Plasma concentrations of clozapine and norclozapine were measured by HPLC with UV detection. Daily doses of clozapine were from 75 to 800 mg/day (median 400 mg/day), plasma concentrations of clozapine varied between 20.8 and 3461.4 ng/mL and of norclozapine between 22.9 and 1287, 4 ng/mL. Women presented higher values than men, users aged 60 years or more were 26% higher than young users (< 26 years old). Smokers had concentrations 35% lower than non-smokers. Concomitant use of fluoxetine affects the level of clozapine, while valproic acid influences plasma concentrations of norclozapine. In Chile, this analytical method for determining the drug and its metabolite is not available in most public hospitals, so the present results provide valuable information to apply in the clinical context in order to optimize treatment and improve therapeutic goals.

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34.
ESTUDIO DE LA AGREGACIÓN DEL PÉPTIDO BETA AMILOIDE Y LA FORMACIÓN DE FIBRILLAS MEDIANTE SIMULACIONES DE DINÁMICA MOLECULAR. Study of amyloid beta peptide aggregation and fibril formation through molecular dynamics simulations.

One of the current leading theories for the physiopathology of Alzheimer's disease (AD), a neurodegenerative disorder and one the most prevalent causes of death in the world according to the World Health Organisation, is the Amyloid theory, that states that the presence of insoluble aggregates of intracellular neurofibrillary tangles of misfolded Tau protein as well as extracellular amyloid beta (Aβ) peptide aggregates denominated "senile plaques" may have notorious neurotoxic effects generating mechanical stress, cellular membrane disruptions and the presence of a permanent oxidative environment due to activation of microglia. Thus, the understanding of this aggregation process of Aβ from a molecular perspective is imperative for the creation of therapeutic alternatives to this disease. Even though, there are multiple 3D structures reported in the PDB both for the peptide and structured fibrils, the Aβ aggregation mechanisms remains unknown. Therefore, using molecular dynamics simulations we seek to gain insights regarding the Aβ fibrils formation by profiling the interactions between Aβ peptides inside the fibrils using residue interaction networks (RINs). Furthermore, we are studying the effects of known anti-aggregation peptides on Aβ fibril formation. Finally, we intend to submit candidate anti-aggregation peptides of our own pipeline, to compare their effects with our standardized anti-aggregation peptides and therefore determine if they show anti-aggregation properties as well.

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35.
ESTUDIO DE UFR2709, UN ANTAGONISTA DE NACHR CON PROMETEDORAS PROPIEDADES ANTI ADICTIVAS. Study of UFR2709, a nAChR antagonist with promising anti-addiction properties.

Neuronal nicotinic acetylcholine receptors are ligand gated ion channels. Upon activation, the pore opening allows the flow of cations inside the plasma membrane, affecting membrane potential and activating intracellular signaling cascades. nAChRs are extensively distributed along the central nervous system, their main function is to influence the release of neurotransmitters trough presynaptic receptors. The use of nAChR agonists like cytisine and varenicline as smoking cessation treatment has been reported, however, little is known about the therapeutic effect of nAChR antagonist over drug addiction. UFR2709 a nicotinic antagonist, reduces short term ethanol intake in rats and inhibits nicotine reward and decreases anxiety on a zebrafish model. The aim of this work was to evaluate if UFR2709 presents stimulating properties during the Open Field Test Protocol with a murine model, in comparison to Saline Control and Nicotine administration. We also determined mRNA relative expression of nAChRs subunits and c-fos in response to each treatment and measured dopamine release by Ex-Vivo Fast Scan Cyclic Voltammetry in the striatum. Additionally, we evaluated the effect of UFR2709 and nicotine in GABAergic synaptic transmission onto CA1 pyramidal neurons in the hippocampus.

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