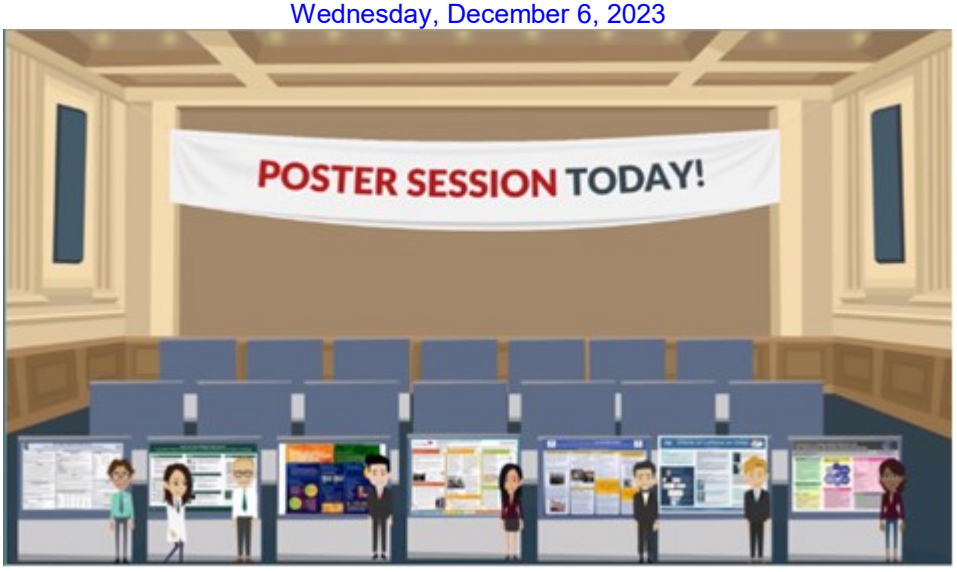
PANEL COMMUNICATIONS
Wednesday, December 6, 2023



1.
POTENCIAL MODULACIÓN DE RECEPTORES GABAA POR CDK5. Potential modulation of GABAA receptors by Cdk5.

GABAA receptors (GABAARs) are critical regulators of neuronal excitability of the CNS. This class of receptors have a prominent relevance as pharmacological targets against pathological anxiety and sleep disorders. GABAARs exhibit diverse conformations due to their subunit variability. The most expressed configurations in the brain are α1β2γ2 and α2β3γ2. The GABAARs activity is regulated by phosphorylation, influencing their function and neuronal localization. In this context, Cdk5 is a proline-directed serine/threonine kinase, whose consensus sequence is the motif (S/T)PX(H/K/R). A robust amount of studies has reported that the Cdk5 activation controls the activity of diverse ion channels, modulating physiological and pathological events of the CNS. Nevertheless, whether GABAARs are targeted by Cdk5 remains unexplored. This work aims to initiate the study of the potential regulation of GABAARs by Cdk5 activity. Our primary sequence alignment analysis identified partial consensus sequences for Cdk5 phosphorylation in the intracellular domain of the subunits α1,α2,α3, β2 and γ1 of mammalian GABAARs. Further in silico analyses indicated that α1, α3 and β2 have a high probability of being phosphorylated by Cdk5. We next analyzed whether the expression and cellular location of GABAARs is influenced by the Cdk5 activity. To evaluate this question, we produce and characterized a recombinant antibody that recognizes GABAARs α1. This antibody was generated from transfected HEK293 cells with an encoding plasmid. Our western blot and inmunocytochemical assays showed that the anti-GABAARs-α1 antibody efficiently recognized the target protein in brain tissue and in HEK293 cells transfected with GABAARs-α1β2 plasmids. We next studied the potential effects of Cdk5 activation on GABAARs-α1β2. To promote the Cdk5 activation, we expressed GABAARs-α1β2 together with p35, the canonical Cdk5 activator. Using HEK293 cell inmunocytochemistry, we found a significant increase of GABAARs-α1β2 expression in the presence of p35. Ongoing experiments will determine whether membrane receptors are also increased. We think that further characterization of this unidentified post-translational regulation of GABAARs may have relevant implications in physiological and pathological processes of the CNS.

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2.
IDENTIFICACIÓN DE BLANCOS TERAPÉUTICOS CLAVE MEDIANTE LAS CUALES EL SECRETOMA DERIVADO DE CÉLULAS MADRE MESENQUIMALES REPARA EL DAÑO DE LA ASFIXIA PERINATAL: UN ENFOQUE DESDE LA FARMACOLOGIA DE SISTEMAS. Identification of key protein targets by which mesenchymal stem cell-derived secretome repair perinatal asphyxia damage: An approach from systems pharmacology.

Hypoxic-ischemic encephalopathy (HIE), secondary to neonatal asphyxia, is a major cause of morbidity and mortality worldwide, lacking effective treatments. Oxygen interruption leads to neuronal death. The reperfusion phase triggers a cascade of events, oxidative stress and inflammation, leading to further neurotoxicity. A potential breakthrough is by treating with mesenchymal stem cell secretome (MSC-S), administered early after hypoxia, showing promising results. Identification of the molecular targets responsible for MSC-S effects remains elusive. Hypothesis: Protein-protein interaction network (PPIN) analysis of deferoxamine (DFX) MSC-S allows the identification of critical protein pathways involved in its effects. Objective: To determine the main protein components in DFX-MSC-S modulating key pathways related to the pathophysiology of HIE. Methods: Three PPIN networks were built: PPIN-1 (MSC-S); PPIN-2 (EHI), and PPIN-3 (merged

networks). To find interactions (primary and secondary) of the entries of each PPIN, the STRING database was queried with a confidence score of 0.7. All PPINs were created and analysed using KNIME 4.7.2 and Cytoscape 3.10. Topological analysis was performed by the Python package NetworkX (https: networkx.org), combined with KNIME workflows. Functional enrichment for each gene was performed with Gene Ontology (GO) biological process annotations, using BiNGO. 3.0. 3 (Biological Networks Gene Ontology Tool), a plugin for Cytoscape, with a significance of 0.01 (p-value) corrected by Bonferroni Family-Wise. Genes were grouped into functional modules using MTGO (Module Detection Using Topological Information and Knowledge GO) algorithms. Results: Two genes of interest, TP53 and SRC, were identified as direct targets of DFX-MSC-S, exhibiting a high topological score within the PPIN-3. SRC is associated with the RAS protein signal transduction cluster, while TP53 plays a role in DNA damage, via p53.

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3.
EVALUACIÓN DE LA TOXICIDAD DE COMPUESTOS NATURALES EN LARVAS DE PEZ CEBRA (DANIO RERIO). Toxicity evaluation of natural compounds on zebrafish (Danio rerio) larvae.

Zebrafish (Danio rerio) larvae have been used to evaluate the protective effects of resveratrol on 27-OH-cholesterol (27-OH-C) induced neuroinflammation. In this regard, chlorogenic acid (CA), which can be extracted from coffee grounds has been attributed to prevent neuroinflammation in cell cultures, but not in animal models. Therefore, there is a need to study the potential neuroprotective effects of CA. Aim: In order to evaluate the neuroprotective effects of chlorogenic acid, it is necessary to study the minimal toxicity dose of 27-OH-C and CA in zebrafish larvae. Methods: Zebrafish larvae were incubated from day post-fertilization (dpf) 3 to 5 with either 27-OH-C (10, 30 and 50 microM) or CA (0.25, 0.5 and 1.0mg/ml). Survival rate was evaluated as the main output in comparison to vehicle-treated larvae. A total of 15 individuals were assessed per condition. Results: 27-OH-C did not affect zebrafish larvae survival rates from 3 to 5 dpf in any of the used doses. However, CA did reduce the survival rate at 0.25mg/ml to 93%, and to 50% with 0.5mg/ml CA on 4 dpf. At 5 dpf survival rates were similar for 0.25mg/ml, while survival rate with 0.5mg/ml CA was 0%. Using 1.0 mg/ml of CA killed all animals at 4 dpf. Conclusion: Administration of 27-OH-C does not promote mortality in zebrafish larvae at any of the tested doses. However, CA, a proposed compound to prevent neuroinflammation, did induce mortality at tested doses. These findings suggest that the proposed preventive effects of CA on 27-OH-C-induced neuroinflammation in zebrafish should be further revised.

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4.
UNA NUEVA MOLÉCULA FLUORESCENTE INFRARROJA LPCC-1995 PERMITE LA DETECCIÓN DE TUMORES SUBCUTÁNEOS EN MODELOS MURINOS. A new infrared fluorescent molecule LPCC-1995 allows the detection of subcutaneous tumors in murine models.

The main treatment for localized cancer is surgery. This procedure has curative intent and seeks to completely remove the tumor and ensure negative surgical margins, since, if these are positive for cancer cells, they correlate with locoregional recurrence of the cancer and decrease the probability of curing the disease. An alternative to improve this process is fluorescence-guided oncologic surgery (FGOS). This procedure uses fluorescent molecules that allow the tumor to be identified in the operative context. However, one of the problems presented by FGOS is the autofluorescence of endogenous molecules at the wavelengths of the fluorophores currently used. The fluorophores that emit a signal in the near infrared (NIR) are of great interest, since in this range of the spectrum the tissues of the organism do not emit fluorescence. Our research group has identified a new NIR fluorescent molecule, and we hypothesized that the molecule LPCC-1995 allows the identification of tumor mass by infrared detection. The results showed that the LPCC-1995 has no cytotoxic effects on LL2 (carcinogenic) and 3T3-L1 (non-cancerous) cell lines. On the other hand, by administering the LPCC-1995 intravenously in mice with subcutaneous tumors of LL2 murine lung cancer. We observed that LPCC-1995 allows the identification of the tumor mass without NIR signal in healthy tissues. Finally, we observed that LPCC-1995 accumulates preferentially in tumor and organs of the reticuloendothelial system such as liver and kidney. Based on these results, we propose that LPCCC-1995 could be used as a NIR fluorescence dye detection for tumors in FGOS.

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5.

EFECTOS DE LA QUIMIOTERAPIA CON ANTRACICLINAS SOBRE CITOQUINAS Y ESTADO RÉDOX DE PACIENTES CON CÁNCER DE MAMA Y SU EVENTUAL IMPACTO EN FUNCIÓN VENTRICULAR A LARGO PLAZO. Effects of Anthracyclines Chemotherapy on the Cytokine and Redox Profile of Breast Cancer patients and their eventual Long-Term Impact on Ventricular Function.

It is unknown whether anthracycline chemotherapy would affect long-term ventricular function, considering the increased life expectancy after breast cancer. Our objective was to evaluate the effect of anthracyclines on ventricular function at 10-year, associated with cytokines, and plasma redox status in patients with breast cancer. Retrospective study of 20 patients with breast cancer received treatment with anthracyclines at the Salvador and Luis Tisné Hospital, Santiago (2010-2012). Plasma cytokines (EGF, Eotaxin, GCSF, GM-CSF, IFNα2, IFNγ, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IL-1ra, IL1α, IL - 1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IP10, MCP1, MIP1α, MIP1β, TNFα, TNFβ and VEGF) using the MILLIPLEX Luminex kit ®, at the beginning (day -7 pre-anthracycline), day +3 after the first cycle were determined. In addition, redox status,
antioxidant capacity (FRAP, ferric reducing ability of plasma) and malondialdehyde (MDA) were measured in plasma samples. LV ejection fraction (LVEF%) and E/e´ ratio at baseline (day -7), and at 10 years (2022), were used as measures of ventricular function.
Results. Cytokines with higher levels day+3 vs. basal (-7), were: EGF 1.5; eotaxin 1.17 times; GMCSF 1.16 times; MCP 1.39 times and VEFG 1.51. The LVEF (%) at 10 years showed no differences, however the value of the E/e´ ratio14 could determine a degree of diastolic dysfunction, and a higher MDA value in the short and long term.
Conclusions. Acute anthracyclines can increase cytokines associated with CV remodeling (EGF, eotaxin, MCP and VEGF), which could be associated with a pro-oxidant state and diastolic dysfunction in the long-term follow-up.

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6.

EXPLORANDO LOS RECEPTORES GABA RDL/LCCH3: PERSPECTIVAS ESTRUCTURALES Y MECANISMOS DE RESISTENCIA A TRAVÉS DEL MODELADO IN SILICO. Exploring gaba rdl/lcch3 receptors structural insights and resistance mechanisms through in silico modeling.

Gamma-aminobutyric acid (GABA) receptors play a pivotal role in modulating neuronal activity as central nervous system inhibitors. These receptors are the targets of both natural and synthetic insecticides. Despite their high expression in both mammals and insects, GABA receptors display distinct pharmacological profiles. In Drosophila, two GABA receptor subunits, RDL (Resistant to dieldrin) and LCCH3 (Ligand-gated chloride channel homolog 3), have been characterized. However, the prevalence of resistance suggests potential structural modifications. Native GABA RDL receptors can exist in a heteromeric conformation, with LCCH3 subunits likely incorporated. In the absence of structural data for GABA RDL and RDL-LCCH3, this study employed homology modeling based on the human β3-GABA structure as a template. After energy minimization and structural assessment, in silico mutagenesis introduced A302S/G mutations into the RDL subunit responsible for insecticide resistance. Subsequent molecular dynamics simulations were conducted to evaluate conformational changes and stability. In comparison, the pore shape and diameter exhibited no significant changes. Regarding hydrophobicity, the mutant model showed a local effect in the vicinity of the mutation. To assess the models for their ability to mimic the development of resistance, protein-ligand docking simulations with insecticides were performed, focusing on the NCA-1A binding site. Notably, dieldrin, endosulfan, and fipronil displayed higher docking scores and deltaGbind in mutant models, indicating reduced affinity for these insecticides compared to the wild type. Our in silico results indicate that the heteromeric structural models can serve as a valuable tool for identifying novel receptor-blocking molecules with potential insecticidal activity. This research not only enhances our understanding of the structural insights and resistance mechanisms of GABA receptors but also establishes a foundation for the development of more efficacious insecticides.

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7.

EFECTO DE IVERMECTINA EN EL DESARROLLO DE LA MEDULA ESPINAL Y LA UNION NEUROMUSCULAR EN XENOPUS LAEVIS. POSIBLE ROL DE RECEPTORES P2X4. Effect of Ivermectin in spinal cord and neuromuscular development on Xenopus laevis. Possible role of P2X4 receptors.

Neurulation is a crucial process implicating the folding of neural plate to form the neural tube, which later differentiates into the brain and spinal cord in chordates. Purinergic receptors, both ionotropic (P2Xn) and metabotropic (P2Yn), are activated by ATP and other nucleotides, establishing the "purinergic signaling" participating in processes like neurulation, progenitor cell expansion, neurogenesis, axon growth, and axonal maturation. Neural tube defects (NTDs) result from impaired neural tube closure, representing principal nervous system birth defects. The use of antiseizure medications (ASMs), during pregnancy, such as valproate, has been linked to NTDs. Thus, demand to assess the ASM safety profile especially in early neural development. Our objective is to examine ivermectin (IVM), a positive allosteric modulator (PAM) of human P2X4 receptors widely used to treat parasitic infections and recently proposed as ASM. In our study, we investigate IVM's effects during neurulation in X. laevis using molecular, pharmacological, and bioinformatics techniques. Our screening reveals the presence of P2X4, P2Y1, P2Y4, P2Y11, and VNUT transcripts. Pharmacological studies show that 10 µM of IVM induces tadpole paralysis (97%) and an increase in melanocyte number (3-fold) and area (1.5-fold) vs. controls (n=8 assays). Preliminary immunohistochemistry results showed an open NT phenotype, decrease (19%) in striated muscle fiber width, presence of vacuoles (8.6x), elongation of the nuclei and changes in acetylcholine receptor area (120%) and intensity (155%). In conclusion, IVM usage during X. laevis neurulation leads to NTDs and consequently affects the establishment of neuromuscular junction architecture and function.

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8.
NUEVO COMPUESTO DE SENECIO MUTANS (CHACHACOMA) REDUCE EL CALCIO INTRACELULAR EN LA RESPUESTA VASCULAR CONTRACTIL DE AORTA DE RATA. New Compounds from Senecio nutans (chachacoma) reduce the intracellular calcium in the Vascular Contractile Response of Rat Aorta.

The native communities of the II Region of Chile use Senecio nutans (Sn), known as "Chachacoma", for the treatment of hypertension or altitude sickness. Objective: To evaluate the effect of metabolites and new compounds from Senecio nutans on intracellular calcium in the vascular response. Methods: As a control condition, aortic rings were contracted with cumulative doses of phenylephrine (PE; 10-10 to 10-5 M). After four successive washes, the protocol was repeated by preincubating with metabolite or oxime (10-5 M) for 20 minutes. Calcium influx was studied in a Ca2+-free medium. Aortic rings were contracted with PE (10-6 M) in a Ca2+-free medium, and CaCl2 (0.1 to 1 mM) was subsequently added to the bath. To assess intracellular calcium levels ([Ca2+]i), KCl (50 mM) was used to depolarize the plasma membrane in vascular smooth muscle cells (A7r5). Cells were loaded with Fluo4-AM (10 μM) to determine changes in intracellular calcium by confocal microscopy. For statistical analysis, Student's test and ANOVA followed by Bonferroni post-hoc ($p<0.05$) were used. The protocols used were approved by the Ethics Committee of the University of Antofagasta (CEIC-275/20). Results: Preincubation of aortic rings with SGI metabolite or oxime-SG4 (10-5 M) significantly decreased ($p<0.001$) the contractile response to phenylephrine (PE). Preincubation of aortic rings with SGI (10-5 M), significantly ($p<0.001$) reduced the contractile response to CaCl2 (89 ± 7% SG-I versus 123 ± 5% control, 1.0 mM CaCl2). All compounds reduced [Ca2+]i in response to KCl in A7r5 cells. Conclusion: Compounds isolated from Senecio nutans could have a potential pharmacological effect in regulating calcium homeostasis in vascular smooth muscle cells.

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9.
DESCIFRANDO EL MECANISMO DE TRANSACTIVACIÓN ENTRE EL RECEPTOR PURINÉRGICO P2Y2 Y HER2 EN CÁNCER GÁSTRICO. Deciphering the mechanisms of the transactivation between the purinergic P2Y2 receptor and HER2 in gastric cancer.

Gastric cancer (GC) is one of the most prevalent cancers in Chile. Among the therapies for this type of cancer, drugs that act against the human epidermal growth factor receptor 2 (HER2) are especially relevant. EGFRs can be indirectly activated by GPCRs in a process called transactivation. Recently, studies have shown that purinergic GPCRs can transactivate EGFRs, constituting a new and attractive pharmacological target for GC. The aim of this study was to determine the effect of P2Y2R/HER2 transactivation in gastric cancer cell lines and primary cultures. First, qPCR assays were performed with cell lines and GC biopsies to quantify P2Y2R and HER2 expression. In cell proliferation studies, GC-derived primary cultures were treated with a UTP gradient from 1 to 100 μM, and we found a concentration dependent increase in cell proliferation induced by UTP. p-EGFR and AKT signaling were immunodetected in AGS cells incubated with 10 and 100 μM UTP for 6 h, demonstrating P2Y2/EGFR transactivation. The expression of HER-2 and P2Y2R in the GC-derived cell lines and GC-biopsies was significantly higher compared to the GES-1 cells derived from healthy gastric mucosa. Finally, we searched in the Kaplan Meier Plotter Database (kmplot.com) for GC survival plots, and we observed that high expression of P2Y2R and HER2 dramatically decreases the time of survival of patients. These results are the first demonstrating P2Y2/HER2 transactivation in GC, with the possibility for the development of future therapies for this disease. Keyword: Transactivation, HER2, P2Y2R, Gastric Cancer.

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10.
ROL PROTECTOR DE S-ALIL-CISTEÍNA CONTRA LOS OLIGOMEROS SOLUBLES DEL PEPTIDO B-AMILOIDE, MEDIANTE LA MODULACIÓN DEL NIVEL DE VDAC1. Protective Role of S-Allyl-Cysteine Against Soluble β-Amyloid Peptide Oligomers Through Modulation of VDAC1 Level.

Alzheimer's Disease (AD) is a neurodegenerative condition for which there is currently no effective treatment. Soluble beta-amyloid peptide oligomers (AβOs) have been postulated as the primary neurotoxic agents in this disease. This study focused on examining and assessing the protective effect of S-allyl-cysteine (SAC), a phytochemical found in aged garlic extract (AGE), which has been described to possess multiple properties. Specifically, we evaluated SAC's protective effect against amyloid toxicity (0.5 μM, 24 hrs) using the MTT assay and Live/Dead kit. We observed that pre-treatment with SAC for 24 hours exerted a protective effect against AβOs at concentrations ranging from 0.1 μM to 1 μM. Subsequently, we assessed Voltage-Dependent Anion Channel 1 (VDAC1) levels through immunocytochemistry. This channel has been implicated in intracellular Ca2+ dyshomeostasis, a critical factor in AD pathophysiology. We also evaluated the relative size of mitochondria using TOM20 as a marker and employed the JC-1 dye to assess mitochondrial membrane potential. By quantifying VDAC1 fluorescence, we determined that SAC (0.5 and 1 μM) was able to prevent the increase in VDAC1 protein levels. Furthermore, at the same concentrations, SAC prevented mitochondrial phenotypic changes and the loss of mitochondrial membrane potential. These results suggest that pre-treatment with SAC has a protective effect against AβOs, particularly with positive effects at the mitochondrial level. Thus, it is

worthwhile to further explore SAC's protective effects against amyloid toxicity.

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11.
CARACTERIZACIÓN Y POTENCIAL ROL NEUROPROTECTOR DE UN ACEITE CANNÁBICO ENRIQUECIDO EN CBD EN MODELOS CELULARES DE NEURODEGENERACIÓN.
Characterization and potential neuroprotective role of CBD enriched cannabic oil in neurodegenerative celular models.

El Cannabidiol (CBD) corresponde a un fitocannabinoide presente en la planta Cannabis sativa el cual modula los receptores del sistema endocannabinoide (CB1 y CB2), receptores tipo proteína G como GPR55, receptores transitorios sensibles a vaniloide (TRPV), receptores de serotonina (5-HTA), entre otros. Durante los últimos años se ha descrito un rol neuroprotector que está relacionado con su participación en el estrés oxidativo, la homeostasis del calcio y modulación del estrés mitocondrial. En este trabajo se evaluará la citotoxicidad de un aceite enriquecido en CBD mediante el ensayo de reducción de 3- (4,5-dimetiltiazol-2-ilo) -2,5-bromuro de difeniltetrazolio (MTT), se caracterizarán los metabolitos presentes en el aceite por medio de HPLC y se analizará cómo dicho aceite modula la agregación del péptido Aβ y el estrés oxidativo causado por el peróxido de hidrogeno. Se espera como resultado que los cannabinoides (y otros fitocompuestos) presentes en el aceite cannábico sean capaces de ejercer un potencial rol neuroprotector en células que serán tratadas con peróxido de hidrógeno y péptido Aβ, disminuyendo los efectos neurotóxicos que causan en las neuronas.

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12.
UNA APROXIMACIÓN DE TERAPIA GÉNICA PARA EL TRATAMIENTO DEL DESORDEN DE USO DE ALCOHOL BASADA EN EL SILENCIAMIENTO DE LA EXPRESIÓN DE LA ALDH2 MEDIANTE TECNOLOGÍA CRISPR/CAS9. A gene-therapy approach for the treatment alcohol use disorders based in the silencing of ALDH2 expression by crispr/cas9 technology.

Alcohol Use Disorder (AUD) is characterized by a loss of control over consumption, increasedtolerance, and withdrawal syndrome. In addition to affecting the brain's reward system, it can leadto anxiety disorders, depression, cognitive impairment, and diseases like alcoholic hepatitis, contributing to thousands of deaths. Pharmacological treatments for AUD have limitations, such as inefficacy, which hinders patient compliance and highlights the need for new therapies. Alcohol is metabolized by alcohol dehydrogenase (ADH) into acetaldehyde, a substrate for mitochondrial aldehyde dehydrogenase (ALDH), producing acetate as a product. Pharmacogenetics has identified gene variants in human populations, such as ADH1B*2 (high activity) and ALDH2*2 (low activity), which provide protection against alcoholism due to a rapid increase in blood acetaldehyde, leading to adverse reactions in the body that deter individuals from consuming alcohol. This suggests the possibility of potential gene therapy using adeno-associated vectors (AAV) for the efficient and safe delivery of genes to overexpress ADH1B*2 and to silence the expression of ALDH2. However, AAVs have the limitation of packaging a limited amount of genetic material, along with temporary genetic expression, which is insufficient to affect a metabolic pathway with a long-term therapeutic focus. Nevertheless, CRISPR/Cas9 technology using small nuclease variants (miniCas9) can overcome this limitation, making permanent genetic editing of ALDH2 possible. In summary, current pharmacological treatment has limitations, but pharmacogenetics and genetic editing offer promising approaches to address this public health issue.

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13.
EFECTO DEL BLOQUEO DE LOS CANALES IÓNICOS HCN EN LA LIBERACIÓN DE DOPAMINA INDUCIDA POR ETANOL EN EL NÚCLEO ACCUMBENS DE RATAS. Effect of hcn ion channel blocking on ethanol-induced dopamine release in the nucleus accumbens of rats.

The mesocorticolimbic system is a neural circuit that mediates the reinforcing survival-related behaviors such as feeding and sexual activity and comprises relevant brain structures, particularly the ventral tegmental area (VTA) and the nucleus accumbens (NAc). When performing these activities or consuming substances of abuse the VTA releases dopamine into the NAc, inducing pleasurable sensations. VTA dopaminergic neurons exhibit a pacemaker-like spontaneous activity, driven by an ion current (Na+, K+), known as the Ih current. This current activates upon hyperpolarization, returning the membrane potential closer to calcium channel activation levels, thus sustaining continuous firing. The Ih current is primarily mediated by HCN (hyperpolarization-activated cyclic nucleotide-gated) channels. Ethanol exposure has been linked to enhanced HCN channel activity, particularly HCN2 in the VTA. Therefore, selective blockade of HCN2 channels holds potential as a novel pharmacological approach for treating alcoholism. In this study we synthesized and confirmed by 1H-NMR the identity of a selective HCN2 channel blocker, labeled 4e. Subsequently, the impact of pharmacological HCN2 channel blockade on ethanol-induced dopamine release in the NAc of rats was investigated through in vivo microdialysis and HPLC coupled with electrochemical detection. In this experiment, three blockers were evaluated: ZD7288 (non-selective), MEL55A (moderately selective for HCN2), and 4e (highly selective for HCN2), each administered individually by stereotaxic surgery into the cerebral ventricle, while ethanol (1 g/kg) was administered intraperitoneally. Simultaneously, dopamine levels in the NAc were monitored. The findings demonstrated that all three blockers dose-dependently reduced ethanol-induced dopamine release in the NAc, with MEL55A and 4e exhibiting stronger effects compared to ZD7288. These results suggest that this approach has promise in mitigating the pleasurable effects of ethanol consumption.

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14.
MODULACIÓN ALOSTÉRICA DE RECEPTORES DE GLICINA CON MUTACIONES VINCULADAS A LA HIPEREKPLEXIA HEREDITARIA.
Allosteric modulation of glycine receptors with mutations linked to hereditary hyperekplexia.

Glycine receptor (GlyR) is an inhibitory pentameric ligand-gated ionic channel expressed in the central nervous system, playing a pivotal role in the modulation of motor control at the spinal cord. Mutations on the gene encoding alpha1GlyR frequently lead to GlyR hypo-functionality, generating a neuromotor disorder called hyperekplexia. To date, several positive allosteric modulators (PAMs) that are able to potentiate the activity of wild-type alpha1GlyR have been identified. Within this group, the tricyclic sulfonamide AM-1488, designed by AMGEN, appears to have an improved specificity and high potency as a glycinergic PAM. However, its actions on alpha1GlyR with mutations related with human hyperekplexia is unknown. Our study evaluated the AM-1488 actions on alpha1GlyR carrying mutations found in hyperekplexic patients (R271Q, P250T, and S267Q) by using bioinformatics and electrophysiological recordings. We first evaluated the AM-1488 interaction with its binding site by molecular docking assays, using an alpha1GlyR crystal structure. The predicted docking scores and deltaGbind confirmed the interaction. The in-silico introduction of "hyperekplexic" mutations on the alpha1GlyR sequence has no significant effect on the PAMs predicted interaction with the receptors. The functional effects of AM-1488 were tested through patch-clamp experiments in HEK293 cells expressing wild-type alpha1GlyRs and three mutated receptors. Our findings indicated that 0.5mM AM-1488 significantly potentiated the wild-type alpha1GlyR function (264.25±17.12%). Similar experiments showed that R271Q and S267Q GlyRs were less sensitive to the compound (R271Q=34.34±14.38%, S267Q=0.81±1.65%). Ongoing work will determine the actions of AM-1488 on the P250T mutant. Our results showed that the AM-1488 does not have the ability to recover the function of two hyperekplexic GlyRs. These findings emphasize the relevance of functional testing of individual mutations found in humans in drug development.

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15.
ACTIVIDAD HEPATOPORTECTORA DEL EXTRACTO DE BAILAHUEN.
Hepatoprotective activity of a Bailahuén extract (Haplopappus rigidus) on acetaminophen-induced liver injury.

In the Andes´ high planes of the Antofagasta Region in Chile, Bailahuén is used in popular medicine and numerous compounds have been isolated to evaluate their medicinal activity. Due to the scientific knowledge of Bailahuén as a protector of the hepatic physiology, the aim of this work is to assess whether aqueous extracts show antioxidant activity and hepatoprotective activity on acetaminophen- induced liver damage. Groups of 7 animals were treated for 10 days with doses of 50, 100, 150 and 200 mg.kg-1 a.w. of Bailahuén aqueous extract. Acetaminophen treatment was carried out after Bailahuén administration with single dose of 1 g.kg-1 a.w. The acetaminophen toxic effect and hepatoprotective activity de Bailahuén was analyzed measuring serum transaminases levels and studying liver histology. Antioxidant activity in vitro showed that the aqueous extract of Bailahuén has a high content of polyphenols and flavonoids with important free radical trapping activity (ABTS and DPPH) and a high reducing power (FRAP). Acetaminophen induced a significant increase of transaminases levels measured three days' post administration. Subjects treated with Bailahuén (100, 150 y 200 mg. Kg -1a w) showed between 64% and 80% decrease of serum levels of AST and ALT. Bailahuén extracts showed hepatoprotective properties as evaluated by histological studies, reducing necrotic areas and inflammation. Interestingly, Bailahuén extracts contains significant amounts of polyphenols and diterpenoids with antioxidant activities that may results in the activation of NFR-2 signaling pathways a key regulator of antioxidant cellular mechanism. The identification of the molecules responsible of these protecting and repairing effects of the Bailahuen awaits further studies.

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16.
EFECTO SOBRE EL TONO VASOMOTOR Y CAPACIDAD ANTIOXIDANTE DE BERBERIS CONGESTIFLORA GAY
Effect on Vasomotor Tone and Antioxidant Capacity of Berberis Congestiflora Gay.

Cardiovascular diseases are the leading cause of morbidity and mortality in arterial hypertension (AH) patients, being the most prevalent risk factor. Native plants, their use as functional foods, and their cardiovascular effects have begun to be of great interest. Berberis congestiflora Gay, whose berry (michay) has been used by the Mapuche ethnomedicine as a nutraceutical for its medicinal properties. Thus, this research aims to determine the polyphenol content and antioxidant capacity of the hydroalcoholic extract of Berberis congestiflora gay, and its effect on vasomotor tone in rat aortic rings. For the determination of total polyphenol content (CTP), total flavonoid content (CTF), and antioxidant capacity, the Folin Cicalteau method, aluminum chloride, and oxygen radical absorbance capacity (ORAC) were used. Phenolic compounds were identified by high-performance liquid chromatography with diode array detection and mass spectrometry. To evaluate the vasomotor response of B. congestiflora (100 and 1000 µg/mL), rat aortic rings with and without endothelium and in the presence or absence of 10-4 M N(ω)-nitro-L-arginine (L- NAME) and 1H-[1,2,4] oxadiazolo[4,3-α]quinoxalino-1-one (ODQ) 10-6 M. The CTP was 1661 mg EAG/100g of fresh sample, the CTF was 871±66.4 mg Quercetin equivalent/100g of fresh sample and an ORAC of 22503 µmol/ET 100g of fresh sample. The metabolomics report included anthocyanins (cyanidin 3-

O glucose), flovonoids (quercetin 3-O glucoside and isorhamnetin 3-O glucose), and the lignan hydroxy-pinoresinol. In aortic rings with endothelium precontracted with phenylephrine (10-6 M), B. congestiflora provoked a concentration-dependent vasodilator response with values of 25 ± 7.6% and 70.4 ± 3.6%. Consumption of the B. congestiflora berry can have beneficial health effects due to the high presence of anthocyanins and flavonoids, providing antioxidant capacity and an endothelium-dependent vasodilator effect.

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17.
EL INHIBIDOR DE KRASG12C, ADAGRASIB, COMBINADO CON SAM486, TIENE UN EFECTO SINÉRGICO EN CÉLULAS DE CÁNCER DE PULMÓN CON MUTACIÓN DE KRASG12C IN VITRO E IN VIVO. The KRASG12C inhibitor adagrasib combined with SAM486 has a synergistic effect in KRASG12C-mutated lung cancer cells in vitro and in vivo.

Adagrasib and sotorasib are novel inhibitors of the KRASG12C, the main driver mutation in Non-small cell lung cancer (NSCLC). KRASG12C inhibitors often face resistance, highlighting the need to explore combination treatments. Spermidine, and spermine, crucial molecules for cancer survival, are elevated in NSCLC. Adenosylmethionine decarboxylase-1 (AMD1) is an enzyme pivotal for spermidine and spermine synthesis and can be selectively inhibited by the compound SAM486. The objective of this work was to study the levels of AMD1 in KRAS-mutated NSCLC cells and evaluate the role of SAM486 in NSCLC cell proliferation alone or in combination with the KRASG12C inhibitors, adagrasib and sotorasib. We used the NSCLC cell lines H358 (KRASG12C), A549 (KRASG12S), CORL-L23 (KRASG12V), and H1299 (KRASwt). AMD1 levels and KRAS-ERK pathway phosphorylation were measured by immunoblotting. Cell proliferation was evaluated by BrdU incorporation and colony formation assay. Cell viability was measured by MTT reduction, and drug combination studies were analyzed using Combenefit and SynergyFinder software, employing the Loewe additivity model. Finally, we evaluated the combination of adagrasib and SAM486 in an in vivo model of lung cancer. SAM486 reduced cell proliferation in NSCLC cells, independent of the KRAS mutation. Also, the KRASG12C-inhibitors, sotorasib and adagrasib, reduced AMD1 levels and cell viability in H358 cells. High synergy scores were observed when using sotorasib and adagrasib in combination with SAM486 in the cells harboring the KRASG12C mutation, as analyzed by Combenefit and SynergyFinder software. Finally, when adagrasib was combined with SAM486 in vivo, the number of lng tumors was reduced significantly. These results suggest that the combination of a KRASG12C inhibitor and an AMD1 inhibitor could lead to a new therapeutic strategy against KRASG12C-mutated tumors.

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18.
RECEPTORES GABA RDL COMO NUEVOS BLANCOS PARA MOLÉCULAS PEQUEÑAS CON POTENCIAL INSECTICIDA. GABA Rdl receptors as new targets for small molecules with insecticidal potential.

The insect GABA receptor studied most intensively is the Rdl variant, which was initially described in Drosophila melanogaster associated with conferring resistance to the insecticide dieldrin (Rdl; resistance to dieldrin). Although initial studies suggested that the Rdl receptor forms homomeric channels, recent studies have shown that it is capable to form functional heteropentamers with the LCCH3 receptor (ligand-gated chloride channel homologue 3). Several functional data have been demonstrated that a single mutation in the position 302 (A302S) confers resistance to several commercial insecticides. Thus, the search of novel compounds able to avoid this resistance mechanism becomes urgent. Due to lack of structural information of Rdl/LCCH3 receptor, we build an RdlA302S/LCCH3 structural model using the recently resolved structure of the human GABAAR beta 3 as a template. Once the model was validated, we performed a virtual screening using the Molport database (5.000.000 molecules), positioning the interaction grid inside the non-competitive antagonist IA binding site. The complexes were analyzed and ranked based on their docking score (DS) and deltaGbind, yielding a set of molecules with 3-fold higher predicted interaction capabilities with GABA Rdl. To experimentally validate the activity of these selected molecules, we expressed GABA Rdl receptors in HEK293 cells. GABA dose-response curves showed an EC50 of 53.7 µM for the wild type and 34.4 µM for the A302S mutant. The mutant showed a decrease in sensitivity to known insecticides, therefore being a suitable test model. These results highlight the value of our models in identifying more selective compounds with insecticidal activity.

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19.
EVALUACIÓN DEL IMPACTO DE MAR1 EN LA CARDIOMIOPATÍA DIABÉTICA EN UN MODELO DE DIABETES TIPO 1. Evaluation of the impact of MaR1 on diabetic cardiomyopathy in a model of type 1 diabetes.

Diabetes is one of the major public health problems and places an enormous social and financial burden on almost all the world's healthcare systems. Currently, clinical and experimental studies have revealed the existence of a specific diabetic cardiomyopathy. In this, alterations at the cardiac tissue level are evident, where different pathophysiological processes contribute to inflammation, fibrosis, hypertrophy and cardiomyocyte death. In recent years, the study of mediators of inflammation resolution have emerged as agents of therapeutic interest. Specialized proresolving mediators (SPMs) are agonists with the potential to stimulate key cellular events in the resolution of inflammation. Evidence indicates that Maresin 1 (MaR1), an omega-3 derived SPM, promotes the resolution of inflammation and exerts cytoprotective effects through inhibition of neutrophil infiltration, proinflammatory cytokines, and promotes polarization to M2 macrophages.

To date, the role of SPMs in diabetic cardiomyopathy has not been well described, let alone the potential role of MaR1. Given that MaR1 is produced and targeted to macrophages, we aim to evaluate the effects that this proresolving mediator has on morphophysiological parameters of cardiac damage in a murine model of early diabetic cardiomyopathy. MaR1 reduces cardiac damage observed in a model of diabetic cardiomyopathy by reducing cardiac hypertrophy and fibrosis observed in the histological analysis by Hematoxylin & Eosin, Picrosirius Red and immunohistochemistry for type I collagen. In this regard, we can say that MaR1 reverses the pathological changes produced by diabetes mellitus at the cardiac level. These results open the possibility of MaR1 as a possible therapeutic agent for early diabetic cardiomyopathy.

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20.
DESARROLLO DE PELÍCULAS HÍBRIDAS CON MICELAS DE NÚCLEO LIPÍDICO CARGADAS CON DOXICICLINA INCORPORADAS MEDIANTE IMPRESIÓN POR INYECCIÓN DE TINTA. Development of hybrid films with lipid core micelles loaded with doxycycline incorporated through inkjet printing.

Doxicyclin is a second generation tetracycline with some limitations regarding it's route of administrarion due to it's aqueous solubility besides it's adverse effects have the capacity to compromise the adhesion to the trearment A common strategie to improve the aqueus solubility of this type of pharmaceutical it's the use of nanoparticles, Especially the use of lipid core miscelles (LCM), wich are easily formulated, have high capacity to catch and mantain lipofilic and hydrofilic pharmaceuticals, and lastly they are capeable of reducing the toxicity of the pharmaceutical in their domain. On the other hand, hydogels are used as an administration system for new pharmaceuticals, where chitosan as alginate presents antimicrobial and gelling activity. This unification can be useful to develop new state of the art pharmaceutical forms, such as hybrid films. However, a recurrent problem regarding conventional pharmaceutial forms are the standarized dosage of tratment, here's where new printing techniques allowing a new personalized treatment administration. Inkjet printing method implies the use of a matrix as canvas and a liquid or ink loaded with the pharmaceutical of interest. Therefore, the objetive of this research is to evaluate the action of Doxicycline contained inside of LCM distributed inside of hybrid films trough a new technique of inkjet printing.
Results show that hybrid films are thing and flexible enough as a matrix to contain the doxacycline loaded LCM's, no relevant difference was observed during the comparison with control. This matrix was
subjectified to various studies to be able to evaluate its physicochemical properties, for future applications as a new pharmaceutical form for optional treatment to bacterial infections of clinical interest. Where microbiological studies will be conducted as needed.

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21.
MODELADO IN-SILICO DE INTERACCIONES MOLECULARES DE TIPO SELECTIVAS ENTRE BENCENOSULFONAMIDAS Y LAS ISOFORMAS HCAVII VS HCAII COMO POTENCIALES AGENTES ANTICONVULSIVOS. In-silico Modeling of Selective Molecular Interactions between Benzene Sulfonamides and hCAVII vs hCAII Isoforms as Potential Anticonvulsant Agents.

Epilepsy is a common neurological disorder that affects millions of people. Cytosolic carbonic anhydrases (hCAII and hCAVII) are promising molecular targets for the design of novel antiepileptic drugs. However, the high structural similarity of these isoforms limits the use of existing drugs due to serious side effects. This study used structure-based drug design approaches to model and understand the basis for the selective inhibition of hCAVII vs hCAII of a set of five benzenesulfonamide derivatives. The results showed that the ligands studied bind to both isoforms with high affinity, but selectivity is enhanced by electrostatic interactions between key residues of hCAVII. Binding free energy calculations showed that the potency of the ligands is due to hydrophobic contacts, while selectivity is due to electrostatic interactions. These findings provide a useful guide for the design of new potent and selective hCAVII inhibitors.

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22.
EFECTO ANTIBACTERIANO DE CIPROFLOXACINO CARGADO EN MICELAS DE NÚCLEO LIPÍDICO SOBRE ESCHERICHIA COLI Y STAPHYLOCOCCUS AUREUS. Antibacterial effect of ciprofloxacin loaded in lipid core micelles on escherichia coli and staphylococcus aureus.

El ciprofloxacino (CP) es una fluoroquinolona de tercera generación considerada como primera línea en el tratamiento de infecciones del tracto urinario, gonorrea, cistitis, entre otras. Este antibiótico puede ser administrado por vía oral, pero presenta limitaciones en la solubilidad acuosa y permeabilidad a membranas que impactan directamente a la biodisponibilidad y, posiblemente, en su efectividad. En ese sentido, la nanotecnología es una estrategia que permitiría resolver dichas limitaciones mediante el desarrollo de nanopartículas (NPs). Uno de los tipos de NPs son las micelas de núcleo lipídico (LCM, del inglés lipid core micelles) que poseen sencillez de formulación, capacidad de autoensamblaje, biocompatibilidad, un diámetro entre 5 a 100nm, además de tener la capacidad de atrapar fármacos poco solubles en agua en el núcleo, mejorar la permeabilidad, disminuir la toxicidad del fármaco contenido, dirigirlas selectivamente al sitio de interés, entre otras. El objetivo de este trabajo de

investigación es evaluar la formulación de CP-LCM que fueron elaboradas mediante la metodología de emulsificación en caliente de baja energía (5), sobre especies bacterianas de comúnmente utilizadas en test de sensibilidad bacteriana tanto medio sólido (test de difusión) así como en medio líquido, Escherichia coli (E.c)(ATCC 25922) y Staphylococcus aureus (S.a) (ATCC BAA1026). Los resultados muestran que la concentración utilizada en los ensayos correspondientes a la CIM, 2CIM y 0,5CIM muestran el efecto antibacteriano similar al ATB de referencia para la especie sensible (E.c), así como para una bacteria resistente (S.a).

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23.
DILUCIDANDO EL PROCESO DE DEACTIVACIÓN Y DESENSIBILIZACIÓN DEL RECEPTOR DE GLICINA ALFA 3 POR NEUROESTEROIDES. Elucidating the de-activation and desensitization process of the glycine receptor α3 by neurosteroids.

The glycine receptors (GlyRs) are inhibitory anionic-permeable channels, which belong to the pentameric ligand-gated ion channels (pLGICs) superfamily, which play a critical role in the control of neural excitability. Electrophysiological and behavioral studies have reported the participation of the glycinergic transmission, mediated mainly by the GlyR composed by the alpha 3 subunit, in processes like anxiety, depression and ethanol addiction. Remarkably, GlyRs containing alpha 3 subunits are expressed in brain regions associated with depressive states, playing a critical role in the control of neuronal excitability in these nucleuses like accumbens and amygdala. In this context, recent experimental data suggest that neurosteroids can modulate the function of the GlyRs compound by the alpha 3 subunit. Our previous results showed that Allopregnanolone enhances the function of the GlyR alpha 3 by 30%, however, the molecular mechanism underlying these effects remains elusive. In the present work, by using site directed mutagenesis and electrophysiological recordings, we evaluated the binding site of Allopregnanolone in the TMD of the GlyR alpha 3 subunit. Our results show that W239 and A303 residues are critical for the interaction with Allopregnanolone. Electrophysiological data showed that Allopregnanolone can significantly affect the transition between activated and de-activated state, as well as the desensitization process. Altogether, our experimental results contribute to understanding how Allopregnanolone can affect the function of the GlyR compound by the alpha 3 subunit, opening new avenues for its allosteric modulation with therapeutic potential.

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24.
CONCURSO DRA. MARÍA EUGENIA LETELIER
EVALUACIÓN DE LA ACTIVIDAD TRIPANOCIDA DE CASTANEDIA SANTAMARTENSIS (ASTERACEAE) E IDENTIFICACIÓN DE COMPONENTES ACTIVOS. Evaluation of the trypanocidal activity of Castanedia santamartensis (Asteraceae) and identification of active components.

The deficit of effective treatments for Chagas disease has led to searching for new substances with therapeutic potential. Natural products possess a wide variety of chemical structural motifs and are thus a valuable source of diverse lead compounds for the development of new drugs. Castanedia santamartensis is endemic to Colombia, and local indigenous communities often use it to treat skin sores from leishmaniasis; however, its mechanism of action against the infective form of Trypanosoma cruzi has not been determined. Thus, we performed chemical and biological studies of two alcoholic leaf extracts of C. santamartensis to identify their active fractions and relate them to a trypanocidal effect and evaluate their mechanism of action. Alcoholic extracts were obtained through cold maceration at room temperature and fractionated using classical column chromatography. Both ethanolic and methanolic extracts displayed activity against T. cruzi. Chemical studies revealed that kaurenoic acid was the major component of one fraction of the methanolic extract and two fractions of the ethanolic extract of C. santamartensis leaves. Moreover, caryophyllene oxide, kaurenol, taraxasterol acetate, pentadecanone, and methyl and ethyl esters of palmitate, as well as a group of phenolic compounds, including ferulic acid, caffeic acid, chlorogenic acid, myricetin, quercitrin, and cryptochlorogenic acid were identified in the most active fractions. Kaurenoic acid and the most active fractions CS400 and CS402 collapsed the mitochondrial membrane potential in trypomastigotes, demonstrating for the first time the likely mechanism against T. cruzi, probably due to interactions with other components of the fractions.

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25.

MARESINA 1: LIGANDO ACTIVADOR DE LOS RECEPTORES NUCLEARES RORA, PPARA Y PPARΓ, IMPLICADOS EN EL METABOLISMO LIPÍDICO, UN ANÁLISIS IN-SILICO. Maresin 1: Activating ligand of nuclear receptors RORα, PPARα and PPARγ, involved in lipid metabolism, an in-silico analysis.

Chronic liver diseases are a worldwide health problem, where Metabolic-associated fatty live disease (MAFLD, ex NAFLD), which is associated with steatosis, is present in about 35% of the population. Steatosis is the accumulation of over 5% of lipid vesicles inside hepatocytes, this is the relevant factor in MASLD and is associated with pathologies such as diabetes mellitus type 2 (DM2). The consumption of Omega-3, in particular DHA and its derivative maresin 1 (MaR1), has been shown to have pro-resolving capacity and to be a potent anti-inflammatory agent, by blocking polymorphonuclear infiltration, stimulating phagocytosis and tissue regeneration. In this study we sought to identify the interactions of MaR1 with nuclear receptors (NRs) activated by fatty acid derivatives and involved in lipid metabolism, adipogenesis, energy balance and inflammation. Among the NRs analyzed we have Retinoid-related orphan receptor alpha (RORα) and Peroxisome proliferator-activated receptor (PPAR)s α and γ. The interaction between these NRs and MaR1 was determined by in silico analysis. Docking study showed the most relevant molecular interactions between MaR1/RORα (-10.165Kcal), MaR1/PPARα (-10.174Kcal) and MaR1/PPARγ (-10.502Kcal). The overall calculated free binding energy ΔGbin (MM/GBSA) showed that MaR1 had the highest affinity for PPARα, PPARγ and RORα receptors, respectively, with Vander Wals force (vdW) and hydrophobic (Lipo) interactions contributing the most to the stabilization of the complexes formed. Both results support our objective, positioning MaR1 as a putative activating ligand of these NRs. This would allow us to propose a potential pharmacological pathway of resolution and hepatoprotection mediated by MaR1.

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26.

MODIFICACIÓN EN LA ESTRUCTURA DE INHIBIDORES SELECTIVOS DE SEROTONINA Y SU INTERACCIÓN CON EL BLANCO FAMACOLÓGICO: UN ENFOQUE COMPUTACIONAL. Change in the structure of serotonin reuptake inhibitors and its interaction with its pharmacological target: a computational approach.

Fluoxetine (FLX) is one of the most widely used specific serotonin reuptake inhibitor (SSRI) to treat mayor depression. It has been shown that FLX has effects beyond the brain, including the gut microbiota. with descriptions of bacterial proteins that bind FLX. Since there is strong evidence of gut symbionts affecting brain function, is it possible that FLX affects the gut microbiota, and thus contribute to its effect on the brain? To test this, we propose to chemically modify FLX, to make it less permeable trough the intestinal wall, and thus making it more available to gut microbes. To achieve this, we added methyl groups to the amine group of FLX to generate the quaternary ammonium group, thus making it less permeable to biological membranes. The reaction product of each step was confirmed through 1H-NMR and 13C-NMR. Moreover, the synthesis and scaling up of this reaction has been optimized, improving reaction yields. In addition, this synthesis procedure has also been carried out with sertraline (SRT) and paroxetine (PAX), as these compounds have similar structures to FLX. The results of bioinformatics analysis of molecular docking between methylated SSRI's and the serotonin transporter has shown that the interaction between modified drugs maintain their interaction with the SERT binding site. These methylated drugs should maintain their interaction with the amino acids of the pharmacological target. Finally, this chemical modification of SSRI's should provide the pharmacological tools needed to test the hypothesis that drugs affecting the brain, also impact on gut microbes, and how the effect on gut symbionts contributes to the antidepressant effects of SSRI's.

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27.

CAMBIOS EN LA EXPRESIÓN DE RECEPTORES PURINÉRGICOS Y PERMEABILIDAD INTESTINAL POR EFECTO DE UN PROBIÓTICO DE LACTOBACILLUS PLANTARUM OBTENIDO DE QUESOS FRESCOS DE CABRA. Changes in the expression of Purinergic receptors and intestinal permeability due to the effect of a *Lactobacillus plantarum* probiotic obtained from fresh goat cheese.

The use of probiotics has increased in recent times due to the beneficial properties they provide to the host, which is why the research for new strains with specific benefits against diseases such as irritable bowel syndrome (IBS) is relevant. This pathology is a disorder of the large intestine that affects the quality of life, its main symptom being visceral pain and changes in intestinal permeability. Purinergic signaling is among the pathways associated with pain, so evaluating the effects of probiotics on these receptors could lead to new therapies. The aim of this study is to determine the effect induced by a probiotic composed of 9 strains of *Lactobacillus plantarum* obtained from goat cheese from Coquimbo region, on the expression of mRNA of two families of purinergic receptors in Caco-2 cells and measurement of paracellular and transcellular permeability with adult Sprague Dawley rats with visceral hypersensitivity when treated with the same probiotic. The probiotic was prepared with 9 strains of *Lactobacillus plantarum*. Caco-2 cells were incubated with different concentrations of the probiotic at different times, after which RNA was extracted and RT-qPCR was performed for different purinergic receptors, ZO-1 and CDH-1. TEER values were also measured in cells with the probiotic. In addition, ex vivo paracellular (Using chamber) and transcellular (everted sac) permeability tests were carried out with adult Sprague Dawley rats with visceral hypersensitivity generated by maternal separation, after two weeks administering the probiotic through an orogastric tube. After incubation with the probiotic, a decrease in the purinergic receptors P2X3 and P2X7 involved in the generation or increase of visceral pain was observed, as well as an increase in the expression of the purinergic receptor P2Y1 (which relaxes intestinal muscles) and genes related to adhesion. On in vitro permeability assays, a recovery of transepithelial resistance was observed when using the probiotic in Caco-2 cells, and on permeability assays with animals, a significant decrease in transcellular permeability and an improvement in transepithelial resistance was observed in animals treated with the probiotic, which corroborates the data obtained with adhesion proteins. These data suggest, for the first time, that this probiotic the *lactobacillus plantarum* would modify the expression of purinergic receptors associated with pain and intestinal motility, and improve intestinal permeability in ex vivo tests, which would give rise to possible new alternatives in the treatment of IBS.

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28.
DILUCIDANDO LA INTERACCIÓN FUNCIONAL ENTRE EL DOMINIO INTRACELULAR DEL RECEPTOR DE GLICINA ALFA 3 Y LA PROTEÍNA DEL COMPLEJO DE EXOCITOSIS SEC8. Elucidating the functional interaction between the intracellular domain of the glycine receptor α3 and the exocytosis complex protein SEC8.

The glycine receptor (GlyR) is a pentameric ligand-gated ion channel (pLGIC) which play a critical role regulating the neuronal excitability. Its dysfunction is associated with pathological conditions such as hyperekplexia, chronic pain and epilepsy. To date, four alpha subunits and one beta subunit have been identified. The pentameric complex, can exist in two configurations: homopentameric with only alpha subunits or heteropentameric with alpha and beta subunits in a 4:1 stoichiometry. Each subunit has an extracellular (ECD), transmembrane (TMD) and intracellular (ICD) domains. Historically, sites for allosteric modulators has been focused on the ECD and TMD, meanwhile the ICD has been related only to the synaptic clustering. However, recent research suggests that the ICD is a target for intracellular modulation, exerted by proteins such as Gbeta-gamma, which potentiated the GlyR alpha1 function. In this context, a novel interaction between GlyR alpha3 ICD and the SEC8 protein has been reported. This interaction enhances the transport and regulates axonal trafficking of GlyR alpha 3. Nevertheless, the impact on GlyR alpha3 function is still unknown. This study, aims to understand the functional effect of GlyR-SEC8 interaction using biochemical, immunohistochemical and electrophysiological approaches. Our experimental results shown that the interaction of GlyR alpha3 with SEC8 produced a left shift in the dose-response curve, apparently due to an increase in the desensitization rate, without in changes in the membrane expression levels or maximal currents. These results opening new lines of research into the regulation of GlyR by intracellular components.

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29.
EVALUACIÓN DE INTERACCIONES FARMACOLÓGICAS POTENCIALES EN PACIENTES INGRESADOS POR ATAQUE CEREBROVASCULAR ISQUÉMICO QUE RECIBIRÁN TERAPIA ANTIPLAQUETARIA DUAL COMO PREVENCIÓN SECUNDARIA. Evaluation of potential pharmacological interactions in patients admitted for ischemic stroke who will receive dual antiplatelet therapy as secondary prevention.

Stroke as the second leading cause of global mortality and the third in the national context. Currently, there is a disparity between national and international clinical guidelines, as the former does not endorse the combination of acetylsalicylic acid and clopidogrel (DAPT) for secondary prevention. Nevertheless, hospitals follow international recommendations. Therefore, it is essential to characterize the variables influencing the efficacy and safety profile of DAPT, including pharmacological interactions (PIs). The study conducted at Carlos Van Buren Hospital analyzed PIs in patients with stroke or transient ischemic attack undergoing DAPT using the CHANCE or SAMMPRIS protocol. An observational and analytical approach was employed, with anonymized and encrypted clinical record data. The study was approved by the Ethics Committee of the Faculty of Pharmacy at the University of Valparaíso and the Scientific Ethical Committee of SSVSA. Demographic, clinical, and pharmacological data were recorded, including age, gender, concurrent medications, comorbidities, diagnosis, and DAPT plan. We utilized Lexicomp® software from UpToDate 2023 to identify and categorize PIs by risk, severity, documentation, and mechanism. Finally, pharmacotherapeutic follow-up strategies were proposed for high-risk interactions. Among the enrolled patients (n=42), the average medication use was 3, with losartan being the most prescribed medication (13.37%). A total of 184 PIs were identified, averaging 4 per patient, with pharmacodynamic PIs predominating (73.91%). The most common PI was the combination of clopidogrel+atorvastatin (10.33%), followed by ASA+metformin (6.52%). Most PIs were classified as risk level C (79.89%), moderate severity (78.69%), and had an acceptable documentation level (82.07%), indicating potential clinical significance and the need for monitoring. The next step involves describing PIs both during hospitalization and at discharge, with the goal of identifying predictive variables for DAPT failure or safety risks.

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30.
EXPRESIÓN DE SVCT2 EN UN MODELO DE ENFERMEDAD DE ALZHEIMER. SVCT2 expression in a model of Alzheimer's disease.

Vitamin C is an essential molecule in all living systems; however, humans are among the few species that are not able to synthetize it and must acquire from the diet. The role of this nutrient in human health and disease is still an important matter of debate, since most pathological processes are linked to oxidative stress and vitamin C, as a reducing agent, should be key in disease prevention, including cancer and neurodegenerative disorders. Still, there is not a clear connection between vitamin C consumption and neurodegeneration. To determine which might be the links between AD and vitamin C uptake machinery we aimed to detect how Aβ exposure on neuronal tissue and cells changes vitamin C uptake capacities by analyzing Na+/Vitamin C cotransporter. In a firsts approach, we test SVCT expression in a murine model of AD, J20 mice. Interestingly, we found increased expression of a mitochondrial form of SVCT2 in this model in comparison to age-match normal mice with the same genetic background. Later, to detect if whether this over-expression was related to Aβ increase, we exposed hippocampal and cortical primary cell culture from normal mice to Aβ oligomers. However, increasing amounts of Aβ oligomers did not alter SVCT2 expression in the mitochondria. In fact, most of SVCT2 was not located within the mitochondria. Surprisingly, SVCT2 expression was not

only detected in the cytosol, but also it was increased after treatment with oligomeric Aβ exposure, as demonstrated by immunofluorescence and WB. Then, in order to know if human cells exhibit some differences with mice, we performed the same analysis in neuronal derived human cells SHSY-5Y, which showed mitochondrial localization of SVCT2. We concluded that even though exposure to amyloids are associated with an increase in SVCT2, this increased expression is not related to the mitochondria. Further analysis should be performed to determine the localization of SVCT2 in neuronal mice models.

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31.

OPTO-BLUE: UNA PLATAFORMA OPOTOGENÉTICA LENTIVIRAL QUE PERMITE LA EXPRESIÓN GÉNICA CONTROLADA INDUCIDA POR LUZ PARA APLICACIONES BIOFARMACÉUTICAS. OPTO-BLUE: An Optogenetic Lentiviral Platform Enabling Controlled Light-Induced Gene Expression for Biopharmaceutical Applications.

Regulated gene expression systems hold immense promise as a means of delivering biopharmaceutical drugs for various diseases. Ligand-induced gene expression platforms offer some control but show some disadvantages due to ligand metabolism and pharmacokinetics. LightOn is an optogenetic-regulated gene expression system that relies on a photosensitive transcription factor known as GAVPO. In response to blue light, GAVPO dimerizes, binds to a specific promoter, and activates the downstream gene of interest (GOI), offering a ligand-free gene induction. In our laboratory, we sought an efficient method for controlling gene expression in neurons and mammalian cells, capitalizing on the lentiviruses' ability to integrate genetic material into the genomes of post-mitotic cells. With this goal in mind, we recently designed and constructed the OPTO-BLUE gene system, an integrated lentivirus housing both components of the LightOn system within a single construct, permitting the incorporation of all genetic elements in a single transduction event. OPTO-BLUE showed a reliable inducible expression of EGFP as the GOI when transduced in HEK293-T cells, with regulation of gene expression achieved by varying the intensity and duration of light exposure. The controlled expression offered by this platform could become amenable when it comes to modulating the proper dose of biopharmaceuticals as a results of gene expression to achieve their therapeutic effects. These findings underscore the potential of the OPTO-BLUE system to enable the precise control of a GOI in mammalian cells using blue light. This suggests its possible applications in biomedical and neuroscientific research, as well as its eventual use in therapies for neurodegenerative diseases and other conditions related to the nervous system, which require controlled gene expression for therapeutic purposes.

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32.

DETECCIÓN DE LA EXPOSICIÓN A ORGANOFOSFORADOS EN MAULE: UN TEST RÁPIDO Y SIMPLE PARA LA DETECCIÓN DE LA ACTIVIDAD ACETILCOLINESTERASA EN ÁREAS AGRÍCOLAS. Detection of exposure to organophosphates in Maule: testing a simple and rapid test for the detection of acetylcholinesterase activity in agricultural areas.

Exposure to agrochemical compounds, particularly organophosphates, is of global concern. Latin America, including Chile, significantly contributes to global agricultural production. The economic growth associated with agriculture leads to extensive pesticide use, often exacerbated by inadequate personal protective measures by agricultural workers. When combined with inadequate implementation and regulation of pesticide usage, this results in both acute and chronic exposure to these compounds. Exposure to organophosphates, which are acetylcholinesterase inhibitors (iAChE), leads to damage in neuromuscular conduction. This, in turn, causes long-term neurobehavioral disorders such as confusion and paralysis, respiratory problems, and metabolic imbalances like obesity and diabetes. Therefore, conducting continuous analysis of worker exposure levels in our region is of great importance to better monitor occupational health risks in the agricultural industry. Therefore, we have developed a detection device for iAChE in an out-of-the-lab format, using a single capillary blood drop in a simple and rapid test adapted from the colorimetric method by Limperos and Ranta, with modifications by EDSON. This iAChe system is currently undergoing in field testing and improvement. To ensure the proper functioning of the iAChe test, we assayed it on Sprague-Dawley rats exposed to sublethal doses of 100% diazinon (i.p 50 mg/Kg). We associate the colorimetric changes observed in the device with the analysis data provided by an external laboratory (colorimetric changes per percentage of exposure). Subsequently, tests were carried out in the communes of Cobun and Talca on 18 subjects exposed or not to organophosphates. In these trials, we found that our test can detect levels ranging from: high exposure to complete absence. The iAChe device must be calibrated to intermediate levels and standardized with national and international reference laboratories. With this iAChE detection device, we aim to detect organophosphate exposure and analyze the real exposure of the agricultural population.

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33.

SGK1: CRIBADO VIRTUAL, SIMULACION DE DINÁMICA MOLÉCULAR, EXPANSIÓN QUÍMICA Y EVALUACION IN VITRO DE NUEVOS INHIBIDORES. SGK1 as a promising target for neurodegeneration: virtual screening, molecular dynamics simulations, chemical expansion and in vitro evaluation of new inhibitors.

Neurodegenerative diseases present a formidable global health challenge, compounded by the absence of effective treatment options. With the limited current efficacy of treatments for these diseases, the exploration of novel therapeutic strategies becomes imperative. For this purpose, SGK1 has

emerged as an intriguing target due to its involvement in neuroinflammation, autophagy, and cellular senescence. This study focuses on the role of SGK1 kinase and its inhibition as a potential pharmacological tool against neurodegeneration. The methodology employed encompasses a comprehensive approach, commencing with a mixed ligand-and-structure based virtual screening, followed by an in-depth examination of the binding mode through molecular dynamics simulations. Furthermore, rational chemical expansion is implemented, leveraging drug design principles. The penetration of the designed compounds into the nervous system is assessed through the Parallel Artificial Membrane Permeability Assay (PAMPA). Ultimately, the neuroprotective potential of the developed compounds is evaluated in vitro using the okadaic acid-induced neurotoxicity model. The results obtained from this study may serve as a foundation for the development of new pharmacological interventions with the potential to arrest or decelerate the progression of neurodegenerative disorders.

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34.

BIOACTIVOS DE MANZANA, LIMÓN Y BAYAS PATAGÓNICAS POSEEN EFECTO PROTECTOR SINÉRGICO CONTRA EL DAÑO INDUCIDO POR LA HIPOXIA EN LAS CÉLULAS DE NEUROBLASTOMA HUMANO.SHY5Y. Bioactives from apple, lemon, and Patagonian berries display a synergistic protective effect against hypoxia-induced damage in Human Neuroblastoma SHY5Y Cells.

During the first five days after ascending to altitudes ≥2500 m.a.s.l., healthy individuals risk developing acute high altitude sickness (AHAS), a syndrome of nonspecific symptoms that include headache, dizziness, and nausea. AHAS can progress to more severe conditions such as cerebral edema and high-altitude pulmonary edema, a non-cardiogenic form of pulmonary edema resulting from hypoxic vasoconstriction that can be fatal. Brain damage due to hypobaric hypoxia can trigger acute inflammatory mechanisms, triggering brain, lung, and systemic inflammation characterized by oxidative stress and the release of proinflammatory cytokines (IL-1β, TNF-α, IL-6). This inflammatory state predisposes one to acute mountain sickness and causes subsequent complications. This problem has no pharmacological treatment except Acetazolamide, with minimal efficacy. This work aims to describe the synergistic neuro-protective effect of water-soluble bioactives from Maqui, Calafate, Apple, and Lemon (10 to 50 ug/mL) in a validated model of cobalt chloride-induced hypoxia in human neuroblastoma SHSY5Y. Results: Our results showed that the combination of water-soluble bioactives from maqui, calafate, lemon, and apple achieves greater protection against hypoxic damage and cell death compared to the individual extracts separately. It was also demonstrated that combining these bioactives has anti-inflammatory effects in human HCM3 microglia activated with LPS (100ng/mL), using IBA-1 expression and proinflammatory cytokines (IL-6, TNF-α) as inflammation markers. These results allow us to conclude that there is a rational basis for developing nutraceuticals based on natural water-soluble compounds from fruits with potential use in the prevention of high altitude sickness.

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