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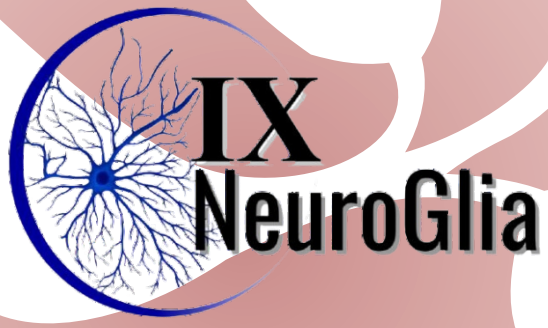

Annals IX International Symposium of Neurochemistry and Physiopathology of Glial Cells

Advanced School in Neurochemistry - 2025

Institute of Sciences of Health – Federal University of Bahia

Salvador – Bahia August 21st to 29th

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SUMÁRIO

PRESENTATION

The IX International Symposium of Neurochemistry and Physiopathology of Glial Cells (IX-NeuroGlia) took place in Salvador, capital of the state of Bahia in Brazil, from August 21 to 29, 2025. The meeting, organised by the Laboratory of Neurochemistry and Cellular Biology of the Federal University of Bahia, brought together researchers from abroad and from all regions of Brazil, highly recognised for their scientific contributions in the field of Neuroscience, as well as graduate and undergraduate students. The conferences covered both basic and applied research with topics that included aspects of neurotoxicity, neuroimmunology, neurodegenerative diseases, metabolic diseases, tumours of the central nervous system, signalling, neuropharmacology and neuroprotection.

The meeting IX-NeuroGlia also premised the realisation of The Advanced School in Neurochemistry (ASNq), designed to complete the training of doctoral students and early-career scientists from Brazil and abroad, and the Neuroscience in School, based at Federal University of Bahia (UFBA), aimed to disseminate scientific knowledge and train high school students and teachers in science.

Around 150 participants attended the meeting, including undergraduate and graduate students, as well as researchers and professionals, enabling interaction of the local academic and scientific community with renowned researchers, encouraging scientific and technological exchanges. Forty abstracts were presented in the Poster Section that comprise this IX-NeuroGlia Annals.

SCIENTIFIC PROGRAM

21/08/2025 (Thursday)

08:30 – Opening ADVANCED SCHOOL IN NEUROCHEMISTRY 2025 - Silvia Lima Costa

08:30-10:30 – Fundamentals for Investigation in Neurochemistry - Structure and Function 1

Balbino Lino dos Santos (UNIVASF): Function and Dysfunction of Nervous System Cells

10:30-11:00 – Coffee Break

11:00-12:30 – Fundamentals for Investigation in Neurochemistry - Structure and Function 2

Clarissa Schitine (UFBA): Main Aspects of Neurodevelopment

Suzana Braga de Souza (UFBA): Neurotransmission

12:30 p.m. – 14:00 – Lunch Break

14:00:16:30 – Fundamentals for Investigation in Neurochemistry - Neuroglial Interactions and Signaling

Silvia Lima Costa (UFBA) – Neuroinflammation: signals, cells and signaling

Maria de Fatima Dias Costa (UFBA) - Role of tryptophan and kynurenine pathway in neuroimmunomodulation

16:30:16:30 – Coffee Break

16:30:18:30 – Fundamentals for Investigation in Neurochemistry - Models of Study

Ravena Pereira do Nascimento (UFBA): In vitro models of study

Alexandre Moraes Pinheiro (UFRB): In vitro and in vivo models of the study for infectious diseases

Juciele Valeria Ribeiro de Oliveira (UFBA): In vivo models of study for neurodegenerative diseases.

Yanier Nunez Figueredo (CIDEM-CU): Alternative in vivo models of study for neurodegenerative diseases.

18:30 – Social Activity

22/08/2025 (Friday)

08:30-16:00 – Technical Training - Principles and Protocols

Cell Cultures, Western blot, Immunocytochemistry and Real Time-qPCR (3 groups)

The ASNq students were divided into groups and trained in cell cultures and in a different protocol of investigation in neurochemistry.

Professors and Young Doctors Mentors:

Alexandre Moraes Pinheiro and Cleonice Creusa dos Santos: Cell cultures and immunocytochemistry assay (Group 1)

Juciele Valeria Oliveira and Erica Novaes Soares: Cell cultures and analysis of protein expression by Western blot (Group 2)

Danielle Takahashi and Monique Reis de Santana: Cell cultures and protein expression by RT-qPCR (Group 3)

08:30-10:30 – Technical Training

10:30-11:00 – Coffee Break

11:00-12:30 – Technical Training

12:30 p.m. – 14:00 – Lunch Break

14:00:16:00 – Technical Training

16:00:16:30 – Coffee Break

16:30:18:00 – Scientific Writing 1

Silvia Lima Costa - Manuscript Writing General Guidelines

Danielle Takahashi – Artificial Intelligence (AI) in Scientific Writing

 # 23/08/2025 (Saturday)

08:30-16:00 – Technical Training – Principles, Protocols and Reports

08:30-10:30 – Technical Training

10:30-11:00 – Coffee Break

11:00-12:30 – Technical Training

12:30 p.m. – 2:00 p.m. – Lunch Break

14:00:16:00 – Technical Training: Guidance to Technical Report

16:00:16:30 – Coffee Break

16:30:18:00 –16:30:18:30 – Fundamentals for Investigation in Neurochemistry - Metabolism and Behaviour

George Emiliano Barreto (UL-IR) – Investigation on Metabolism

Marisol Lamprea (UNC-CO) - Investigation on Behaviour

 # 25/08/2025 (Monday)

08:30-10:00 – ASNq -Technical Training - Students' presentation of results of experiments

Mentors:

Alexandre Moraes Pinheiro, Cleonice Creusa dos Santos, Danielle Takahashi, Erica Novaes Soares, Juciele Valeria Oliveira and Monique Reis de Santana.

10:00-10:30 – Coffee Break

10:30-12:00 – ASNq -Technical Training - Students' presentation of results of experiments

Mentors:

Alexandre Moraes Pinheiro, Cleonice Creusa dos Santos, Danielle Takahashi, Erica Novaes Soares, Juciele Valeria Oliveira, and Monique Reis de Santana.

12:00 p.m. – 13:30 – Lunch Break

13:30 Opening IX NeuroGlia

13:40 - 16:20 – IX NeuroGlia - Glial Cells Interactions and Therapy

13:50 Senior Lecturer: Marisol Lamprea-Rodriguez (Universidad Nacional de Colombia, Colombia) - Differential susceptibility of the developing brain to drugs and stress: an experimental approach.

14:40 Senior Lecturer: Arthur Morgan Butt (University of Portsmouth, United Kingdom) - Astrocytes in human central nervous system diseases: a frontier for new therapies

15:20 Senior Lecturer: Ricardo Augusto de Melo Reis (UFRJ) - Purinergic P2X7 receptor and the endocannabinoid system interactions in neuro-glial systems.

16:20-16:30 – Coffee Break

16:30 - 18:30 Poster Section

 # 26/08/2025 (Tuesday)

08:30-10:00 – ASNq Students Session 1

Presentation of postgraduate students' projects. Discussion with Professors and Lecturers.

10:0-10:30 – Coffee Break

10:00-12:00 – ASNq: Fundamentals for Investigation in Neurochemistry

Arthur Butt, Dulce Papy-Garcia, Miguel Borda and Rommy Von Bernhardi

12:00 p.m. – 13:30 – Lunch Break

13:30 - 18:00 - IX NeuroGlia I - Glial Cells Function, Dysfunction and Therapy I

13:30- Senior Lecturer - George Barreto (U. Limerick, Ireland): Mitochondrial dysfunction in neurometabolic diseases: Hormones to the battlefront.

14:20 Senior Lecturer: Adriano Assis (UCPEL) - Stroke patient-derived serum modulates redox and inflammatory parameters in astroglial cells.

15:10 Young Doctor: Thaise Toutain (UCSAL) - Convergences between functional brain networks in different altered states of consciousness.

15:00-16:20 – Coffee Break

16:20 Senior Lecturer - Miguel Borda (UNAV-SP): Anthocyanins & cognitive function: a placebo-controlled trial.

17:10 Senior Lecturer: Victor Diogenes Silva (UFBA): Aminochrome and molecular mechanisms in Parkinson's disease.

 # 27/08/2025 (Wednesday)

08:30-10:00 – ASNq Students Session 2

Presentation of postgraduate students' projects. Discussion with Professors and Lecturers.

10:00-10:30 – Coffee Break

10:30-12:00 – ASNq: Fundamentals for Investigation in Neurochemistry

Maria Trinidad Herrero, Silvia Oliveira-Bravo, Patricia Cassina, and Adriano Assis.

12:00 p.m. – 13:30 – Lunch Break

13:30 - 18:00 – IX NeuroGlia - Glial Cells Function, Dysfunction and Therapy II

13:30 Senior Lecturer: Silvia Oliveira Bravo - Synthetic chalcones to prevent white matter disease.

14:20 Senior Lecturer: Patricia Cassina (ULR, Uruguay) - Mitochondria in non-neuronal cells: a role in amyotrophic lateral sclerosis progression.

15:10 Young Doctor: Lucas Oliveira - Anti-neuroinflammatory and neuroprotective effects of flavonoids in amyotrophic lateral sclerosis models.

16:00:16:20 – Coffee Break

16:20. Senior Lecturer: Maria Trinidad Herrero (UM-Spain) - Human amygdala: a hub related to neurodegenerative diseases.

17:10 Senior Lecturer: Yanier Figueredo (CIDEM-CU) - Zebrafish, a popular model for the study of neurological diseases

 # 28/08/2025 (Thursday)

08:30-10:00 – ASNq: Principles of Ethics in investigation and Animal Use

Songeli Menezes Freire (UFBA-BR):

Victor Diogenes Amaral da Silva (UFBA -BR)

10:00-11:30 – Coffee Break

10:30-12:00 - ASNq: Fundamentals for Investigation in Neurochemistry

Henning Ulrich, Ricardo Reis, Mauro Pinto

12:30 p.m. – 13:30 – Lunch Break

14:00 - 18:00 – IX NeuroGlia - Microphysiological Systems in Brain Tumours and NDD

14:00 Senior Lecturer: Claudiana Lameu (USP-BR) - Purines and kinins receptors as study and therapeutic targets in neurological diseases

14:50 Young Doctor: Monique Reis de Santana (UFBA) – Targeting AhR and Kynurenine pathway for brain tumours therapy.

15:40 Lecturer: Balbino Lino dos Santos (UNIVASF-BR): Control of neuroinflammation and neuroprotection by polyphenols for NDD therapy.

16:00:16:20 – Coffee Break

16:20 Senior Lecturer: Henning Ulrich (USP-BR) - Purines and kinins receptors as study and therapeutic targets in neurological diseases.

17:10 Lecturer: Mauro Pinto (UFG-BR) - Neuroprotective and Neurorestorative Potential of GlyT1 Inhibition.

 # 29/08/2025 (Friday)

08:30- Scientific Writing 2

Danielle Takahashi and Maria de Fatima Dias Costa

10:30-11:00 – Coffee Break

11:00- ASNq - Scientific Writing 3

Silvia Lima Costa, Danielle Takahashi and Maria de Fatima Dias Costa

12:30 p.m. – 14:00 – Lunch Break

14:00 - 18:00 – IX NeuroGlia - IX NeuroGlia - Advances in Clinical Studies for SNC Disease

14:00 Senior Lecturer: Dulce Papy (UPEC, FR) – Specific heparan sulphate chains and the selective cell vulnerability to degeneration in Alzheimer's disease.

14:50 Senior Lecturer: Rommy Von Bernhardi (U. Chile) - Age-associated changes in microglial cell regulation: implications for neurodegenerative diseases.

15:40 Young Doctor: Taísa Machado (UFBA) – Genotyping of patients with Alzheimer's disease in Salvador.

16:00:16:20 – Coffee Break

16:20 Senior Lecturer: Bruno Solano Souza (CPGM/Fiocruz; ID-Or, Brazil) - Decoding Autism: Investigating Genetic and Neurobiological Mechanisms with Induced Pluripotent Stem Cells.

17:00 Senior Lecturer: Silvia Lima Costa (UFBA, Brazil) - Control of neuroinflammation by polyphenols for therapy of brain diseases in perspective.

17:50 - Closuring]

ABSTRACTS POSTER SECTION

MOLECULAR IMPACTS OF SCN2A LOSS-OF-FUNCTION MUTATIONS IN IPSC-DERIVED NEURONS FROM AUTISTIC INDIVIDUALS

Adne Vitória Rocha de Lima[123], *Erik Aranha Rossi*[123], *Elisama Silva Araújo*[123], *Bruno Solano de Freitas Souza*[123]

[1] Gonçalo Moniz Foundation, Oswaldo Cruz Institute, Salvador, Brazil. [2] Centre for Biotechnology and Cell Therapy, São Rafael Hospital, Salvador, Brazil. [3] D'Or Institute for Research and Education, Salvador, Brazil

Introduction: Autism Spectrum Disorder (ASD) is a group of neurodevelopmental conditions characterised by persistent deficits in communication and social interaction, along with restricted and repetitive patterns of behaviour, interests, or activities. The global prevalence of ASD is estimated at approximately 1 in 100 children. Among genes associated with neurodevelopmental disorders, *SCN2A* stands out due to its strong statistical association with ASD. It encodes the voltage-gated sodium channel Nav1.2, which is essential for neuronal excitability. However, the mechanisms through which *SCN2A* variants contribute to ASD pathophysiology remain poorly understood. In this context, induced pluripotent stem cells (iPSCs) represent a promising tool for disease modelling, enabling the in vitro investigation of genotype–phenotype relationships. **Objective:** To investigate the molecular effects of *SCN2A* loss-of-function mutations in iPSC-derived neurons from ASD patients, focusing on Nav1.2 genes and protein expression and its impact on neuronal morphology. **Methods:** Three control iPSC lines from neurotypical individuals and three patient iPSC lines carrying *SCN2A* nonsense variants were cultured, validated for pluripotency, and differentiated into excitatory neurons through doxycycline-inducible expression of Neurogenin-2 (NGN2). Gene expression was analysed by RT-PCR, protein expression by Western Blot, and neuronal morphology by immunofluorescence, particularly the distribution of Nav1.2 and dendritic arborization. **Results:** All iPSC lines maintained pluripotency and were efficiently differentiated into excitatory neurons. Mutant lines showed significantly reduced *SCN2A* expression at both mRNA and protein levels. Immunofluorescence revealed altered Nav1.2 distribution, reduced sodium channel expression, and impaired dendritic complexity. **Conclusion:** These findings suggest that *SCN2A* mutations impact not only molecular expression but also neuronal morphology, potentially affecting neural circuit connectivity and function in ASD. **Acknowledgements:** CAPES, FME and CNPq.

Keywords: SCN2A; ASD; iPSC-derived neurons.

STRESS-INDUCED DEFICITS IN THE EXTINCTION OF CONTEXTUAL CONDITIONED FEAR ARE REDUCED BY AYAHUASCA IN MALE RATS

Antonio Furtado da Silva Júnior[1]; Rafael Guimarães dos Santos[2]; Leonardo Barbosa Moraes Resstel[1].

[1] Pharmacology Department, Laboratory of Neuropharmacology, FMRP/USP; [2] Neuroscience and Behaviour Department, Laboratory of Psychopharmacology, HC-FMRP/USP.

Introduction: Ayahuasca is a beverage used for ritualistic purposes, prepared from the decoction of two plants: *Banisteriopsis caapi* and *Psychotria viridis*. Ayahuasca may facilitate the extinction of conditioned fear and impair the reconsolidation of aversive memories. Stress is a well-established factor that worsens the extinction of conditioned fear. Thereby, Single Prolonged Stress (SPS) is a valuable tool for investigating impairments in the extinction and generalisation of aversive memories. **Objectives:** Therefore, this study aims to investigate the effects of ayahuasca on the extinction of contextual fear memories and how stress influences this process, including the generalisation of aversive contexts. **Methodology:** Male Wistar rats were divided into a control group and the SRS group (2 h of tube restraint, 20 min forced swimming and ether exposure with an additional 20 min forced swim 7 days later). Both groups were exposed to an aversive context (Context A) across three sessions: conditioning (3 electric footshocks), extinction (30 min without shocks) and testing (5 min without shocks in either Context A or Context B for generalisation assessment). Ayahuasca was administered at a dose of 0.3 mg/kg either 1 hour before or after the extinction session. **Results:** The administration of ayahuasca before the extinction session increased freezing behaviour during extinction in SRS animals compared to SRS vehicle. Additionally, SRS animals showed generalisation and impaired extinction during the test session, which were not affected by ayahuasca. Generalisation and extinction deficit observed in the SRS group were reversed when ayahuasca was administered after the extinction session. No changes were observed in ayahuasca group controls. **Conclusion:** Our findings suggest that ayahuasca increases the aversiveness associated with stress during fear conditioning extinction, and it produces an antiaversive effect on fear generalisation and extinction deficits when administered in different extinction session times. **Support:** Capes and CNPq.

Keywords: SRS; Ayahuasca; Contextual fear extinction.

AGATHISFLAVONE ATTENUATES NEUROINFLAMMATION THROUGH REGULATION OF MIR-146A AND MIR-155 IN ACTIVATED HUMAN MICROGLIA

Balbino Lino dos Santos [1,2,*], Cleonice Creusa dos Santos [1], Karina Costa da Silva [1], Carolina Kymie Vasques Nonaka [3], Bruno Solano de Freitas Souza [3,4], Jorge Mauricio David[5], Juciele Valéria Ribeiro de Oliveira [1], Maria de Fátima Dias Costa [1,6], Arthur Morgan Butt [7], Victor Diogenes Amaral da Silva [1] and Silvia Lima Costa [1,6,8,*]

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Introduction: MicroRNAs (miRs) are key post-transcriptional regulators of gene expression in glial cells and play critical roles in the pathogenesis of neurodegenerative disorders, including Alzheimer's disease (AD). **Objective**: In this study, we examined the modulatory effects of agathisflavone—a biflavonoid isolated from *Cenostigma pyramidale* (Tul.) leaves—on the expression of microRNAs and pro-inflammatory mediators in activated human microglia. **Methods**: C20 microglial cells were stimulated with either β-amyloid oligomers (Aβ, 500 nM for four h) or lipopolysaccharide (LPS, one µg/mL for 24 h), followed by treatment with agathisflavone (1 µM) for 24 h. **Results**: Both Aβ and LPS triggered a pro-inflammatory response in microglia, characterised by elevated levels of miR-146a, miR-155, IL1-β, IL-6, and NOS2. Agathisflavone treatment significantly attenuated the expression of miR-146a and miR-155, as well as the associated inflammatory cytokines. Moreover, Aβ-induced phosphorylation of STAT3 (p-STAT3) was also diminished following agathisflavone exposure. **Conclusion**: These findings suggest that agathisflavone exerts anti-inflammatory effects in microglia, at least in part, through modulation of miRs, supporting its potential relevance in therapeutic strategies targeting neuroinflammation and Alzheimer's disease. **Acknowledgements:** CAPES, CNPq, FINEP and UFBA.

Keywords: agathisflavone; human microglia; miRNAs.

MODULATION OF GLIAL REACTIVITY BY CANNABIGEROL AND CANNABIDIOL REDUCES L-DOPA-INDUCED DYSKINESIA IN HEMIPARKINSONIAN RATS

Bianca Andretto de Mattos[1], Glauce Crivelaro do Nascimento[2], José Alexandre Crippa[3], Francisco Guimaraes[4], Elaine Del Bel[2].

[1]Department of Physiology, Medical School of Ribeirao Preto, University of São Paulo, Ribeirao Preto, Brazil; [2]Department of Basic and Oral Biology, Dental School of Ribeirao Preto, University of São Paulo, Ribeirao Preto, Brazil; [3]Department of Neuroscience and Behaviour, Medical School of Ribeirao Preto; [4]Department of Pharmacology, Medical School of Ribeirao Preto, Brazil.

Introduction: Cannabigerol (CBG) and cannabidiol (CBD) are phytocannabinoids known for their neuroprotective, anti-inflammatory, and antioxidant properties. Recent evidence suggests the pharmacological modulation of the endocannabinoid system as a therapeutic strategy to alleviate L-DOPA-induced dyskinesia (LID) in Parkinson's disease (PD). **Aims:** This study aimed to evaluate the antidyskinetic effects of CBG and CBD, and to investigate the underlying molecular mechanisms, with a particular focus on striatal neuroinflammation. **Methods:** Rats received a unilateral 6-OHDA infusion into the medial forebrain bundle to induce a hemiparkinsonian model of dopaminergic degeneration. After one week of L-DOPA treatment, animals develop severe abnormal involuntary movements (AIMs). Then, rats were treated with CBG (1, 5, or 10 mg/kg) or CBD (10 or 30 mg/kg), separately, or in combination, 30 minutes before L-DOPA treatment, for 2 weeks. **Results:** We found that only CBD30 and CBG5 were effective in significantly reducing orolingual, limb, and axial AIMs. Notably, co-administration of subeffective doses of CBD10+CBG10 also produced a significant synergistic reduction in dyskinesia. To investigate the molecular mechanisms underlying the cannabinoid's antidyskinetic effects, we evaluated the expression of the immediate early gene FosB, which was markedly upregulated in the ipsilateral striatum of L-DOPA-treated animals, and this effect was significantly attenuated by treatment with CBG5, CBD30, and CBG/CBD. We also examined neuroinflammatory changes associated with L-DOPA treatment. L-DOPA increased the presence of reactive microglia and astrocytes in the sensorimotor and associative domains of the ipsilateral striatum. Treatment with CBG5, CBD30, and CBG10+CBD10 significantly reduced glial expression in the lesioned striatum. **Conclusion:** Antidyskinetic effects of CBG and CBD are strongly associated with their ability to suppress neuroinflammation and reduce glial activation in the striatum. These findings highlight the critical role of neuroinflammation in LID and reinforce the therapeutic potential of phytocannabinoid-based approaches for the management of this pathology. **Acknowledgements:** CAPES; FAPESP; CNPq; FMRP; USP.

Keywords: Cannabinoid; L-DOPA-induced dyskinesia; Neuroinflammation.

TUMOR GROWTH DYNAMICS USING GENERALIZED MATHEMATICAL MODELS AND EXPERIMENTAL DATA

Bianca Matias Almeida[1], Juliana Pombo Dantas Coelho[1], Paulo Vitor Barbosa Oliveira[3], Pablo Roberto Vasquez dos Anjos[1], Marcos Arize[1], Arícia Fatzaun Perèe[1], Rodrigo Fernando Lugon Cornejo von Marttens[1], Irlã Santos Lima[2], Cleonice Creusa dos Santos[2], Silvia Lima Costa[2], Suani Tavares Rubim de Pinho[1].

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[3]Instituto de Biociências, Universidade Estadual Paulista, Botucatu, Brasil.

Introduction: Glioblastoma is one of the most aggressive brain tumours, characterised by rapid cell proliferation and high resistance to treatment. Mathematical modelling helps understand tumour growth and evaluate therapies. The use of experimental data obtained from cell cultures contributes to the construction and validation of these models. **Objective:** To investigate the growth dynamics of glioblastomas using generalised mathematical models applied to experimental data from tumour cell cultures. **Methods:** Glioblastoma cultures were established with different initial quantities (50 to 1000 cells per well). Cell counting was initially performed visually using optical microscopy images. To enable large-scale analysis, we are developing an automated counting strategy using computer vision and machine learning. In this direction, we are exploring techniques from cosmological imaging and a human-consensus segmentation approach. **Results:** Visual counting enabled the generation of growth curves for low-density conditions. The Tsoularis-Wallace model fits better with 50 cells, while the Gompertz model fits those with 100. Automation aims to improve accuracy and efficiency. These results will be used to train models for high-density counting. **Conclusion:** This study presents a proposal for integrating experimental data and mathematical modelling in the analysis of glioblastoma growth. The implementation of computational support tools is expected to contribute to consolidating this approach in contexts involving large volumes of data.
Acknowledgements: PIBIC/UFBA, Laboratory of Neurochemistry and Cell Biology (ICS/UFBA).

Keywords: glioblastoma; mathematical modelling; experimental data.

BIOPROSPECTING OF *LUZURIAGA RADICANS* FRUITS: ANTIOXIDANT CAPACITY AND NEUROPROTECTIVE ACTIVITY IN SH-SY5Y CELLS

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Introduction: The consumption of edible fruits rich in polyphenolic compounds has been associated with reduced levels of reactive oxygen species (ROS) and various health benefits, including protection against oxidative stress (OS). The *Luzuriaga* genus, comprising only four described species worldwide, is a small and often overlooked plant group that produces edible fruits. Remarkably, three of these species are native to the Valdivian temperate rainforest ecoregion in southern Chile. However, there is limited scientific information regarding their antioxidant properties and potential health effects. **Objectives:** To investigate the antioxidant capacity, neuroprotective effects, and enzymatic inhibitory activity of *Luzuriaga radicans* fruit-rich extracts (LrFREx) *in vitro*. **Methods:** LrFREx was analysed for total phenolic and flavonoid content and antioxidant capacity using DPPH, ABTS, and ORAC assays. Neuroprotective potential was assessed in SH-SY5Y neuroblastoma cells under H_2O_2-induced oxidative stress at 1.5, 15, and 150 µg/mL, using the Alamar Blue assay to determine cell viability. In addition, the inhibitory effects of LrFREx on tyrosinase and acetylcholinesterase activities were evaluated at 750, 500, and 250 µg/mL with kojic acid and THA as positive controls. **Results:** LrFREx demonstrated antioxidant activity and a concentration-dependent neuroprotective effect. At 15 µg/mL, it significantly enhanced cell viability compared to Trolox, while maintaining high viability at 1.5 µg/mL. At 150 µg/mL, the extract showed limited protection. Statistical analysis (ANOVA and post hoc t-tests) confirmed significant differences favouring the extract at low and moderate concentrations ($p < 0.05$). In enzymatic assays, LrFREx inhibited tyrosinase (62.03% at 750 µg/mL) and acetylcholinesterase (69.44% at 750 µg/mL), demonstrating moderate activity, particularly against AChE. **Conclusions:** *Luzuriaga radicans* fruit extracts showed a safe profile, significant antioxidant and neuroprotective effects at low concentrations, and moderate enzymatic inhibitory activity. These findings support its potential as a natural source of neuroactive and multifunctional phytochemicals. **Acknowledgements:** FONDECYT Iniciación 11240910.

Keywords: edible fruits; SH-SY5Y cells; neuroprotective activity.

SYNTHESIS OF BIARYL DERIVATIVES FROM FLAVONOID CHRYSIN

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Introduction: Flavonoids are an important class of molecules present in nature, characterised by a three-ring core with small variations in their structure, which gives them broad biological and pharmacological activity, including for neurological diseases. **Objectives:** This research focuses on the halogenation of chrysin at the C8 and C6 positions, aiming to address the challenge in synthesising aryl partners for Suzuki-Miyaura cross-couplings (SM). **Methods:** Commercially available chrysin was used for alkylation**,** with K_2CO_3, Me_2SO_4, in acetone at 60°C, overnight. For halogenation: N-iodosuccinimide (NIS) or N-bromosuccinimide (NBS) in DMF at 70°C - 51% (NBS)/88% (NIS). For SM couplings, two methods are employed: Method A involves commercially available boronic acids, $Pd(OAc)_2$ (0.03 mol%), SPhos (0.006 mol%), and 2.5 equivalents of $CsCO_3$ in a 6:1 dioxane/water solution. Method B utilises 2.0 equivalents of Tolyl-$B(OH)_2$, $Pd(OAc)_2$, and K_3PO_4 in toluene at 100°C. **Results:** To the family of C8 derivatives, the flavone halides were coupled by SM conditions (Method A) with commercial boronic acids, furnishing the C8 biaryl crysin derivatives with similar yields in most cases by use of bromine or iodide substrates. **Conclusions:** N-Containing boronic acids failed in these SM couplings. The synthesis of C6 derivatives involves a selective alkylation of chrysin, which undergoes selective C6 iodination with NIS. However, the use of similar SM conditions did not lead to biaryl derivatives. Due to this, a new protocol to SM coupling was applied (Method B), allowing a synthesis of our first C6 biaryl derivative. Although the moderate yield, this new SM coupling condition gives us an opportunity for the synthesis of a new family of derivatives.
Acknowledgements: CNPq, FAPESB, UFBA, Cienam, GPSQ, CAPES.

Keywords: Chrysin, Derivatives, Suzuki-Miyaura Cross-coupling.

INVESTIGATION OF THE ANTI-INFLAMMATORY AND ANTITUMOR PROPERTIES OF MYRICETIN IN HUMAN GLIOMA CELLS

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Introduction: Inflammation in the tumour microenvironment plays a crucial role in glioma progression. The neuroinflammatory process includes the participation of standard recognition receptors, including Toll-like receptors (TLRs). In this context, the search for natural compounds capable of modulating inflammation in the central nervous system and acting on the tumour microenvironment becomes particularly relevant. Myricetin (MYR), which is a flavonoid with promising prospects due to its multiple biological activities, may have a therapeutic effect against neuroinflammation. **Objective**: To demonstrate the inhibitory potential of myricetin against TLR-4/MD-2 and NLRP3-inflammasome and evaluate the cytotoxicity of flavonoids considering cell viability parameters. **Methodology**: The AutoDockTools, AutoDockVina and Discovery Studio programs were used. In the *in vitro* studies, human glioma cells from (U87, U343, U251 and GL15) were treated with MYR at concentrations of 0.1 to 200 µM. Cell viability was evaluated by MTT assay, and phase contrast photos were analysed to assess morphology after 24, 48, and 72 hours of treatment. **Results**: Myricetin interacted with 13 amino acids of the hydrophobic nucleus of MD-2 of the TLR-4/MD-2 complex. The free energy of interaction of MYR with the dimeric complex was close to that of the inhibitor TAK-242. It was observed that myricetin interacted with 16 amino acids of the NACHT domain of the NLRP3 very close to the binding site of the pharmacological inhibitor of the ATPase activity of the NLRP3 inflammasome, MCC950. MYR and MCC950 share interactions with 10 similar amino acid residues. It was observed that myricetine is cytotoxic in GL15 and U343 cultures at a concentration of 75µM after 72 hours, whereas in U251 and U87 cultures, this effect occurs at a concentration of 200µM. At cytotoxic concentrations, myricetin induces a morphology change in all glioma cultures. **Conclusions**: These results indicate that myricetin can interfere with the activation of TLR-4/MD-2 and NLRP3 and has anti-glioma activity, which encourages further study. **Acknowledgements**: FAPESB, CAPES, CNPq, and UFBA.

Keywords: myricetin; TRL-4/MD-2; glioma.

EVALUATION OF THE ANTITUMOR EFFECTS OF AGATHISFLAVONE AND APIGENIN IN 3D CELL CULTURE MODELS

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Introduction: Glioblastoma (GBM) is the most common and aggressive primary malignant neoplasm of the Central Nervous System (CNS). This tumour has high potential to migrate, invade and proliferate in healthy tissue, which hinders its treatment. Apigenin and Agatisflavone are flavonoids, plants' secondary metabolites. They are present in nearly all fruits and vegetables and have many therapeutic properties, among them antitumoral. However, the direct targets of these flavonoids on the tumoral microenvironment remain to be investigated. Objective: this work investigated the antitumoral effects of Apigenin and Agathisflavone on tumoral viability and development in 3D cultures. Methodology: the methods involved the culture of human tumour-derived cell lineages (GL15 and U343) in agarose micromolds for the development of 3D culture. Development and morphological parameters were monitored for seven days through phase contrast microscopy, then analysed with AnaSP software. Cell viability was analysed through propidium iodide after 48 h from flavonoid exposure. Tumoral migration was analysed after 72h from flavonoid exposure by cell count of migrated cells on phase contrast photomicrographs. Results: our results show that apigenin and agathisflavone inhibited development, altered cell morphology and decreased cell viability in GL-15 3D cultures. In U343 cultures, flavonoids did not alter cell morphology and development, but did affect cell migration and tumoral viability. Discussion: Our results show that tested flavonoids act on the tumoral microenvironment, inhibiting its growth and viability, but further studies must be performed to elucidate flavonoids' cytotoxicity mechanisms in glioma cells and thus open perspectives to their use as adjuvants in antitumoral therapy. Acknowledgements: CNPQ, FAPESB, INCT- Translational Neuroscience

Keywords: Flavonoids, Glioblastoma, 3D Culture.

PROTECTIVE EFFECT OF THE FLAVONOID RUTIN AGAINST OGD DAMAGE IN PRIMARY RETINAL CULTURES

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Introduction: Retinal neurodegeneration and glial dysfunction are hallmarks of vision-threatening retinopathies, with retinal detachment causing significant neuronal loss through ischemic mechanisms. The flavonoid rutin has demonstrated neuroprotective, neurogenic and immunomodulatory properties in neural systems, but its effects on the retinal neuroglial network remain unexplored. This study investigates rutin's potential as a protective molecule for retinal neurons and Müller glia responses under ischemic conditions by oxygen-glucose deprivation (OGD). **Objectives:** We aimed to establish an *in vitro* model of retinal ischemia using primary mixed retinal cultures containing neurons and glia to study rutin's ability to mitigate OGD-induced cell death. **Methods:** Primary mixed retinal cultures were prepared from postnatal day 0-4 mice and cultivated for 7 days or until they achieved confluency, at a maximum of 15 DIV. Rutin's cytotoxicity was assessed via MTT assay (0.1-35µM, 24-72h). For neuroprotection studies, cultures were either pretreated with rutin or exposed to conditioned medium from rutin-treated Müller glia before undergoing OGD. Cell death was quantified through propidium iodide staining and fluorescence microscopy. The study was approved by the Animal Ethics Committee CEUA-UFBA (protocol no. 6731220818). **Results:** Cultures were characterised by morphology and immunocytochemistry (βIII-tubulin and GFAP). The Immunocytochemical analysis confirmed the presence of retinal neurons, Müller glia and astrocytes in cultures. Rutin showed no cytotoxicity at any tested concentration and any time point ($p>0.05$, Kruskal-Wallis with Dunn's test). **Conclusions:** Rutin demonstrated a safe profile in mixed retinal cultures, showing no cytotoxicity across all tested concentrations. These findings validate further investigation as a neuroprotective agent in OGD models, with relevance to retina disease. **Acknowledgements:** CAPES, FAPESB, CNPq

Keywords: Retina, Rutin, Retinal detachment.

SEX- AND ESTRUS-DEPENDENT EFFECTS OF CANNABINOIDS ON MECHANICAL ALLODYNIA AND ASTROCYTIC DYSFUNCTION IN A RAT MODEL OF TRIGEMINAL NEURALGIA

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Introduction: Trigeminal neuralgia (TN) is a chronic pain condition with clear sex-specific differences in pain sensitivity and pharmacological responses. Cannabinoids are promising analgesics with glial-modulating effects, but their interaction with sex and hormonal status remains unclear in orofacial pain models**. Objectives:** To investigate the analgesic efficacy of cannabidiol (CBD), cannabigerol (CBG), and full-spectrum cannabis extract (FULL) in male and female rats with nerve injury, and to examine associated molecular changes in the spinal trigeminal nucleus caudalis (Sp5C). **Methods:** Male and female Wistar-Hannover rats were subjected to infraorbital nerve constriction (ION-CCI). Estrous cycle staging was performed in females via vaginal cytology. Mechanical allodynia was assessed using von Frey filaments, and the rotarod test evaluated motor coordination. Animals were treated intraperitoneally with CBD (10 mg/kg), CBG (3 or 10 mg/kg), or FULL (3 or 10 mg/kg). Brainstem sections were collected for double immunofluorescence staining of GLT-1 (astrocytic glutamate transporter) and GFAP (astrocyte activation marker) in the Sp5C. **Results:** Female rats in the diestrus II phase exhibited significantly increased mechanical sensitivity compared to other phases. Cannabinoids reduced allodynia in a sex- and dose-dependent manner: in females, CBD (10 mg/kg), CBG (3 mg/kg), and FULL (3 mg/kg) were effective, while in males, only the highest doses of CBG and FULL (10 mg/kg) showed significant antinociceptive effects. The ION-CCI surgery impaired motor coordination, but cannabinoid treatments did not exacerbate these effects. Immunofluorescence analysis revealed that surgery decreased GLT-1 and increased GFAP expression in the Sp5C. CBD reversed these molecular changes in a sex-dependent manner. **Conclusions:** These findings demonstrate that cannabinoid-induced analgesia and astrocytic modulation are influenced by both sex and estrous cycle. CBD effectively restores glutamate homeostasis and reduces astrocytic reactivity. **Acknowledgements:** FAPESP, CAPES, CNPq

Keywords: trigeminal neuralgia; sex differences; astrocytes.

AGATHISFLAVONE MODULATES THE KYNURENINE PATHWAY AND GLIAL INFLAMMATORY RESPONSES WITH IMPLICATIONS FOR NEUROPROTECTION

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Introduction: The central nervous system (CNS) relies on complex and dynamic interactions between neurons and glial cells. Astrocytes supply essential nutrients for brain metabolism and regulate the chemical environment surrounding neurons, whereas microglia play critical roles in defence, homeostasis, and responses to injury. Both astrocytes and microglia contribute to the regulation of excitotoxicity and inflammation mediated by the metabolism of tryptophan (Trp) via the kynurenine pathway (KP). Trp catabolism through the KP generates neuroactive metabolites that play critical roles in neuroinflammation and neurodegeneration. **Objectives:** In this study, we investigated the ability of agathisflavone (FAB), a biflavonoid with known anti-inflammatory and neuroprotective properties, to modulate KP and glial responses under inflammatory conditions. **Methods:** Human iPSC-derived astrocytes, primary rat astrocytes and microglia, and the human microglial C20 cell line were treated with FAB alone or in combination with lipopolysaccharide (LPS), quinolinic acid (QUIN), or the IDO inhibitor 1-methyl-D-tryptophan (1-MT). **Results:** FAB preserved glial viability, attenuated the expression of pro-inflammatory genes (iNOS, IL-1β), increased IL-10 production, and altered the activities of KP enzymes in a stimulus- and cell-type-dependent manner. High-performance liquid chromatography confirmed shifts in KP metabolite profiles, including decreased QUIN levels. Otherwise, PC12 cells exposed to glial conditioned medium from FAB-treated cultures exhibited improved survival and preserved neuronal morphology. **Conclusions:** These findings indicate that FAB modulates KP metabolism and glial inflammatory signalling to promote a neuroprotective environment and support its potential as a candidate for adjuvant therapeutic strategies in neurodegenerative diseases**.** **Acknowledgements:** CNPq, CAPES

Keywords: Tryptophan; kynurenines; agathisflavone; IDO; Glial cell.

EVALUATION OF THE NEUROPROTECTIVE POTENTIAL OF THE FLAVONOIDS HESPERITIN AND HESPERIDIN IN HT22 AND C20 CELLS

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INTRODUCTION: Neuroinflammation is an intrinsic pathophysiological response of the central nervous system, characterised by the activation of microglia and the subsequent release of pro-inflammatory cytokines. Although initially protective, uncontrolled or prolonged neuroinflammation is a critical factor in the progression of traumatic pathologies, such as Traumatic Brain Injury (TBI) and Spinal Cord Injury (SCI). In this context, substances of natural origin with antioxidant and anti-inflammatory properties have been studied as potential neuroprotective agents. **OBJECTIVES:** To investigate in vitro the anti-inflammatory effect of the flavanones hesperidin and hesperetin in microglial cell lines (C20) and murine hippocampal neurons (HT22); to analyse their modulatory action on the neuroinflammatory response and to evaluate possible morphological changes triggered by the presence of these molecules. **METHODOLOGY**: C20 and HT22 cell cultures were treated with hesperidin and hesperetin at concentrations ranging from 0.1 µM to 100 µM. Cell viability was assessed by MTT assay after 24 hours. Cell morphology was analysed by phase contrast microscopy and Rosenfeld staining to observe structural changes associated with inflammation and treatment. **RESULTS**: Preliminary results showed that both flavonoids maintained or increased cell viability compared to the control (0.01% DMSO). In HT22 cells, the compounds did not show toxicity, suggesting a potential neuroprotective effect. Morphological analysis demonstrated that these molecules promote changes consistent with a less activated state of microglia. **FUTURE PERSPECTIVES**: We intend to further study using a model of neuroinflammation induced by LPS (lipopolysaccharide). This model will mimic an acute inflammatory scenario, similar to that which occurs in the early stages of spinal cord injury (SCI), to evaluate neuroprotective activity against inflammatory stress. This approach will allow us to determine whether these compounds are capable of attenuating secondary neuronal damage resulting from post-SCI neuroinflammation, paving the way for future in vivo investigations and the development of new therapies. **Acknowledgements**: CAPES, CNPq, Labnq, PMBqBM.

KEYWORDS: neuroinflammation; flavonoids; neuromodulation.

NEUROPROTECTIVE EFFECT OF EXTRACELLULAR VESICLES IN A MODEL OF ISCHEMIC STROKE WITH GLUTAMATERGIC NEURONS DERIVED FROM INDUCED PLURIPOTENT STEM CELLS (IPSCS)

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Introduction: Ischemic stroke is a leading cause of death and long-term disability, with current therapies limited by narrow time windows and risk of hemorrhagic transformation. Extracellular vesicles (EVs) have emerged as a promising cell-free therapeutic strategy for ischemic stroke, due to their role in promoting neuroprotection. Besides that, the advent of induced pluripotent stem cells (iPSCs) has significantly advanced neurological disease research. **Objective:** Investigate the neuroprotective potential of EVs derived from mesenchymal stem cells (MSCs) and astrocytes in an *in vitro* OGD/R (oxygen-glucose deprivation/reperfusion) model using human iPSC-derived neurons. **Methodology:** iPSCs from a healthy donor were differentiated into cortical neurons via doxycycline-induced NGN2 expression. These neurons were subjected to OGD/R conditions and assessed for cell viability, HIF-1α expression, and morphological integrity. EVs were isolated from MSCs and iPSC-derived astrocytes and applied post-OGD/R to assess their therapeutic potential. **Results:** Differentiated glutamatergic neurons exhibited appropriate morphology and expression of markers such as TUJ1, MAP2, NEUN and VGLUT. OGD/R exposure led to reduced viability, upregulated HIF-1α, and notable morphological damage. Treatment with EVs from both MSCs and astrocytes partially mitigated these effects, suggesting a neuroprotective role. **Conclusion:** EV-based interventions improved neuronal viability and attenuated damage in the OGD/R model, supporting their potential as neuroprotective agents in ischemic injury contexts. **Acknowledgements:** CAPES, INOVA FIOCRUZ, IDOR, FIOCRUZ

Keywords: Induced Pluripotent Stem Cells, Nervous System Diseases, Cell Therapy.

TRANSCRIPTIONAL RESCUE OF SCN2A EXPRESSION VIA CRISPRA IN HIPSC-DERIVED NEURONAL MODELS OF AUTISM WITH HAPLOINSUFFICIENCY

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Introduction: The SCN2A gene encodes the sodium channel NaV1.2, which is critical for neuronal function. Mutations in this gene are associated with neurodevelopmental disorders, including autism spectrum disorder (ASD). Variants introducing premature stop codons (PTCs) can lead to haploinsufficiency by reducing NaV1.2 expression through nonsense-mediated decay (NMD). **Aim**: To investigate the consequences of two SCN2A variants (R856X and Q169Dfs*13X) identified in ASD patients and to evaluate the use of the CRISPR activation system (CRISPRa) to restore functional allele expression. **Method**: We used iPSCs derived from neurotypical individuals and ASD patients carrying SCN2A mutations, inducing cortical neuron differentiation via doxycycline. Immunofluorescence, RT-qPCR, and electrophysiological assays characterised neurons. We also applied CRISPRa to increase SCN2A expression and assess phenotype reversal. **Results**: Mutant neurons showed reduced SCN2A expression, lower synaptic density (SYN1, HOMER1), decreased dendritic spine number and axon initial segment (AIS) length, and reduced action potential frequency (patch-clamp). Treatment with cycloheximide (CHX) increased SCN2A expression in patient cells, confirming NMD involvement. We tested three sgRNAs for CRISPRa and selected the most efficient and specific. SCN2A activation led to increased SCN2A mRNA and NaV1.2 expression, upregulation of AnkG and synaptic genes, and functional recovery in MEA assays, with firing patterns similar to controls. **Conclusions**: SCN2A PTC variants reduce gene expression and impair neuronal function. CRISPRa-mediated activation of SCN2A represents a potential therapeutic approach to restore neuronal function in ASD-SCN2A models. Future steps include testing additional variants and performing RNA-seq to identify pathways modulated by CRISPRa, advancing our understanding of functional rescue mechanisms.

Keywords: CRISPRa; SCN2a; Autism Spectrum Disorder (ASD).

TARGETING NEUROINFLAMMATION: KININ B2 RECEPTOR ANTAGONISM MITIGATES INFLAMMATORY RESPONSES IN A FAMILIAL ALZHEIMER'S DISEASE MOUSE MODEL

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Introduction: Neuroinflammation plays a key role in Alzheimer's disease (AD) progression. Kininergic signalling, mediated by bradykinin (BK) and its kinin-B2 receptor (B2R), is stimulated in AD, affecting blood-brain barrier (BBB) permeability and inflammation. Here, we aimed to investigate the effects of the B2R on BBB permeabilisation and immune cell infiltration. **Methodology:** The mouse model of AD was developed by intracerebroventricular (i.c.v.) injections of oligomeric Aβ peptide (AβOS) in C57BL6 males. HOE-140 (50 pmol/site, i.c.v.) was administered 30 minutes before oligomers or saline. Serum cytokine levels were measured using the BD™ Cytometric Bead Array (CBA) mouse inflammation kit. BBB integrity was analysed using Fluorescein (0.1 mg/mL, i.p.). Cerebral leukocyte infiltrates were obtained 48 hours post-treatment, with immune cell diversity determined by flow cytometry. All procedures were approved by the Ethics Committee for Animal Research of the University of São Paulo (Process 5250180515). **Results:** AβOS increased BBB permeability, while B2R inhibition with HOE-140 provided significant protection against this effect. B2R antagonism significantly decreased pro-inflammatory IL-6 levels and increased IL-10 levels in serum in the AD mouse model. B2R blockade diminished inflammatory monocyte numbers in mice with experimental AD. The frequency of CD11b+, Ly6G+ neutrophils was significantly reduced in AD mice 48 hours post-treatment. Non-neutrophil CD11b+, Ly6G- leukocytes were significantly increased in mice with experimental AD. Mice with experimental AD showed an increase in the number of CD206+, CD86- microglial cells (M2-like macrophages) that are activated under conditions of HOE-140 treatment. **Conclusion:** B2R modulates BBB permeability, pro-inflammatory cytokines, and immune cell infiltration in an AD mouse model. Thus, the B2R blockade could be a potential target for slowing neuroinflammation progression in AD. **Acknowledgements:** FAPESP (2018/0763-4) and CNPq, Brazil.

Key words: Oligomeric amyloid-beta (AβOS); HOE-140; Cytokines; Flow cytometry; Immune cell infiltration.

ANTITUMOR EFFECTS OF MACAMIDES ON GLIOBLASTOMA CELL LINES AND 3D MICROTUMORS

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Introduction: Glioblastoma (GBM) is the most aggressive primary brain tumour, characterised by poor prognosis and resistance to current therapies. Natural compounds, such as macamides from *Lepidium meyenii* (maca), have emerged as promising antitumor agents. **Objective:** To evaluate the effect of macamides on GBM cell lines and 3D microtumors, in comparison to primary astrocyte culture and human astrocytes derived from iPSC cells. **Methods:** Macamides (M4 and M5) were synthesised by a condensation reaction using different amines and fatty acids, and their cytotoxic activity was evaluated against C6 rat glioma cells, U87, GL15, and U343 human GBM cells, primary astrocyte culture, and human astrocytes derived from iPSC cells. The scratch assay was used to evaluate the cell migration capacity of U87 cells. Flow cytometry analysis was used to analyse the effect of macamides on the cell cycle of U87 cells. Western blot analysis was performed to evaluate the effect of macamides on PI3K/AKT and STAT3 pathways in U87 cells. A 3D microtumor model was generated using U87 and U343 cells in agarose molds, and the microtumors were exposed to M4 or M5 and analysed. Morphology was monitored by phase contrast microscopy, and viability was assessed by fluorescence with propidium iodide and DiOC18. **Results**: Macamides M4 and M5 reduced the viability of C6, U87, GL15 and U343 cells without affecting primary astrocytes. Toxicity was observed in iPSC-derived astrocytes only at concentrations higher than>100 µM. Macamides inhibited U87 lcells migration and induced G0/G1 cell cycle arrest. A trend toward reduced expression of PI3K, AKT, and STAT3 in U87 cells was also observed. In 3D models, macamides reduced microtumor viability and altered morphology, decreasing circularity, compactness, convexity, solidity, and sphericity. **Conclusion:** Macamides exert antitumor effects on GBM by reducing cell viability and migration, inducing cell cycle arrest, and possibly modulating key oncogenic pathways. They also impair 3D microtumor viability and structure, supporting their potential as novel therapeutic candidates for glioblastoma. **Acknowledgements:** CAPES and FAPESB.

Keywords: Peruvian maca; glioblastoma; spheroids.

CHARACTERIZATION OF AN *IN VIVO* MODEL OF EARLY-STAGE PARKINSON'S DISEASE INDUCED WITH THE ENDOGENOUS NEUROTOXIN AMINOCHROME TO STUDY THE NEUROPROTECTIVE EFFECT OF NICOTINE

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Introduction: The clinical diagnosis of Parkinson's disease (PD) is based on the presence of motor signs, such as bradykinesia, rigidity and resting tremor, which occur in the intermediate stage of the disease. However, the study of the prodromal phase of PD is of great interest to the scientific community, aiming to understand the onset of motor changes. In this phase, motor signs already exist, but are difficult to diagnose. Studies have shown that the criteria for diagnosing PD in the prodromal phase should include clinical motor markers. Thus, the development of a prodromal model of PD is of great relevance for the investigation of neuroprotective mechanisms of compounds that are related to the prevention of dopaminergic degeneration, such as nicotine. **Objective:** to evaluate behavioural changes associated with the early phase of Parkinson's disease and, in this, to study the neuroprotective effect of pulsatile intranasal administration of nicotine. **Methods:** Male Wistar rats weighing an average of 270-300 grams were randomly assigned to control (CTR), aminochrome (AMI), nicotine 1mg/kg (NIC1), nicotine 2mg/kg (NIC2), aminochrome + nicotine 1mg/kg (AMI+NIC1) and aminochrome + nicotine 2mg/kg (AMI+NIC2) groups to assess motor and exploratory activity and anxiety-like behavior. The entire procedure was approved by CEUA ICS protocol no. 5644140923. **Results:** Preliminary results showed that animals in the aminochrome group presented reduced exploratory behaviour and anxiety-like behaviour in the open field test compared to the control group, and that treatment with nicotine prevented these changes. **Conclusion:** Thus, striatal injection of aminochrome generates motor and emotional changes related to the prodromal phase of PD at day 25th after stereotaxic surgery, which is prevented by pulsatile intranasal nicotine treatment. **Acknowledgements:** FAPESB; CNPq.

Keywords: Aminochrome, nicotine, neuroprotection.

NARINGENIN AND ITS DIPRENYLATED SYNTHETIC DERIVATIVE MODULATE ASTROCYTE REACTIVITY AND ARE NEUROPROTECTIVE

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Introduction: Neurodegenerative diseases (NDDs) such as Alzheimer's, multiple sclerosis and Parkinson's share the exacerbation of glial activity, with release of inflammatory factors and reactive oxygen species (ROS), promoting neurodegeneration. Flavonoid naringenin and its prenylated derivatives demonstrate high lipophilicity and antioxidant effects in glial cell cultures. **Objectives:** To evaluate the effects of naringenin and its diprenylated synthetic derivative on astrocyte reactivity and neuroprotection. **Methods:** The toxicity of naringenin and its derivative 7,4-O-diprenylnaringenin was tested in neuronal PC12 cells (1-100 µM) using MTT and propidium iodide assays after 12 or 24 h. Primary cortical astrocytes from neonatal Wistar rats (P0-2) were stimulated with LPS (1 µg/mL/24 h) and/or treated with the compounds (10 µM), and astrocytic reactivity was analysed by immunofluorescence for GFAP and the redox state by the 2'-7'-Dichlorodihydrofluorescein diacetate (DCFH-DA) assay. Neuroprotective effects were assessed in PC12 cells exposed to astrocyte-conditioned medium in different conditions. **Results and Conclusion:** Naringenin and its synthetic derivatives were not toxic to PC12 cells and reduced astrocytic reactivity, as demonstrated by reduced GFAP expression and modulation of the LPS-induced phenotype, also reducing the production of ROS. Flavonoid-treated astrocyte-conditioned medium protected PC12 cells from toxicity, unlike the medium from LPS-stimulated astrocytes. Among the compounds, 7,4-O-diprenylnaringenin showed the strongest neuroprotective effect. These results emphasise the potential of naringenin and its derivatives as modulators of neuroinflammation and neuroprotective agents. **Acknowledgements:** CNPq, CAPES.

Keywords: naringenin; prenylated flavonoids; astrocytes; antioxidants.

RUTIN POTENTIATES THE ACTION OF TEMOZOLOMIDE IN GLIOBLASTOMA MICROTUMORS BY REDUCING CELL VIABILITY AND MIGRATION, REGULATING STAT3 AND PI3K/AKT PATHWAYS, AND DECREASING ROS LEVELS

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Introduction: Glioblastoma (GBM) is the most aggressive primary neoplasm of the central nervous system, with high cellular heterogeneity and chemoresistance to treatments including temozolomide (TMZ). Three-dimensional (3D) models, such as microtumors, better simulate the tumour microenvironment and are essential for screening new therapies. Rutin, a flavonoid with antioxidant and antitumor properties, has been demonstrated in 2D cultures but remains underexplored in 3D models combined with TMZ. **Objective:** In this study, we evaluated the effects of rutin alone or combined with TMZ on growth, viability, and redox state in GBM microtumors. **Methods:** For the tumorigenicity assay, GBM cells of the GL15 and U343 cell lines were plated in agarose molds and exposed on the same day to rutin (5–30µM), TMZ (500–1000µM), or combination, and analyzed after 72 h. Morphology was monitored by phase contrast microscopy, and viability was assessed by fluorescence with propidium iodide and DiOC18. ROS levels were quantified by fluorescence using DCFH-DA. For migration and signalling pathways, GL15 and U343 microtumors were cultured for seven days for stabilisation and exposed on the 7th day. Migration was evaluated in stable spheroids cultured on adherent plates for 72 h. Western Blotting analysed STAT3 and PI3K/AKT pathways after 48 h of treatment. **Results:** The cell viability in GBM microtumor decreased in a concentration-dependent manner after both TMZ and Rutin treatment, with a synergistic effect for TMZ (500 µM) + Rutin (15 µM). Migration was significantly inhibited with rutin alone (15 µM) or in combination. Treatment with TMZ alone induced an increase in ROS levels, while rutin alone and the combination with TMZ reduced these levels. Combined TMZ + Rutin exposure also decreased the expression of STAT3 and PI3K/AKT in GL15 and U343 spheroids. **Conclusion:** Rutin exerts multifaceted antitumor action in a 3D GBM model, reducing viability, migration and ROS, effects associated with modulation of STAT3 and PI3K/AKT signalling, standing out as a potential adjuvant in combined therapies. **Acknowledges:** CNPq and FAPESB.

Keywords: Glioblastoma; rutin; spheroids.

DIAGNOSIS OF PROGRESSIVE SUPRANUCLEAR PALSY (PSP): A SYSTEMATIC REVIEW

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Introduction: Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder first described in 1964, characterised by heterogeneous degeneration affecting the brainstem, basal ganglia, and cerebellum. The classic phenotype, Richardson's syndrome (PSP-RS), presents with vertical gaze palsy, postural instability, and cognitive decline. However, atypical phenotypes like PSP-Parkinsonism (PSP-P) and PSP-Frontotemporal Dementia (PSP-FTD) often mimic other neurodegenerative diseases, leading to misdiagnosis and delayed treatment. In 1996, NINDS established the first PSP diagnostic criteria, classifying patients as "Probable" or "Possible" PSP but excluding atypical phenotypes. The 2017 MDS-PSP criteria expanded these, incorporating akinesia and cognitive dysfunction to cover diverse phenotypes. However, its reliance on postural instability still biases diagnoses toward classic PSP-RS, underrepresenting variants. Both systems face limitations in capturing PSP's full clinical spectrum. **Objective:** This systematic review aims to identify the main challenges in the clinical diagnosis of PSP, focusing on differentiating its phenotypes (PSP-RS, PSP-P, and PSP-FTD) and evaluating the accuracy of current diagnostic criteria. **Methods:** The review will follow PRISMA 2020 guidelines. Searches will be conducted in PubMed, LILACS, and Scopus using descriptors such as "Progressive Supranuclear Palsy," "PSP-RS," "PSP-P," "PSP-FTD," and "diagnostic criteria." Inclusion criteria comprise original articles in Portuguese, English, or Spanish, while review articles will be excluded. Data extraction will include study characteristics, clinical features of PSP phenotypes, and diagnostic criteria. Quality assessment will be performed using the Joanna Briggs Institute checklist. **Expected Results:** This systematic review of PSP diagnostic criteria aims to identify gaps contributing to frequent misdiagnoses, supporting improved early detection in clinical practice and research to enhance patient prognosis. **Acknowledgements:** This study was supported by the Escola Bahiana de Medicina e Saúde Pública.

Keywords: Progressive Supranuclear Palsy; Diagnosis; Neurodegenerative Diseases.

PROSPECTION OF NEUROPROTECTIVE AND ANTI-INFLAMMATORY OF THE FLAVONOID CHRYSIN AND ITS SYNTHETIC DERIVATIVES IN IN VITRO MODELS OF NEUROINFLAMMATION ASSOCIATED WITH MULTIPLE SCLEROSIS

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Introduction: Multiple sclerosis (MS) is an autoimmune, demyelinating and progressive disease affecting the central nervous system (CNS), leading to permanent brain and spinal cord lesions. Neuroinflammation is a chronic inflammatory response frequently associated with neurodegenerative diseases such as MS. Current treatments are mainly based on immunomodulators, which, although they reduce inflammatory activity, do not prevent the progression of neural damage nor promote remyelination of affected axons. Natural flavonoids have attracted attention due to their anti-inflammatory, antioxidant and neuroprotective properties. **Objective:** This study aimed to evaluate the neuroprotective and anti-inflammatory effects of chrysin and its synthetic methoxylated derivatives in in vitro models of neuroinflammation. **Methodology:** The cytotoxicity of chrysin and its derivatives (1–100 µM) was evaluated in PC12 neural cell line cultures and in primary cultures of cortical astrocytes from Wistar rats. To assess the neuroprotective action of these flavonoids, differentiated SH-SY5Y neuronal cells were exposed to inflammatory damage induced by lipopolysaccharide (LPS, 5 µg/mL) and then treated or not with the compounds at a concentration of 10 µM for 24 hours. **Results:** It was observed that chrysin and its monomethoxylated, dimethoxylated, and iodinated dimethoxylated derivatives did not affect the viability of PC12 cells; only chrysin itself showed toxicity toward astrocytes at the highest concentrations tested (50–100 µM). Os flavonoides at a 10 µM concentration demonstrated a neuroprotective effect against LPS-induced damage in SH-SY5Y cells. These preliminary results indicate that among the compounds tested, the methoxylated chrysin molecule exhibited better protective effects and lower toxicity, encouraging further studies to characterise, in more complex models such as primary cerebellar tissue cultures, the potential of these compounds as candidate adjuvant biopharmaceuticals for the treatment of multiple sclerosis. Ongoing studies aim to characterise the inflammatory profile of glial cells exposed to the compounds and to evaluate their promyelinating capacity in cultures of mouse cerebellar neurons.

Keywords: chrysin, methoxylated flavonoid, neuroinflammation.

STUDY OF SOLID TUMOR GROWTH THROUGH MATHEMATICAL MODELS WITH FRACTIONAL DERIVATIVES AND GENERALIZED FUNCTIONS

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Introduction: This work adopts an approach to study the growth of solid tumours using mathematical models of differential equations, specifically focusing on population growth models. **Methods:** By incorporating fractional derivatives and generalised functions, the models aim to enhance the representation of tumour growth dynamics, offering a more flexible and accurate depiction compared to traditional models, also adjusting to real tumour data. The inclusion of these mathematical elements addresses the limitations of conventional approaches, providing a better understanding of the underlying biological processes. We provide a systematic compilation of previous models from the literature, establishing a one-to-one generalisation of those models with ordinary derivatives to those with fractional derivatives. Furthermore, we organise the models rewritten with q-functions, providing a comprehensive framework for analysing tumour growth. **Results:** Starting from the most general model, which corresponds to the Tsoularis-Wallace model, we demonstrate how all other models can be derived, showcasing the versatility of our approach. In addition, we perform model fitting using experimental in vitro data of glioblastoma growth cultivated in the LABNQ-ICS UFBA, exposing the models to a real context. We have shown that, using those experimental in vitro data for 50 initial cells, the Tsoularis-Wallace model promotes the best fitting of data, reinforcing the importance of considering also deformed functions for better description of tumour growth. **Conclusions:** The developed framework allows a systematic comparison between tumour growth models based on ordinary and fractional derivatives, as well as based on q-deformations. The analysis supports the inclusion of generalised mathematical elements in the study of tumour growth and provides a basis for further investigations using real data.

Keywords: Glioblastoma, Tumoral Growth Models, Fittings of Experimental Data.

ASSESSMENT OF PHENOTYPIC CHANGES AND REACTIVE ASTROGLIOSIS IN HUMAN IPSC-DERIVED ASTROCYTES FROM INDIVIDUALS WITH AUTISM SPECTRUM DISORDER

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Introduction: Astrocytes are essential for maintaining central nervous system (CNS) homeostasis, and their dysfunction has been implicated in autism spectrum disorder (ASD). Genetic, epigenetic, and environmental factors in ASD may influence astrocytic responses to inflammation, triggering reactive astrogliosis, a process involving morphological changes, altered gene expression, and cytokine release. However, phenotypic alterations in ASD astrocytes remain poorly understood. **Objectives:** To investigate reactive astrogliosis in human iPSC-derived astrocytes from ASD patients compared to healthy controls by evaluating astrocytic markers, cytokine expression, and morphology. **Methods:** Astrocytes were differentiated from iPSCs via a neural stem cell stage and cultured in astrocyte-inducing medium for 3 weeks, followed by four additional weeks for maturation. Mature astrocytes were serum-deprived and treated with TNF-α to induce reactive astrogliosis. Astrocytic identity and maturation were assessed by immunocytochemistry for GFAP and Vimentin, respectively. Expression of IL1B, TNFα, IL10, IL6, and BDNF was analysed by qPCR. **Results:** iPSCs from ASD patients and controls differentiated successfully into astrocytes expressing classical markers. ASD astrocytes showed increased Vimentin expression, suggesting lower maturation. Cytokine analysis revealed distinct profiles in ASD astrocytes, including altered IL1B, TNFα, IL10, IL6, and BDNF expression. **Conclusion:** ASD astrocytes exhibit altered responses to inflammatory stimuli, indicating dysregulated reactive astrogliosis and maturation. These differences may contribute to ASD pathophysiology. **Acknowledgements:** CAPES, Fiocruz and FAPESB.

Keywords: Astrocytes, Autism Spectrum Disorder, Reactive Gliosis.

LIPOSOMES AS A DELIVERY SYSTEM FOR RUTIN IN THE TREATMENT OF GLIOBLASTOMA MULTIFORME

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Introduction: Glioblastoma multiforme (GBM) is one of the most aggressive brain tumours, with high recurrence rates, poor survival, and limited therapeutic efficacy, largely due to the presence of the blood–brain barrier (BBB). Nanocarriers have emerged as a promising strategy, enabling controlled drug release, dose reduction, and targeted delivery to specific tissues, which may enhance cellular uptake and therapeutic efficacy, particularly in hard-to-reach organs. Concurrently, there is growing interest in natural compounds in oncology. Rutin, a plant-derived flavonoid with antioxidant, anti-inflammatory, and antiproliferative properties, has shown promise in GBM treatment. However, its low bioavailability limits clinical application. Combining these approaches offers an innovative and promising alternative to enhance GBM treatment by overcoming the limitations of conventional therapies. **Objectives:** In this context, the present study aimed to develop and characterise liposomes for rutin delivery in the treatment of glioblastoma multiforme. **Methods:** Liposomes were prepared using the ethanol injection method. The resulting liposomes were characterised in terms of particle size, polydispersity index (PDI), pH, and surface charge. **Results:** The developed liposomes showed an average size of 98.48 nm ± 22.0 nm, PDI of 0.229 ± 0.05, pH 5.45 ± 0.24, and zeta potential of -5.4 mV ± 2.0. These values indicate a suitable size and PDI, which are important for facilitating BBB permeation. The slightly negative zeta potential suggests good colloidal stability and reduced recognition by the immune system, while the acidic pH may assist in the intracellular release of rutin. **Conclusion:** Further studies will be conducted to encapsulate rutin and evaluate its therapeutic potential in the developed system. The results obtained so far indicate that the liposomes exhibit physicochemical properties compatible with brain delivery, representing a promising and innovative strategy for GBM treatment, with the potential for increased efficacy and reduced systemic toxicity compared to conventional chemotherapy. **Support:** CNPq

Keywords: liposomes; flavonoids; Glioblastoma multiforme.

DEVELOPMENT OF PEGYLATED NANOLIPOSOMES CONTAINING RUTIN FOR THE TREATMENT OF GLIOBLASTOMAS

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Introduction: Drug delivery to the brain poses a challenge, especially in the treatment of central nervous system (CNS) diseases. Glioblastoma is the most common and most lethal brain tumour. Recently, rutin, a flavonoid found in plants, has demonstrated promising neuroprotective and antitumor properties. However, rutin has low bioavailability, primarily due to its low aqueous solubility and limited membrane permeability. These factors hinder its biological effects in vivo. Rutin encapsulation in controlled-release systems, such as liposomes, may be an alternative to improve the efficacy of glioblastoma treatment. **Objective:** In this context, the objective of this work was to develop and characterise pegylated nanoliposomes as a rutin carrier for the treatment of glioblastoma (GBM). **Methods:** The formulations were prepared by the dry lipid film hydration method, followed by homogenization in a probe sonicator. The samples were characterised by size and size distribution by dynamic laser light scattering, surface charge by zeta potential, pH, thermal profile by differential scanning calorimetry (DSC), and particle surface evaluation by infrared (IR) spectroscopy. **Results:** The pegylated liposomes presented a monomodal distribution with average diameters of 100 nm and PDI < 0.25. The incorporation of rutin into the pegylated formulations altered the surface charge of the liposomes, demonstrating that the incorporation altered the organisation of the lipid bilayer, resulting in changes in surface charges. IR analyses revealed no presence of rutin in the aqueous medium or on the liposomal surface. Thermal profiles indicated that the lipid bilayers remain in the fluid phase at 36-37.5 °C, favourable for biological applications, without any degradation events up to 60 °C. **Conclusion**: The results obtained showed that stable pegylated nanoliposomes containing rutin were produced. Encapsulation efficiency analyses are ongoing, as is the functionalization of the liposomes with aptamers on the surface, contributing to innovative approaches in neuro-oncology. **Support:** CNPq and Singular Pharma.

Keywords: Liposomes; Flavonoids; Cancer.

SYNAPTIC AND GLIAL CHARACTERIZATION OF DORSAL COCHLEAR NUCLEUS (DCN) DURING PRE- AND POSTHEARING DEVELOPMENTAL PERIODS

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Introduction: Astrocytes and microglial cells are essential for brain development, as they regulate and orchestrate synaptic refinement. The Dorsal Cochlear Nucleus (DCN), one of the first central stations in the auditory pathway, exhibits a layered, cerebellar-like organisation with specific neurons connected to the auditory nerve. In mice, hearing onset occurs postnatally, and sensory sound experience impacts glial cells within the auditory circuit. **Objective:** Thus, we spatially and temporally characterised neurons, astrocytes, and microglial cells in the DCN during auditory development. Furthermore, we performed a layer-specific analysis of pre- and postsynaptic glutamatergic proteins to identify local DCN-layer connections throughout auditory development. **Methods:** To assess the auditory threshold, we performed the Auditory Brainstem Response (ABR) test on C57BL mice at P10-P14. We used immunofluorescence to characterise astrocytes (GFAP and SOX9), microglia (Iba-1), and neurons (NeuN) both before (P11) and after (P21) hearing onset. Additionally, we investigated the spatio-temporal profiling of pre- and postsynaptic glutamatergic proteins (GluA1, GluA2, VGlut1, VGlut2, and PSD-95). **Results:** We found that the auditory threshold decreased at P14, coinciding with the opening of the external auditory canal. While GFAP expression was not affected, the percentage of $SOX9^+$ cells decreased after hearing onset. Microglial cells were present across all layers of the DCN during early developmental stages but showed a reduction in density following the onset of hearing. NeuN expression shifted after the onset of hearing, suggesting that sound experience might aid in neural maturation. Pre- and postsynaptic glutamatergic proteins also showed distinct expression patterns after hearing onset, overlapping with astrocytes and microglia in specific layers and developmental periods. **Conclusion:** We suggest that sensory sound experience influences neuronal maturation and that bidirectional crosstalk with glial cells contributes to circuit refinement and maturation during auditory development in the DCN.

Keywords: Glial cells; Auditory system development; Synaptic refinement.

THE EFFECT OF THE RUTIN ON CELLULAR PLASTICITY IN NEURAL CULTURE MODELS

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Introduction: Neuroplasticity is the ability of the neural network to remodel itself into new functional synapses continually, and can be regulated by plant derivatives, such as flavonoids. Rutin is a flavonol and a potential therapeutic drug due to its in vitro and in vivo modulatory effect on cellular plasticity and neuroinflammation. Previous work has extensively utilised the PC12 cell line, derived from rat adrenal medulla pheochromocytoma, for in vitro research on drug cytotoxicity, neuroinflammation, and neuroplasticity. Another study model is that of the primary culture of cerebellar cells. The cerebellum is responsible for the perception and progression of sensory and motor skills, modulation of cognitive and emotional capacities, in addition to an atypical neurogenic niche. **Objectives:** Characterise the effect of rutin on morphogenesis, cellular plasticity and the anti-inflammatory processes in primary culture models of cerebellum and PC12 lineage. **Methods:** Cerebellar primary cultures were prepared from mice (P0-P3), and undifferentiated PC12 cells were treated with rutin at concentrations of 0.1, 0.5, 1, and 5 µM (PC12) and 0.1 and 1 µM (cerebellum). The MTT test determined cytotoxicity after 24h, 48h and 72h of treatment with rutin. The propidium iodide test analysed the neuroprotection potential after 12h (PC12) or 24h (cerebellum) of exposure to LPS 1µg/mL (cerebellum) or five µg/mL (PC12) and subsequently 24h of treatment with rutin. Cellular morphology was demonstrated by phase contrast microscopy, panoptic staining and immunofluorescence. **Results: Neither** culture showed a reduction in cell viability at any of the rutin concentrations tested. By phase contrast microscopy, it was observed that, in the PC12 cultures, the remaining adhered cells presented vacuolization and cytoplasmic retraction suggestive of stress as the concentration and time of exposure to rutin increased, while the cells of the cerebellum culture showed no changes in the extracellular medium or morphology in any rutin treatment group. In the cerebellum culture, morphologies suggestive of astrocytes were observed, in addition to neurons that grew predominantly grouped in dense islands. **Conclusion:** Cell viability by the propidium iodide test and morphological characterisation by immunofluorescence still need to be investigated. **Support:** CAPES, PPGIm (UFBA).

Keywords: neuroplasticity, neuroinflammation, rutin.

EVALUATION OF THE CYTOTOXIC AND IMMUNOMODULATORY PROPERTIES OF AGATHISFLAVONE IN ASTROCYTES AND MACROPHAGES UNDER ALZHEIMER'S DISEASE-ASSOCIATED INFLAMMATION

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Introduction: Alzheimer's disease (AD) has a multifactorial origin and is characterized by progressive Introduction: Alzheimer's disease (AD) has a multifactorial origin and is characterised by progressive cognitive decline and results from amyloid plaque deposition, neuroinflammation, and glial reactivity. The complex interplay between neurodegenerative, inflammatory, and oxidative processes in AD poses a major challenge for the development of effective therapeutic strategies. Flavonoids have been extensively investigated for their antioxidant and anti-inflammatory properties, showing significant therapeutic potential within these pathological contexts. **Objective:** This study aimed to identify the action of flavonoids on human astrocytes and peripheral immune cells under inflammatory stimuli to characterise the potential use as new adjuvant treatments for AD. **Methods:** THP1 differentiated macrophages and human iPSC-derived astrocytes were treated with agathisflavone (bis-apigenin), apigenin, or rutin (0.1 to 40 µM) for 24 h, and toxicity was determined by MTT assay. Also, human monocyte-derived macrophages, isolated from whole blood from healthy donors, were stimulated or not with LPS (1 µg/mL) + IFN-γ (100 UI/mL) and treated or not with flavonoids (1 and 5 µM). **Results:** Flavonoids weren't toxic in human macrophages and astrocytes at any concentration below 20 µM. In contrast, the one µM concentration increased the viability of macrophages and astrocytes, exhibiting a proliferative profile. Concentrations of 1 and 5 µM demonstrated cytoprotective effects against LPS and IFN-γ-induced damage in these cells. **Conclusion**: Our findings highlight the cytoprotective effect of flavonoids against inflammatory damage in human astrocytes and macrophages. These results support the determination of effective concentrations of flavonoids for preclinical assays aimed at treating astrocytes and macrophages derived from AD patients. **Support:**Fundação Maria Emília, CAPES and CNPq.

Key words: Neuroinflammation; flavonoids; Alzheimer's.

FLAVONOID RUTIN REDUCES INTESTINAL INFLAMMATION IN AN EXPERIMENTAL MODEL OF PARKINSON'S DISEASE

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Introduction: The enteric nervous system (ENS), a complex network of neurons and glial cells, is essential for maintaining intestinal homeostasis and is implicated in neurodegenerative diseases such as Parkinson's disease (PD). The gut-brain axis, modulated by gut microbiota (GM), is influenced by dietary compounds that can alter its composition. Despite advances in the understanding of PD pathophysiology, effective treatments remain limited, underscoring the need for novel therapeutic approaches. Among plant-derived compounds, the flavonoid rutin has shown significant antioxidant, anti-inflammatory, and neuroprotective properties in vivo. **Objective:** This study evaluated the effects of rutin on leukocyte infiltration, intestinal morphology, and GM composition in an experimental model of PD. **Methodology:** Adult male Wistar rats received a stereotaxic injection of 6-hydroxydopamine (6-OHDA) and were treated orally with rutin (10 mg/kg) for 14 days. Intestinal segments were analysed histomorphometrically, and faecal samples were assessed for the abundance of Firmicutes, Bacteroidetes, Prevotellacea, Enterobacteraceae, *Bifidobacterium* sp, and *Lactobacillus* sp. by PCR. **Results:** Rutin administration significantly reduced intraepithelial lymphocyte infiltration and goblet cell numbers in the ileum and colon and prevented hyperplasia of Paneth cells in the ileum. Importantly, GM composition remained unchanged following rutin treatment. These findings demonstrated that rutin reduces intestinal inflammation in PD models without altering gut microbiota composition, highlighting its potential as a therapeutic strategy.
Support: CNPq

Keywords: rutin, enteric nervous system, gut microbiota.

CYTOTOXICITY AND NEUROTROPHIC POTENTIAL OF *HYPERICUM PERFORATUM* EXTRACT IN PC12 CELLS

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Introduction: Hypericum perforatum L., commonly known as St. John's Wort, is a medicinal plant traditionally used in the treatment of depressive and anxiety disorders, due to the presence of bioactive compounds such as hyperforin, hypericin, and flavonoids, which exhibit neuroactive and anti-inflammatory properties. Among these compounds, hyperforin stands out for its ability to modulate neurotransmitter systems, making it a subject of growing interest in neuropharmacological research. **Objective:** This study aimed to evaluate the cytotoxicity of the ethanolic extract of Hypericum perforatum in PC12 cells, a neuroblastoma-derived cell line frequently used in neurobiological research. **Methods:** Initially, hyperforin was extracted by an immersion method and chemically characterised by high-performance liquid chromatography (HPLC), revealing absorbance peaks compatible with hyperforin presence. For cytotoxicity assessment, PC12 cells were exposed to increasing concentrations of the extract (0.1 to 200 µg/mL) for 24 hours. Cell viability was determined using the MTT colourimetric assay and morphological evaluation under phase-contrast microscopy. **Results:** The results demonstrated that concentrations between 10 and 25 µg/mL promoted increased metabolic activity and induced neuronal-like morphology with dendritic projections, whereas concentrations above 50 µg/mL led to morphological alterations consistent with apoptosis and a significant reduction in cell viability. **Conclusion:** Hypericum perforatum extract exerts a biphasic effect on PC12 cells, being cytotoxic at high concentrations and potentially neurotrophic at low doses, indicating the need for further studies to elucidate its mechanisms of action and safety in in vivo models.

Keywords: St. John's wort, PC12 cells, excitotoxicity, neurotrophic potential.

MODULATION OF CONNEXINS AND A-SYNUCLEIN PROPAGATION BY CAPE IN PARKINSON'S DISEASE MODELS: MOLECULAR INSIGHTS FROM IN VITRO

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Introduction: The intercellular propagation of α-synuclein aggregates is a critical feature in Parkinson's disease (PD). Connexins such as Cx43 and Cx32 are essential for glial communication and may influence protein transmission and neuroinflammatory processes. Caffeic acid phenethyl ester (CAPE), a bioactive propolis-derived compound, exhibits neuroprotective and anti-inflammatory effects through NF-κB inhibition and mitochondrial preservation. **Objective:** To investigate the effects of CAPE on connexin expression and α-synuclein propagation in cells. **Methods:** Human SH-SY5Y and N2a cells (wild-type and CRISPR-Cas9 knockout for Cx43/Cx32) were transfected with α-synuclein-GFP and treated with 6-OHDA and increasing concentrations of CAPE. Immunofluorescence, ELISA, and qPCR analysed expression of connexins, NF-κB, IL-1β, and α-synuclein. **Results:** CAPE increased Cx43/Cx32 expression and reduced the intercellular spread of α-synuclein. CAPE treatment also inhibited NF-κB nuclear translocation and reduced IL-1β and TNF-α levels. **Conclusion:** CAPE modulates connexin expression and mitigates α-synuclein propagation by suppressing neuroinflammatory signalling. These findings support its potential as a therapeutic agent in PD and related neurodegenerative diseases.

Keywords: connexins; α-synuclein; neuroinflammation.

EXPLORING THE EFFECTS OF CANNABIDIOL ON TEMPOROMANDIBULAR JOINT PAIN: CENTRAL AND PERIPHERAL INFLAMMATORY PATHWAYS IN A PRECLINICAL MODEL

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Introduction: Temporomandibular dysfunction (TMD) is a multifactorial pathological condition and a leading cause of non-odontogenic orofacial pain. Effective therapeutic strategies for TMD are crucial to enhance clinical management, alleviate pain, and mitigate the functional and emotional burdens associated with this condition. Moreover, advancing the understanding of its underlying mechanisms is essential for improving treatment outcomes. Cannabidiol (CBD) has gained attention as a promising therapeutic agent due to its multifaceted pharmacological properties, including analgesic, anti-inflammatory, anticonvulsant, anxiolytic, antidepressant, and antipsychotic effects. **Objectives:** This study aimed to evaluate the therapeutic potential of CBD in a preclinical model of temporomandibular joint (TMJ) inflammatory pain. **Methods:** Male Wistar Hannover rats were subjected to bilateral intra-articular injections of Complete Freund's Adjuvant (CFA) to induce persistent TMJ inflammation. CBD treatment (3, 10, or 30 mg/kg) was administered for seven consecutive days, starting 14 days post-CFA injection. Orofacial allodynia and hyperalgesia were assessed using the Von Frey and orofacial formalin tests. Pro- and anti-inflammatory cytokine levels were quantified in the TMJ, trigeminal ganglion (TG), and spinal trigeminal nucleus (Sp5c) using ELISA. Additionally, astrocyte and microglia activation in the Sp5c was evaluated through immunohistochemistry. **Results:** CBD demonstrated significant antinociceptive effects, with the 30 mg/kg dose effectively reducing mechanical allodynia and hyperalgesia. Moreover, CBD treatment suppressed pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, and IFN-γ) and upregulated the anti-inflammatory cytokine IL-10 in both the TG and Sp5c, highlighting its central and peripheral anti-inflammatory mechanisms. Immunohistochemical analysis further revealed attenuated astrocyte and microglial activation in the Sp5c following CBD administration. **Conclusions:** These findings underscore the potential of CBD as a therapeutic alternative for the management of chronic inflammatory pain in TMD, offering a foundation for developing safer and more effective approaches for orofacial pain conditions. **Support:** CAPES, CNPq and FAPESP

Keywords: Cannabidiol; Cytokines; Glia.

COMPARISON OF THE CYTOTOXICITY OF APIGENIN AND DERIVATIVES USING THE MTT ASSAY IN PC12 CELLS

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Introduction: Apigenin is a natural flavonoid found in various plants, such as chamomile, celery, and parsley, recognised for its antioxidant, anti-inflammatory, and cellular pathway-modulating properties associated with neuroprotection. Studies suggest that apigenin inhibits the entry of immune cells into the central nervous system (CNS) and prevents neuroinflammation by modulating leukocyte migration across the blood-brain barrier. Furthermore, apigenin has been shown to reduce iNOS expression and nitric oxide and prostaglandin E2 (PGE2) production in microglial cells and macrophages, reinforcing its therapeutic potential in neurodegenerative diseases. **Objectives:** The study aims to evaluate the cytotoxicity of apigenin (API) and its derivatives in the PC12 cell line. **Methods:** PC12 cells were cultured and treated with five concentrations (1, 10, 20, 50, and 100 µM) of apigenin and four derivatives: trimethoxylated apigenin, dimethoxylated apigenin C6, and iodinated trimethoxylated apigenin C8. After 24 hours of treatment, the cell viability assay was performed using the MTT method. **Results:** The analysis demonstrated that iodinated trimethoxylated apigenin C8 showed significantly lower cytotoxicity compared to apigenin and the other derivatives. While apigenin and the derivatives exhibited dose-dependent effects with possible reduction in cell viability, iodinated trimethoxylated apigenin C8 maintained cell viability at all concentrations tested, indicating low cytotoxicity in the MTT assay. **Conclusion:** The findings suggest that the introduction of specific chemical groups, such as in C8-iodinated trimethoxylated apigenin, can reduce toxicity without compromising biological activity, making it a promising candidate for future neuroprotective studies. However, further investigation is needed to elucidate the molecular mechanisms responsible for this difference in cytotoxicity and evaluate the therapeutic efficacy of these compounds. **Support:** CNPq, CAPES.

Keywords: Apigenin; cytotoxicity; neuroprotection.

INVESTIGATION OF PARVALBUMIN INTERNEURONS AND PERINEURONAL NETS IN BRAIN REGIONS ASSOCIATED WITH MOTOR AND COGNITIVE SIDE EFFECTS OF TYPICAL ANTIPSYCHOTICS

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Introduction: Parvalbumin-positive GABAergic interneurons (PVIs) form local inhibitory circuits and are regulated by perineuronal nets (PNNs), which support synaptic plasticity and neuronal stability. Disruptions in PVIs and PNNs have been associated with schizophrenia. Typical antipsychotics, such as haloperidol, alleviate positive symptoms but can induce tardive dyskinesia (TD), characterised by involuntary orofacial movements—vacuous chewing movements (VCMs) in rodents—and cognitive impairment. While the involvement of PVIs in other motor disorders is well established, their specific role, along with that of PNNs, in the pathophysiology of TD remains poorly understood. **Aims:** This study aimed to elucidate the role of PVIs and PNNs in the emergence of haloperidol-induced VCMs and cognitive impairments in rodents. **Methodology:** Male Swiss mice were treated for 21 days with haloperidol (3 mg/kg, s.c.) or clozapine (15 mg/kg, s.c.). Behavioural assessments were performed one day before treatment and on day 22. Evaluations included VCMs (quantified as mouth openings with or without tongue protrusion and mandibular tremors), memory performance via the novel object recognition (NOR) test, and locomotor activity. Following the last behavioural test, animals received an additional dose of the assigned drug and were euthanised 90 minutes later. Brains were collected for immunofluorescence analysis of PV/PNN and PV/FosB expression in the prefrontal cortex, motor cortex, dorsolateral striatum, and dorsal hippocampus. The study was approved by the Animal Use Ethics Committee (protocol no. 2023.1.669.58.4). **Results:** Our findings show that haloperidol induces VCMs and produces a marginal impairment in long-term memory ($p = 0.06$), without significantly affecting locomotor activity, suggesting a primarily cognitive rather than motor deficit. Immunofluorescence showed that neither antipsychotic altered PV/PNNs expression in the brain regions examined. Additionally, colocalization between PV/FosB was not different across groups. **Conclusion:** Our results suggest that, under the conditions tested, haloperidol-induced behavioural alterations are not associated with changes in PV/PNNs expression. **Support:** CNPq.

Keywords: parvalbumin, perineuronal nets, haloperidol.

COMBINATION OF TEMOZOLOMIDE WITH APTAMER-9 POTENTIALIZES TOXICITY TO HUMAN GLIOBLASTOMA CELLS

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Glioblastoma (GBM) is the most common and aggressive primary malignant neoplasm of the CNS and represents a significant clinical problem in which the median survival of patients is 15 months after diagnosis, and current treatments are not effective. Aptamers are selected oligonucleotides capable of recognising protein epitopes with great specificity and have a promising potential in diagnostic and therapeutic applications, due to their high specificity, low molecular weight, low immunogenicity and ease of production/manipulation. **Objective**: This study investigated the effects of DNA aptamers alone and combined with the chemotherapy drug temozolomide (TMZ) on the viability of chemoresistant human GBM cells, given the development of new adjuvant therapies. **Methods:** Human GL15 GBM cells were treated with aptamer 9 (Apt 9) at concentrations of 0.001 to 5 µM, or combinations of Apt 9 (0.1 µM or one µM) with TMZ (500 µM). After 48 hours of treatment, cell viability was assessed using the WST-1 assay. In parallel, morphological analyses were performed by phase contrast microscopy to assess cell density and integrity. **Results:** Treatment with Apt 9 alone, at a concentration of 5 µM, resulted in an approximately 24% reduction in cell viability compared to the control. The combination of Apt 9 (1 µM) with TMZ (500 µM) promoted a significant decrease in viability, both compared to the control and to that treated with TMZ alone. Morphological analyses confirmed the effects on cell viability, with lower density and cellular alterations in the conditions that presented a greater cytotoxic effect. **Conclusion:** Apt 9 demonstrated potential as an adjuvant agent in GBM therapy, enhancing the cytotoxic effect of TMZ on GBM cells. Further studies will be conducted to elucidate mechanisms of action and the effects on tumorigenicity. **Support:** FAPESB and CNPq.

Keywords: glioblastoma, aptamer, chemotherapy.

QUERCETIN DERIVATIVES AS POTENTIAL THERAPEUTIC CANDIDATES FOR GLIOBLASTOMA

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Introduction: Glioblastoma (GBM) is the most common and lethal primary brain tumour in adults. Current therapies are palliative, and median survival remains under 15 months. Quercetin (Q), a natural flavonoid, presents antitumor and anti-inflammatory effects but has poor solubility, stability, and bioavailability. Structural modifications like metal complexation and acetylation may improve pharmacological performance. **Objectives:** To enhance quercetin's properties via chemical modification and evaluate the biological activity of its metal complexes and acetylated derivative in GBM models. **Methods:** Q derivatives (QCu, QZn, QMg, Q5) were synthesised and characterised. Cytotoxicity was assessed in U87 and U251 cells using RealTime-Glo MT®. Selectivity was tested in primary rat astrocytes. Migration was evaluated by wound healing. HPLC analysed the kynurenine pathway, and docking studies were performed using TDO (PDB: 5TIA). **Results:** All derivatives showed lower IC_{50} than Q in GBM cells. Q5 was the most potent (36.81 µM in U251). Astrocytes remained viable, though Q and Q5 induced morphological changes and GFAP expression. Q and Q5 inhibited cell migration, while QCu and QZn increased motility. All compounds reduced KYN and preserved TRP under IFN-γ stimulation. Q5 also lowered 3-HAA and KYNA levels. Docking analysis indicated stronger TDO binding than tryptophan, especially for Q5 in chains B and C. **Conclusion:** Quercetin derivatives, particularly Q5, showed enhanced cytotoxicity, antimigratory effects, and immunometabolic modulation, supporting their therapeutic potential in GBM. **Acknowledgements**: This work was supported by CAPES, FAPESB and CNPq.

Keywords: high-grade glioma; flavonoid derivatives; tryptophan metabolism.

STUDY OF THE MOTOR EFFECT OF DOXYCYCLINE AND ITS DERIVATIVE WITHOUT ANTIBIOTIC ACTION, DDOX, IN HEMIPARKINSONIAN ANIMALS INDUCED WITH 6-HYDROXYDOPAMINE

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Introduction: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, with treatments limited to symptomatic relief and declining efficacy over time. Tetracyclines exhibit neuroprotective, antioxidant, and anti-inflammatory properties, making them promising therapeutic candidates. However, chronic use raises concerns about antibiotic resistance and gut microbiota imbalance, highlighting the need for non-antimicrobial derivatives with similar effects. **Objective:** This study aimed to evaluate the motor effects of doxycycline (DOX) and its derivative without antibiotic action, DDOX, in hemiparkinsonian animals induced with 6-hydroxydopamine (6-OHDA). **Methods**: *Wistar-Hannover* rats (CEP-FORP-USP 2020.1.473.58.0) of both sexes underwent stereotaxic surgery for unilateral infusion of 6-hydroxydopamine. Fifteen days after injury, animals were assessed for akinesia and allocated into experimental groups with comparable lesion severity for 14-day treatments. Brain and plasma samples were collected for analysis by immunohistochemistry, ELISA, and/or high-performance liquid chromatography. **Results:** 6-OHDA induced a complete lesion of dopaminergic neurons in the substantia nigra compacta and corpus striatum. Male animals showed motor impairment in all tests used, while females only in the akinesia test. DOX reversed akinesia in both sexes, with effects observed on the 7th day in females and 14th day in males, as did DDOX. DOX and DDOX promoted an improvement in motor performance in males in the rotarod test. These effects were similar to those of L-DOPA in both sexes. 6-OHDA alone did not alter plasma levels of TNF-α and IL-10 cytokines. L-DOPA increased the number of reactive astrocytes, which was not altered by treatment with DOX, and microglia. L-DOPA and DOX in males increased dopamine levels in the ipsilateral striatum. **Conclusion:** The results with the derivative confirm that the motor benefit is independent of antimicrobial activity. These findings support the potential of DOX derivatives as safe and viable alternatives for long-term therapeutic strategies targeting motor symptoms in PD. **Acknowledgements:** CAPES, FAPESP, CNPQ and FMRP.

Keywords: Neurodegeneration; Parkinson's disease; Tetracyclines.

THE APOCAROTENOID 9-CIS-BIXIN PURIFIED FROM *BIXA ORELLANA* L. SEEDS EXERTS ANTIGLIOMA ACTIVITY IN VITRO ASTROCYTES

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Introduction: Glioblastoma is the most common and lethal cerebral tumour of glial origin, and no advances in therapeutics have been able to assure a significant increase in the median survival of patients. Therefore, it is necessary to research new alternatives to improve therapeutic efficacy, including improving patients' immune response and reducing side effects. Bixa orellana L. is a tropical plant, popularly known as "annatto" and "urucum" in Brazil, with medicinal properties already described, highlighting the anti-inflammatory effects associated with antioxidant activity, and attributed mainly to its carotenoids bixin and cis-bixin in vitro. Selective antitumoral effects of bixin against myeloma cells were described, as well as its properties inhibiting inflammation and oxidative stress in a model of neuroinflammation in vivo. **Objective:** This study evaluated the toxicity of 9-cis-bixin, purified from B. orellana L. seeds, to glioma cells and the capacity to modulate the reactivity of astrocytes and immune effector cells in the central nervous system. **Methods:** For this human (U251) and murine (C6) glioma cell cultures, cortical murine astrocyte cultures and C6/astrocytes co-cultures were treated with 9-cis-bixin (0.1-100 µM). After 24 to 72 h treatments, cell viability was determined by MTT test, cell cycle and apoptosis/necrosis by FACS, and cell morphology by phase contrast microscopy and immunocytochemistry. To characterise the inflammatory profile, the ELISA assay for IL-10 and TNFα was performed. **Results:** 9-cis-bixin killed selectively C6 and U251 glioma cells in a dose- and time-dependent manner, with IC50 values of 56 µM and 55 µM, respectively, but did not affect the viability of astrocytes. Morphological degeneration was observed in treated glioma cells but not in murine primary culture astrocytes. 9-cis-bixin at IC50 affected the distribution of glioma cells in the cycle phases (G1, S, G2) and, after 72 h cells, glioma cells also showed a profile of late apoptosis and necrosis (SE), with greater sensitivity of C6 cells, and no effects on normal astrocytes. In astrocyte cultures, 9-cis-bixin at half IC50 (25.30 µM) did not affect the level of pro-inflammatory cytokine TNFα but increased levels of the regulatory cytokine IL-10. Moreover, in C6/astrocyte co-cultures, the carotenoid (55 µM) induced increased GFAP expression in astrocytes, indicative of reactivity and decreased the proportion of DIP-labelled C6 cells, reinforcing its selective toxicity for tumour cells and the capacity to modulate astrocyte response. **Conclusion:** Mechanisms of the control of astrocyte reactivity that can impact the anti-glioma activity are under investigation. **Support:** CNPq

Keywords: bixin, astrocyte, glioblastoma, immunomodulatory

IMPACT OF ASTROCYTE METABOLISM OF MONOCROTALINE PYRROL ON VIABILITY OF HIPOCAMPAL NEURONS

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Introduction: Monocrotaline (MCT) is a pyrrolizidine alkaloid (PA) and is the most important plant toxin affecting animals and humans. Studies have characterised the presence of PAs in plants and in human and animal foods. MCT has well-characterised hepatotoxic and pneumotoxic effects attributed to its active pyrrole metabolites; however, metabolites of MCT and other PAs have already been found and measured in the brain of experimentally intoxicated rats. Astrocytes, together with brain endothelial cells (BECs), form the blood–brain barrier (BBB), which regulates the entry of substances into the brain, and confers selectivity. Our previous in vitro studies showed that MCT and its metabolite DHMCT induce astrocytic reactivity and toxicity to neurons, attributed to astrocyte P450 metabolism to reactive metabolites. **Objective:** In the present study, we evaluated the effects of MCT exposure to astrocytes on the viability of hippocampal neurons in vitro. **Methods:** MCT was purified from *Crotalaria retusa* seeds. Astrocytes obtained from newborn Wistar rats (P0-2) were exposed to MCT (1-500 µM for 24 h. HP22 hippocampal neurons were then exposed directly to MCT (1-500 µM) or exposed to the conditioned medium (secretome) derived from astrocytes previously treated with MCT (100–500 µM, CMAMCT). Cell viability was evaluated by the WST assay, and cell morphology by phase contrast microscopy. **Results:** MCT was not toxic to AST at the concentrations adopted and induced a concentration-dependent increase in cell dehydrogenase after 24 h of treatment; the astrocytes exposed to the highest MCT concentrations (100–500 µM) acquired a more reactive phenotype, suggesting resistance to damage and drug metabolism. MCT was not toxic to HP22 neurons after 24 h of treatment. However, exposure of HP22 neurons to the CMAMCT for 24 h induced changes in cell morphology and vacuolization, characterising toxicity. **Conclusion:** in this study, we observed that products of MCT metabolism by astrocytes can be toxic to hippocampal neurons. Further studies will be conducted to elucidate the mechanisms of MCT metabolism in astrocytes in association with brain endothelial cells and their impacts on neuronal viability. **Support:** CNPq.

Keywords: monocrotalina; astrocyte metabolism; neurotoxicity.

INTEGRATED IN SILICO AND IN VITRO APPROACHES FOR THE IDENTIFICATION OF ARYL HYDROCARBON RECEPTOR ANTAGONISTS

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Introduction: The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor of the bHLH-PAS Family that participates in oncogenic processes. Natural products have been studied as potential AHR modulators. **Objective:** This study aimed to identify novel AHR antagonists from natural products through *in silico* and *in vitro* approaches. **Methods:** Two different search methods were employed: 1) *In vitro* and structure-based virtual screening; 2) Hierarchical virtual screening. The EROD activity assay was used to evaluate the modulation of AHR activity by flavonoid naringenin in human breast cancer cells (MCF7). Structural-based virtual screening was guided by key molecular interactions observed between known AHR antagonists and critical residues within the AHR ligand-binding domain. Hierarchical virtual screening was used to select molecules of natural origin with stereoelectronic characteristics for AHR. **Results and Discussion:** The *in vitro assay* and structure-based virtual screening demonstrate that flavonoid naringenin exhibits the ability to inhibit AHR activity in a dose-dependent manner in the presence of the agonist TCDD. Simulations of hierarchical virtual screening showed that coumarin auraptene exhibited high binding affinity (score: -9.52) and interacted with key AHR residues: Gln383, Phe295, Pro297, Phe324, Ala367 and Val381. **Conclusion:** The protocol allowed the identification of the molecules auraptene and naringenin, with important antagonist activity. **Support:** OpenEye Scientific and CAPES.

Keywords: Cancer, natural products, aryl hydrocarbon receptor.

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