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Sulfur-containing compounds are an underexplored class of molecules in bioinorganic chemistry, with most works of research focused on nitrogen and oxygen-containing molecules. The presence of sulfur in drugs is promising because of its larger atomic volume, lower electronegativity and higher polarizability, which allows it to interact in unique ways with biomolecules and affect specific cell processes. Molecules containing both sulfur and nitrogen are highly versatile and particularly attractive due to the presence of hard and soft donors, enabling the coordination to a wide variety of metal centers in diverse binding modes. Recent studies depict stable S,N-coordinated metal complexes with interesting anticancer properties. In this work, we describe the synthesis and preliminary in vitro studies of an adamantane-derived Schiff Base containing nitrogen and sulfur with potential antitumor properties. Schiff Bases are prepared from the condensation between a carbonylic compound and an amine. Here, the amine in question was amantadine, which belongs to the class of aminoadamantanes. These compounds have rigid cage-shaped structures that promote drug stability and their further distribution in drug plasma, by shielding adjacent functional groups from metabolic cleavage. Aminoadamantane Schiff bases are particularly envisaged for drug development, with reported activities over some types of tumor, and biological activities have been linked to their interaction with biomolecules such as DNA, peptides and enzymes. The Schiff base of interest was prepared from the reaction between amantadine and 2-tiophencarboxaldexyde in methanol, conducted under reflux for 3 hours, leading to the formation of a white precipitate. The solid was washed with distilled water and dried in a desiccator over P2O5. Yield 59%. Elemental analysis led to the molecular formula C15H19NS. Preliminary studies were carried out to assess the cytotoxicity of the compounds. In this assay, Vero E6 cells (kidney tissue derived from a normal, adult African green monkey) were treated with the Schiff base at the concentrations of 50, 10 and 2 μM. Then, cell viability was assessed by MTT assay 72h later. DMSO was used as untreated control. Analyzing the effects on viability, we found that cell viability was 98.5% after treatment with the Schiff base even at the highest concentration. As the preliminary in vitro studies indicate that this compound is not toxic for normal cells, further biologic studies with the novel Schiff base are envisaged to evaluate its activity over cancer cells.

Keywords: Schiff bases, Aminoadamantanes, Amantadine, Cell proliferation, MTT assay.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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THE WASHOUT PHENOMENON AS A THERANOSTIC CHALLENGE: A KINETIC ANALYSIS OF 18F-PSMA UPTAKE IN ADVANCED HEPATOCELLULAR CARCINOMA

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Introduction/Justification: Hepatocellular Carcinoma (HCC) is a highly lethal neoplasm characterized by intense angiogenesis. While Prostate-Specific Membrane Antigen (PSMA) was originally associated with prostate cancer, it is extensively overexpressed in the endothelial cells of the tumor neovasculature in HCC, rather than in the tumor cells themselves. This characteristic positions 18F-PSMA PET/CT as a promising in vivo biomarker for angiogenesis. However, unlike the metabolic trapping observed with other tracers, the temporal behavior of PSMA in HCC is not fully understood. Understanding the kinetic profile of this radiotracer is critical for the "Theranostics" approach, as rapid washout poses a significant challenge regarding the absorbed radiation dose and the efficacy of future Radioligand Therapies (RLT). This study investigates the kinetic behavior of 18F-PSMA in HCC, focusing specifically on the washout pattern observed in dual-time point imaging. **Objectives:** To evaluate the kinetic profile and temporal stability of 18F-PSMA uptake in patients with advanced Hepatocellular Carcinoma using a dual-time point PET/CT protocol. Specifically,the study aims to quantify the variation in Maximum Standardized Uptake Value (SUVmax) between early and late acquisitions to characterize the washout phenomenon. **Materials and Methods:** This prospective, single-center cohort study was conducted at blinding. The protocol included patients with confirmed advanced or unresectable HCC. Participants underwent a dual-time point 18F-PSMA PET/CT scan. Images were acquired at two distinct time points: Early (90 minutes post-injection) and Late (150 minutes post-injection). The primary quantitative parameter analyzed was the SUVmax of the hepatic lesions. The kinetic variation (SUVmax) was calculated using the formula: DeltaSUVmax(%) = [(Late SUVmax - Early SUVmax) /Early SUVmax] $\times$ 100. A negative DeltaSUVmax indicates a washout pattern, while a positive value indicates accumulation/retention. **Results:** The cohort consisted of 11 patients (median age 77 years). The 18F-PSMA PET/CT showed positive uptake in the 10 of 11 patients. The kinetic analysis revealed a predominant pattern of signal reduction over time. In the early phase, the mean SUVmax of the lesions was (23.9 $\pm$ 10.5). In the late phase, there was a decrease in signal intensity, with the mean SUVmax dropping to 18.3 $\pm$ 8.3. The calculation of

DeltaSUVmax confirmed a consistent washout phenomenon, with a mean variation of -21.69% ± 28.83%. This kinetic behavior contrasts with the progressive accumulation often seen in tumors where the target is internalized and retained intracellularly. **Conclusion:** The study demonstrates that 18F-PSMA in Hepatocellular Carcinoma exhibits a distinct kinetic profile characterized by significant washout between 90 and 150 minutes. This finding supports the hypothesis that PSMA uptake in HCC is primarily related to neovascular density and perfusion dynamics rather than metabolic trapping. These results are clinically relevant for the development of Theranostics in HCC: the rapid washout suggests that a therapeutic approach for PSMA-targeted radioligands may not be possible. Furthermore, it indicates that earlier imaging acquisition times may provide better tumor-to-background contrast than delayed images.

Keywords: Hepatocellular Carcinoma, PSMA, Kinetics, Angiogenesis, Washout.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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IN SILICO STUDY OF SOME PHARMACOKINETIC AND PHARMACOLOGICAL PROPERTIES OF THREE ANACARDIC ACIDS IN THE CONTEXT OF SKIN DISEASES

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Introduction: Melanoma is a highly aggressive skin cancer characterized by pronounced tissue invasion and early metastases, driven by extracellular matrix remodeling. Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, play a central role in this process and are key contributors to melanoma progression, making them attractive therapeutic targets. Among natural products, anacardic acids derived from cashew pulp and nut (Anacardium occidentale) have shown relevant biological properties, including antioxidant and anti-inflammatory effects, as well as inhibitory activity against several enzymes such as xanthine oxidase, lipoxygenase, and histone acetyltransferase. These properties suggest a potential role in regulating processes associated with the tumor microenvironment and extracellular matrix remodeling, thereby justifying their investigation in the context of melanoma. **Objectives:** To evaluate in silico the physicochemical, pharmacokinetic and toxicological properties of three anacardic acids (monoene, diene and triene) and their modulating potential on metalloproteinases MMP-2 (1QIB) and MMP-9 (2OVX). **Material and Methods:** Physicochemical (lipophilicity and aqueous solubility), pharmacokinetic (absorption and metabolism), and toxicological (skin sensitivity, hepatotoxicity, mutagenicity, and carcinogenicity) properties were predicted using SwissADME and ADMET Predictor platforms. Molecular docking was performed in DockThor platform using the crystallographic structures of MMP-2 (PDB:1QIB) and MMP-9 (PDB:2OVX) obtained from the Protein Data Bank. The chemical structures of 6-[8′(Z),11′(Z),14′-pentadecatrienyl] salicylic acid (triene anacardic acid), 6-[8′(Z),11′(Z)-pentadecadienyl] salicylic acid (diene anacardic acid), and 6-[8′(Z)-pentadecenyl] salicylic acid (monoene anacardic acid) were obtained from PubChem database. Protein-ligand interactions were evaluated based on binding energy, intermolecular interaction profiles, and engagement of residues within or proximal to the catalytic site. **Results:** In silico analyses indicated that the three anacardic acids exhibit high lipophilicity and low aqueous solubility, favoring skin retention and topical use. Predicted skin absorption was observed; however, CYP2C9 inhibition may limit concomitant oral administration with drugs of narrow therapeutic index. Toxicological predictions showed low risk of mutagenicity, carcinogenicity and hepatotoxicity, despite skin sensitization potential, indicating a mainly local risk manageable through dose and formulation strategies. Docking studies revealed binding of anacardic acids, particularly the diene derivative, to catalytically relevant regions of MMP-2 and MMP-9, suggesting potential enzymatic modulation. **Conclusion:** The in silico findings suggest that, in addition to favorable skin permeation and low predicted toxicity, diene anacardic acid showed affinity for both MMPs, indicating potential to modulate targets associated to melanoma tumor microenvironment. Further preclinical studies are required to confirm the therapeutic applicability of anacardic acids in melanoma.

Keywords: Anacardium officinale, Drug screening, Melanoma, Anacardic acids.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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ANTI-INTEGRIN PEPTIDE WITH DOTA CHELATOR RADIOLABELED WITH GA-68 AS A THERANOSTIC AGENT IN GLIOBLASTOMA

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