

Issue

01



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PROLOGUE



It is a pleasure to present a new stage in the development of Horizontes de Investigación y Desarrollo, a scientific journal created to strengthen the dissemination of research and to provide a formal space for the communication of scientific, technological, social, and interdisciplinary knowledge generated within the Instituto Politécnico Nacional and in collaboration with other academic institutions.

After publishing its inaugural issue, the journal continues its commitment to promoting academic rigor, scientific integrity, and the visibility of postgraduate research.

The contributions included in this volume reflect the diversity of research at our Institute and demonstrates the scientific and technological capabilities of our community but also highlights the importance of addressing current challenges from a range of disciplines, methodologies, and perspectives. The articles cover four main areas: Physical and Mathematical Sciences and Engineering, Medical and Biological Sciences, Social and Administrative Sciences, and Interdisciplinary Studies.

Each manuscript included in this volume underwent an editorial and academic evaluation process designed to ensure the quality, originality, methodological rigor and relevance of the contributions. This process is fundamental to the development of the journal, as it fosters a culture of

responsible scientific communication and offers postgraduate students the opportunity to improve their academic writing, respond to peer review and participate directly in the practices that underpin academic publishing.

The continuity of Horizontes de Investigación y Desarrollo also represents an important institutional commitment. Beyond publishing research findings, the journal aims to contribute to the training of new generations of researchers by providing a space for communicating, debating, and improving scientific work. In this regard, each volume of the journal serves both as a record of the research conducted by our community and as an opportunity to reinforce the values of rigor, ethics, collaboration, and social responsibility that must accompany the generation of knowledge.

In this volume, we have made further progress in consolidating the journal's editorial processes, strengthening our criteria for academic evaluation, open access, and continuous improvement. This has enabled us to create a publication with a clear identity, capable of growing and increasing the visibility of the scientific contributions produced by the institute's postgraduate student community.

I would like to express my appreciation and gratitude to the students, advisors, reviewers, area coordinators, and editorial team, whose work and commitment have made the publication of this volume possible. Their participation ensures the continuity of a project that aims not only to disseminate research but also to strengthen the academic community that produces it.

I kindly invite readers to explore the contributions presented in this volume, to appreciate the effort behind each research project, and to continue supporting platforms that foster scientific dialogue, interdisciplinary collaboration, and the responsible generation of knowledge for the benefit of society.

Martha Leticia Vázquez González
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HORIZONTES

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Physical-Mathematical Sciences and Engineering

18-I-PO ELECTROCHEMICAL REDUCTION OF NITRATES OVER $\text{Bi}_2\text{O}_3\text{-Cu}_2\text{O-ZnO/C}$ -BASED ELECTROCATALYST

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Abstract: Nitrogen oxide (NO_x) emissions from industrial processes and internal combustion engines pose a serious threat to human health and the environment by saturating freshwater reservoirs with nitrites, nitrates through the nitrogen natural cycle. The electroreduction of nitrates (eNO_3RR) represents a promising alternative for transforming these pollutants into value-added products such as nitrogen, ammonia, hydrazine, and hydroxylamine. In this work, oxide-based electrocatalysts of Bi, Cu, and Zn were developed using the co-precipitation method due to the chemical affinity of their components toward nitrogenous species capable of catalyzing and modifying the selectivity of the reaction toward products of interest. The optimization of the $\text{Bi}_2\text{O}_3\text{-Cu}_2\text{O-ZnO}$ electrocatalytic matrix requires precise control to obtain the desired morphology and composition (2:2:1). Morphological and structural characterization were performed using XRD and SEM-EDS techniques. The electrochemical evaluation was performed using Cyclic Voltammetry (CV), Chronoamperometry (CA), Electrochemical Surface Area (ECSA), and Tafel techniques, allowing the generation of faradic current densities of -1.67 and -8.95 mA cm^{-2} , exhibiting considerable electrocatalytic activity to reduce protons (H^+) and various forms of NO_x species (nitrites and nitrates), respectively, in addition to exhibit good electrochemical stability for the studied reaction.

Keywords: Electrochemistry, Electrocatalysts, HER, eNO_3RR , Selectivity-Conversion.

1. INTRODUCTION

The electroreduction of nitrates has emerged as a transformative technology positioned to address two of the most pressing global challenges, i). the widespread nitrate pollution, and ii). the carbon-intensive production of ammonia [1-2]. The exploitation of agricultural and industrial activities has created a global nitrogen imbalance, resulting in a crisis that endangers freshwater ecosystems and human health. In this context, the eNO_3RR offers a promising alternative which operates under ambient conditions and utilizes clean electricity, providing a dual-purpose solution that purifies contaminated water and converts harmful pollutants into valuable chemical resources, such as ammonia, hydrazine, hydroxylamine or benign nitrogen gas (N_2) through low-energy conversion pathways that provides a sustainable alternative to conventional processes which contributes to global carbon dioxide (CO_2) emissions [3-4].

The strategic importance of eNO_3RR is further amplified by its alignment with the United Nations 2030 Sustainable Development Goals. The electrocatalysts ability to purify water makes it a direct contributor to SDG 6 (Clean Water and Sanitation). Simultaneously, its role in promoting sustainable processes and the coupling with technological inventions (as

renewable energies) is a key enabler for SDG 13 (Climate Action) [5].

While significant scientific and engineering challenges remain a challenge, including the electrocatalyst stability, mass transfer limitations, and competition from the hydrogen evolution reaction (HER). [6-7] To overcome these deficits in the field of eNO_3RR research, non-noble metal catalysts, particularly those based on copper (Cu), have attracted intense attention due to their low cost, high activity, and potential for large-scale applications. Recent developments in material sciences have introduced advanced catalyst architectures, such as single-atom catalysts (SACs) and nanostructures, which are a class of materials that offer precise control over reaction pathways and intermediates at the electrocatalysts interphase [8-11].

Therefore, this work focuses on evaluating the activity between Bi, Cu and Zn oxides synthesized *in situ* through the co-precipitation method, the materials were physiochemically evaluated by SEM and XRD. In order to determine the electrochemical activity for HER and eNO_3RR reactions, a 1 M NaOH support electrolyte was used and the electrochemical techniques of CV, CA, ECSA and Tafel were employed.

2. MATERIALS AND METHODS

2.1. Co-precipitation synthesis of Bi_2O_3 - Cu_2O -ZnO oxide matrix

At room temperature, stoichiometric amounts (2:2:1) of bismuth chloride ($BiCl_3$), copper chloride ($CuCl_2$) and zinc chloride monohydrate ($ZnCl_2 \cdot H_2O$) were added to obtain Bi_2O_3 - Cu_2O -ZnO, in a 0.5 M solution of sodium citrate dihydrate ($C_6H_5Na_3O_7 \cdot 2H_2O$) as a stabilizing agent.

After solubilization, a 3 M solution of sodium hydroxide (NaOH) and 0.25 M of l-ascorbic acid were added simultaneously at a rate of $8 \text{ mL} \cdot \text{min}^{-1}$ under intense magnetic stirring for 20 minutes. The resulting precipitate was recovered by centrifugation and then washed

with deionized water, ethanol and acetone, and dried in a muffle furnace at 60°C for 30 minutes.

2.2. Electrochemical suspension

To perform the electrochemical evaluation, an ink-like microemulsion was prepared by adding equal parts of electrocatalyst and Vulcan carbon as a support, Aquivion® solution as a binder, and isopropanol as a solvent. The ink was then sonicated for 20 minutes and allowed to cool to room temperature. Finally, a $1 \mu\text{L}$ aliquot of ink was deposited on a 3 mm diameter glassy carbon substrate, and the solvent was allowed to evaporate for 5 minutes.

2.3. Electrochemical evaluation

The electrochemical evaluation was carried out under atmospheric conditions of pressure and temperature, in a conventional 50 mL cell with 3 electrodes using a 3 mm diameter glassy carbon as the working electrode, a graphite rod as the counter electrode and a reversible hydrogen electrode (RHE) as the reference electrode. In a 1 M NaOH supporting electrolyte saturated with N_2 (99%, INFRA) for 10 minutes to evaluate the HER, and for the tests in presence of nitrates, a 1 M NaOH + 0.1 M $NaNO_3$ electrolyte was used for the eNO_3RR evaluation.

2.4. Compositional and morphological characterization

The morphology of Bi_2O_3 - Cu_2O -ZnO was identified by SEM, JEOL JSM-6701F at 10 kV, using secondary electrons (SEI) and backscattered electrons (BSE) to determine the morphology and dispersion of the electrocatalyst. Additionally, EDS analysis was carried out to obtain the spectrum of elements present in the samples.

The crystallographic structure and phase composition was determined by XRD using a SIEMENS D5000 diffractometer with $Cu-K\alpha$ radiation ($\lambda = 1.5406 \text{ \AA}$) in a 2θ range from 20 to 100° .

3. RESULTS AND DISCUSSION

3.1 Physicochemical results

Figure 1(A-B) shows SEM micrographs of the $\text{Bi}_2\text{O}_3\text{-Cu}_2\text{O-ZnO}$ sample taken with secondary electrons (SEI) at X10,000 and backscattered electrons (BSE) at X50,000, respectively, where the morphology of the materials synthesized by the co-precipitation method can be appreciated. It can be observed that the Cu_2O and ZnO particles form spherical/semispherical particles with a tendency to agglomeration due to cohesive (electrostatic) forces and high surface energy (Gibbs). On the other hand, in Figure 1 (B), the brighter lamellar particles composed of Bi_2O_3 , which are characteristic of this compound, tend to form segregated structures.

Figure 1 (C) presents a histogram generated from a population of 150 particles from 3 different micrographs to obtain a global sample using ImageJ software. The histogram indicates an approximate particle size of 277 nm, with the majority of particles falling within the range of 175 to 345 nm. The EDS spectrum, Figure 1 (D), revealed the elemental composition of the sample, where peaks associated with Bi, Cu, Zn, and O were identified, confirming a pure oxide matrix with.

Figure 2 shows the diffraction pattern for $\text{Bi}_2\text{O}_3\text{-Cu}_2\text{O-ZnO}$, where the crystalline phases for Cu_2O (red), ZnO (green), and Bi_2O_3 (blue) were identified according to ICDD cards 00-005-0667, 03-065-0523, 04-003-2034, and 00-029-0236. For Bi_2O_3 , the α and β phases of this compound were identified and grouped under the same format (blue cloverleaf) for simplicity. It is important to notice that ZnO and Cu_2O share similar d-spicing as their most dominant reflections are (111), (200), (220) and (311). For ZnO the center in 2θ for those reflections are located in 36.414, 42.297, 65.358 and 73.496 $^\circ$, respectively. Whereas for Cu_2O the reflections are located in 36.418, 42.297, 61.344 and 73.526 $^\circ$, respectively, according to ICDD.

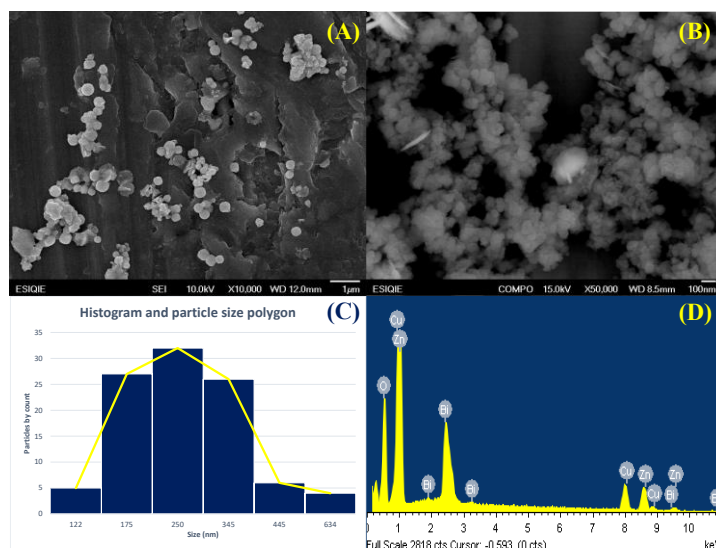


Figure 1. SEI (A) and BSE (B) micrographs, histogram, (C) and elemental composition (D) of $\text{Bi}_2\text{O}_3\text{-Cu}_2\text{O-ZnO}$.

The high crystallinity of the electrocatalyst could be related to its partial bonding (conjugation) to oxygen during the synthesis (minimizing the thermodynamic free energy). Crystallite size analysis was performed using the modified Scherrer equation (1), revealing crystallite sizes of 10 nm for the $\text{Cu}_2\text{O-ZnO}$ solid solution and 8 nm for Bi_2O_3 .

$$\rho^{(\text{intercept})} = \frac{K \lambda}{L} \quad \text{Eq. (1)}$$

Where, K is a physical constant, λ is the wavelength used ($\text{CuK}\alpha$) and L is the crystallite size. No further crystallographic phases were found, confirming a pure compound made of Bi, Cu, and Zn oxides.

3.2 Electrochemical results

The electrochemical surface area (ECSA) is an important parameter on electrocatalysis as it allows the comparison between multiple electrocatalysts and allow the normalization of the faradic current. The ECSA was calculated using CV in a 1 M KCl + 10 mM $\text{K}[\text{Fe}(\text{CN})_6]_3$ as supporting electrolyte, in a potential window from 0.75 to 1.05 V/RHE, at different scan rates (140, 100, 80, 60, 40, 20, and 10 $\text{mV}\cdot\text{s}^{-1}$).

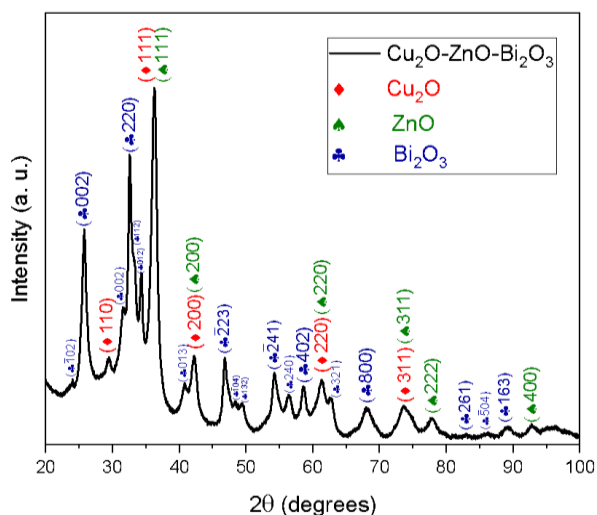


Figure 2. Diffraction pattern for Bi₂O₃-Cu₂O-ZnO.

The Randles-Sevcik model (2) was employed to show the response of current as a function of the square-root of the scan rate.

$$i_p = 2.69 \times 10^5 A C D^{\frac{1}{2}} n^{\frac{1}{2}} v^{\frac{1}{2}} \quad \text{Eq. (2)}$$

Where i_p , is the peak current; 2.69×10^5 is a physical constant from the Randles-Sevcik equation; A , is the electrochemical surface area; C , is the concentration of redox species; D , is the diffusion coefficient; n , is the number of transferred electrons; and v , is the scan rate.

Figure 3 displays the plots linked with the Fe²⁺/Fe³⁺ redox couple on Bi₂O₃-Cu₂O-ZnO electrocatalyst surface.

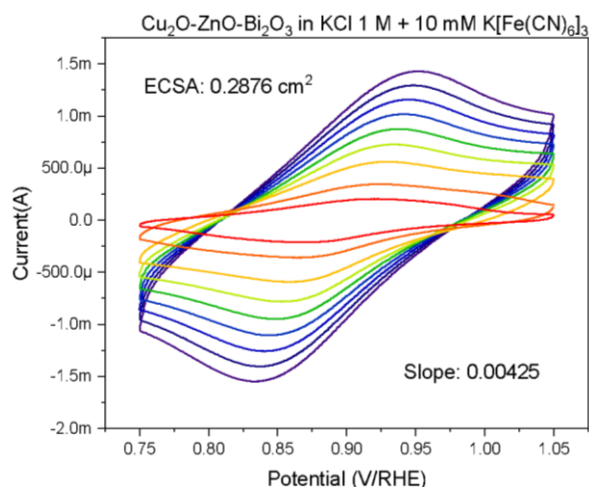


Figure 3. ECSA determination at various scan rates in 1M KCl + 10 mM K[Fe(CN)₆]₃ electrolyte for Bi₂O₃-Cu₂O-ZnO

The obtained relationship (slope) between the scan rate and the faradic current determined the real ECSA value at 0.2876 cm².

Cyclic voltammetry technique was carried out in a potential window of 0.2 to -1.6 V/RHE at a scan rate of 20 mV·s⁻¹ in a 1 M NaOH support electrolyte in the presence and absence of nitrate ions (NO₃⁻). In Figure 4, two cathodic peaks and two anodic peaks corresponding to the redox processes of Cu₂O (C₁, A₂) and ZnO (C₂, A₁) were identified. At -1.6 V it can be seen that in absence of (NO₃⁻), the generated current -0.48 mA is attributed to the HER (black line). While in the presence of the analyte (red line), a current of -2.57 mA is obtained, attributed to eNO₃RR, which demonstrates its ability to perform the model reaction. Additionally, by affecting the generated current with the ECSA value obtained in Figure 3, current densities (j) of -1.6 and -8.9 mA·cm⁻², were obtained, respectively. Demonstrating the electrocatalytic activity of the material to carry out the adsorption, conversion, and desorption processes of eNO₃RR.

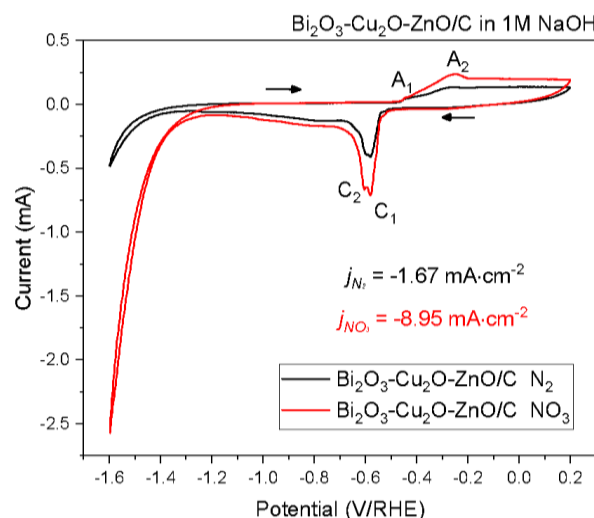


Figure 4. i-E profiles of Bi₂O₃-Cu₂O-ZnO at 20 mV·s⁻¹ in absence and presence of NO₃⁻.

Chronoamperometry technique was used to determine the electrocatalyst activity and stability at several potentials (0.2, 0, -0.2, -0.4, -0.6, -0.8, -1, -1.2, -1.4, -1.6 V/RHE). It can be noticed that at potentials lower than -1.2 V the faradic current is -0.05 mA, indicating no

reaction processes. At -1.4 V, hydrogen production is clearly lower than eNO₃RR, however, both currents remain at a low level since the optimal potential for the electrocatalyst is at -1.6 V. At this potential, a clear preference from the Bi₂O₃-Cu₂O-ZnO takes place to carry out eNO₃RR over HER can be observed, see Tafel section, achieving a steady state (j_{ss}) current density of -0.8 and -4.5 mA·cm⁻², respectively.

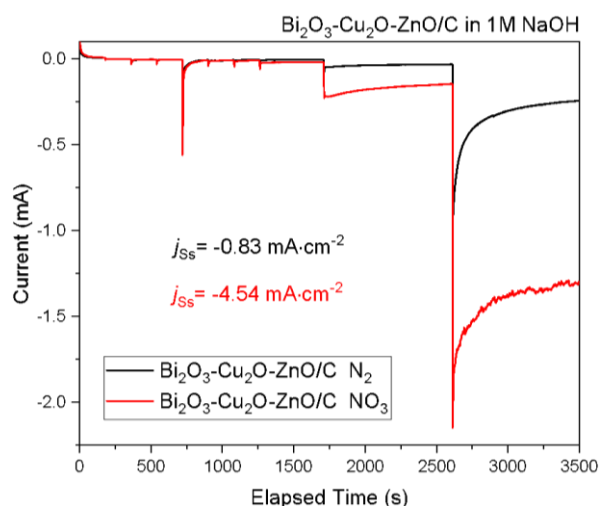


Figure 5. Chronoamperometry for Bi₂O₃-Cu₂O-ZnO in absence and presence of NO₃⁻.

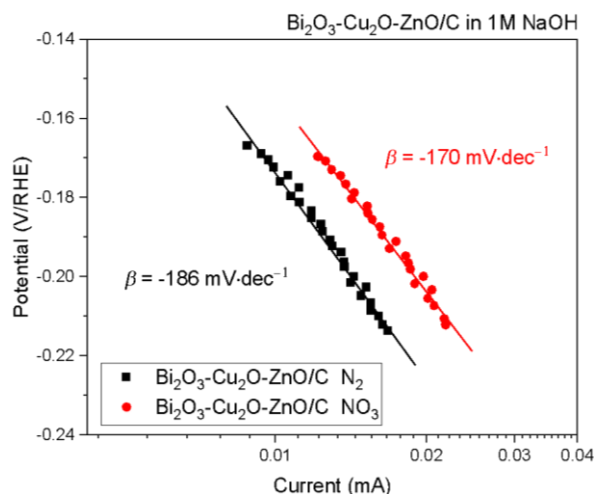


Figure 6. Tafel slopes for Bi₂O₃-Cu₂O-ZnO in absence and presence of NO₃⁻.

Lastly, to evaluate the electrocatalyst's affinity for HER and eNO₃RR in a 1M NaOH supporting electrolyte, Figure 6, the Tafel slopes were analyzed in the low-field region, obtaining values of -186 and -170 mV·dec⁻¹, respectively.

This analysis confirms the material affinity to carry out eNO₃RR over the HER.

4. CONCLUSIONS

The co-precipitation synthesis allowed the successful formation of Bi₂O₃-Cu₂O-ZnO matrix oxide. SEM-EDS analysis demonstrated (i) the presence of the constituent elements and (ii) the morphology of the catalysts, revealing that Bi₂O₃-Cu₂O-ZnO exhibits high homogeneity in size distribution and morphology, resulting in an increased number of available active sites. Furthermore, the diffraction pattern confirmed the desired crystalline phases in the electrocatalyst (Cu₂O, ZnO, and Bi₂O₃) and allowed for the calculation of the crystallite size at 10 nm for the Cu₂O-ZnO solid solution and 8 nm for Bi₂O₃, respectively. The electrochemical evaluation demonstrated that the electrocatalyst is mildly active for HER. However, the Bi₂O₃-Cu₂O-ZnO/C is much more active for eNO₃RR due to preferred reaction kinetics for NO₃⁻ species at the electrocatalyst surface, in addition to possess a higher number of active sites corroborated by ECSA data (0.2876 cm⁻²), resulting in a higher current density (-1.6 and -8.9 mA·cm⁻², respectively) and consequently a higher conversion percentage, resulting in higher nitrogenated reduction products and hydrogen for potential application in the agrochemical field and fuel cells applications, respectively.

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Conflicts of interest

The authors declare no conflict of interest.

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304-I-PP MODAL ANALYSIS AND NEURAL NETWORKS FOR STRUCTURAL DAMAGE DETECTION

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Abstract: This study integrates modal analysis with neural networks for structural damage detection. Computations were performed in Google Colab, modeling a four-degree-of-freedom system without damping. Samples were generated by reducing the stiffness matrix (1% to 9%) to simulate damage, keeping the mass matrix constant. Two neural networks were designed to predict the modal and stiffness matrices from the first row of the modal matrix obtained via Frequency Domain Decomposition (FDD), achieving a low mean squared error for the stiffness matrix. The original, test, and predicted modal and stiffness matrices are presented, demonstrating the feasibility of the proposed approach.

Keywords: Structural Health Monitoring, Operational Modal Analysis, Incomplete Modal Data, Feedforward Neural Networks.

1. INTRODUCTION

Structural monitoring is critical for ensuring the safety of structures. However, obtaining reliable dynamic properties in real-world scenarios involves significant challenges, such as the uncertainties inherent in estimating the natural frequencies of buildings [1]. To process these properties, techniques like the Frequency Domain Decomposition (FDD), formalized for ambient responses by Brincker, Zhang, and Andersen [2], have become essential for modal identification. Furthermore, detecting damage with limited modal data, such as from a single

accelerometer, poses an ongoing challenge. Historically, researchers have addressed incomplete or noisy data by optimizing and correcting measured modes, as proposed by Baruch and Bar-Itzhack [3]. Subsequent advancements have focused on methodologies capable of localizing and detecting structural damage even when complete baseline modal parameters or initial information are unavailable [4, 5]. Among these significant contributions is the Baseline Stiffness Method developed by Rodríguez-Rocha et al. [6], which successfully determines a pre-damage reference state and identifies structural damage using modal information solely from the damaged structure.

Parallel to these analytical approaches, the foundational application of machine learning for structural damage detection was demonstrated early on by Wu, Ghaboussi, and Garrett [7]. Since then, these techniques have proven highly effective in addressing data scarcity; for instance, Kourehli [8] demonstrated the feasibility of using artificial neural networks to assess structural damage directly from incomplete modal data. Building upon this progression towards robust detection with limited baseline information, this work explores whether it is feasible to detect structural damage using neural networks—implemented via the TensorFlow framework [9]—to predict complete modal and stiffness matrices from partial data. If viable, this approach could be applied in real-world scenarios, reducing the number of sensors needed for structural monitoring and thereby lowering costs.

2. MATERIALS AND METHODS

2.1 Structural Model

A four-degree-of-freedom (DOF) system is idealized as a building with concentrated masses and springs, without damping (Figure1). The mass matrix, kept constant in this study, is diagonal:

$$m_1 = 1500 \text{ Kg}$$

$$m_2 = 3000 \text{ Kg}$$

$$m_3 = 3000 \text{ Kg}$$

$$m_4 = 4500 \text{ Kg}$$

$$\mathbf{M} = \begin{bmatrix} m_1 & 0 & 0 & 0 \\ 0 & m_2 & 0 & 0 \\ 0 & 0 & m_3 & 0 \\ 0 & 0 & 0 & m_4 \end{bmatrix}$$

The stiffness matrix is tridiagonal, defined as:

$$\mathbf{K} = \begin{bmatrix} k_1 & -k_1 & 0 & 0 \\ -k_1 & k_1 + k_2 & -k_2 & 0 \\ 0 & -k_2 & k_2 + k_3 & -k_3 \\ 0 & 0 & -k_3 & k_3 + k_4 \end{bmatrix}$$

with stiffness coefficients:

$$k_1 = 800000 \text{ N/m}$$

$$k_2 = 1600000 \text{ N/m}$$

$$k_3 = 2400000 \text{ N/m}$$

$$k_4 = 3200000 \text{ N/m}$$

Substituting these values, the resulting matrices are:

$$\mathbf{M} = \begin{bmatrix} 1500 & 0 & 0 & 0 \\ 0 & 3000 & 0 & 0 \\ 0 & 0 & 3000 & 0 \\ 0 & 0 & 0 & 4500 \end{bmatrix}$$

$$\mathbf{K} = \begin{bmatrix} 800000 & 0 & 0 & 0 \\ 0 & 1600000 & 0 & 0 \\ 0 & 0 & 2400000 & 0 \\ 0 & 0 & 0 & 3200000 \end{bmatrix}$$

2.2 Modal Analysis of the Original System

The eigenvalue problem is solved [10] to obtain the modal matrix Φ . Eq (1):

$$(\mathbf{K} - \omega^2)\Phi = 0 \quad \text{Eq. (1)}$$

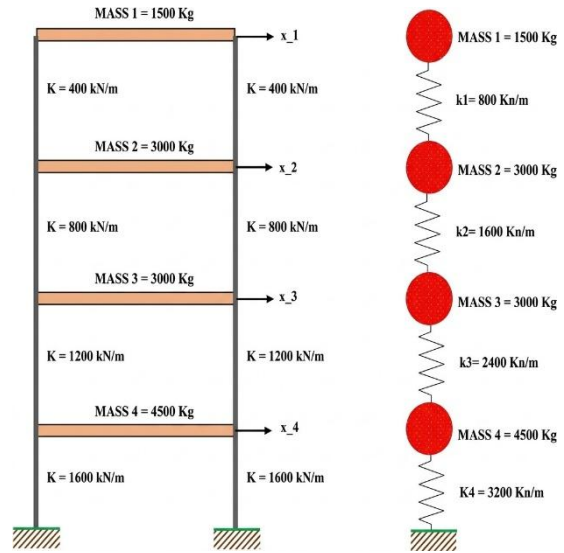


Figure 1. Idealized diagram of the 4-DOF building modeled as a mass-spring system.

To illustrate the proposed methodology, a Time History Analysis is performed considering a unidirectional horizontal ground motion [10]. Specifically, the East-West (E-W) acceleration component recorded at the SCT station during the September 19, 1985 Mexico City earthquake was applied along the horizontal degrees of freedom, solving Eq(2)

$$\mathbf{M}\ddot{\mathbf{x}} + \mathbf{K}\dot{\mathbf{x}} = \mathbf{F}(t) \quad \text{Eq. (2)}$$

using the *odeint* integration method. Acceleration records from all masses are treated as ambient vibration and processed via Frequency Domain Decomposition (FDD) [2] to obtain the acceleration frequency spectrum (Figure 2), computing the cross-spectral density

$S_{xx}(\omega)$ and applying SVD:

$$S_{xx}(\omega) = \mathbf{U}\Sigma\mathbf{V}^T$$

2.3 Damage Simulation

Damage was simulated by reducing stiffness by 5% for each element: $k_1 = 800000 \text{ N/m}$, $k_2 = 1600000 \text{ N/m}$, $k_3 = 2400000 \text{ N/m}$, $k_4 = 3200000 \text{ N/m}$ generating the damaged stiffness matrix $\mathbf{K}_d$:

$$K_d = \begin{bmatrix} 760000 & -760000 & 0 & 0 \\ -760000 & 2280000 & -1520000 & 0 \\ 0 & -1520000 & 3800000 & -2280000 \\ 0 & 0 & -2280000 & 5300000 \end{bmatrix}$$

The mass matrix remains constant. Dynamic analysis and FDD are repeated with a data length of 1558, $npserg = 799$, and a frequency resolution of 0.064 Hz to obtain the damaged modal matrix Φ_{dFDD} . The first row of Φ_{dFDD}

$\Phi_{dpartial} = [0.0152, -0.0175, 0.0111, -0.0021]$ is used as input for the neural network in four cases: using all 4 values, the first 3 values, the first 2 values, and the first value.

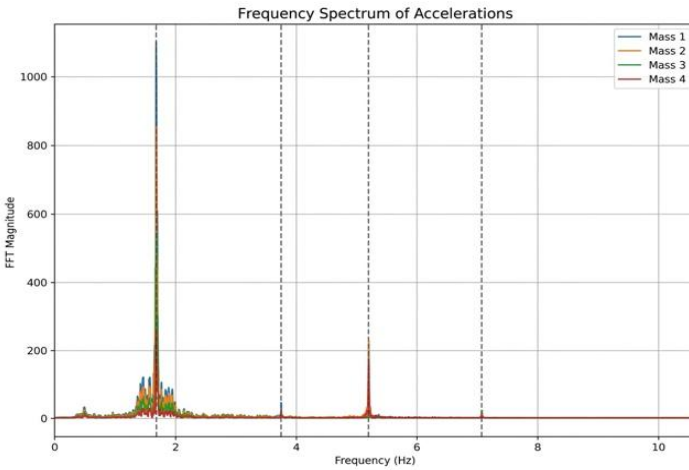


Figure 2. Acceleration frequency spectrum obtained via Frequency Domain Decomposition (FDD) for the damaged system.

2.4 Neural Network

Training data were generated by simulating stiffness reductions (1% to 9% for each k_i , plus combinations) with 100,000 samples. Two feedforward neural networks (2048-1024-512-256-128-64 nodes, ELU and SELU activations, L2 regularization, 0.3 dropout) (Figure 3) were trained using TensorFlow [9] to predict Φ_d and K_d from $\Phi_{dpartial}$ (complete first row or subsets of 2 or 1 values) following the premise of incomplete modal vectors [8].

MSE was used for the modal matrix, and a custom loss function for the stiffness matrix, weighting errors in k_i by a factor of 50.0. The Adam optimizer (learning rate 0.00005), early stopping (patience 25), and learning rate

reduction (factor 0.2, minimum $1e-6$) were employed. Four cases were evaluated: using all 4 values, 3 values, 2 values, and 1 value.

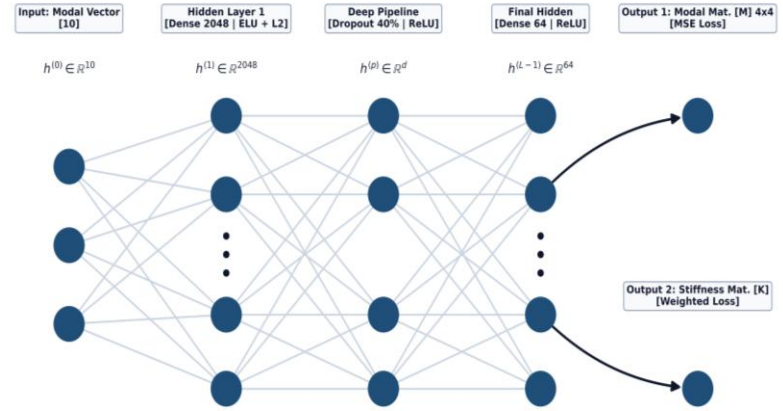


Figure 3. Architecture of the feedforward neural network designed for modal and stiffness prediction.

2.5 Damage Detection

Damage is detected by comparing predicted stiffness coefficients k_{ipred} with the original ones $k_{i,original}$ using the damage index, defined as:

$$Damage\ Index_i = \frac{|k_{i,original} - k_{ipred}|}{k_{i,original}}$$

Where $k_{i,original}$ corresponds to undamaged values $k_1 = 800000\ N/m$, $k_2 = 1600000\ N/m$, $k_3 = 2400000\ N/m$, $k_4 = 3200000\ N/m$. The simulated damage reduces each k_i by 5% yielding expected values: $k_1 = 760000\ N/m$, $k_2 = 1520000\ N/m$, $k_3 = 2280000\ N/m$, $k_4 = 3040000\ N/m$. The neural network predicts K_d from fragments of the first row of Φ_{dFDD} and percentage differences Δ_{ki} are

calculated for the cases of 4, 3, 2, and 1 input values. Figure(4) shows the Δ_{ki} values for each case, with a reference line at 5% to indicate proximity to the expected value. Figure (5) displays the proximity of each Δ_{ki} to the 5% target, highlighting the deviations across cases.

The results show that all cases detect damage with indices close to the expected 5%. The 4-value case is the most accurate for k_1 (0.151% from 5%) and k_3 (0.189% from 5%), while the 1-

value case is the most accurate for k_2 (0.121% from 5%) and the 3-value case for k_4 (0.259% from 5%). Although accuracy decreases slightly with fewer input values, even a single value achieves acceptable detection, with Δ_{ki} within or slightly above the 5% threshold. The MAE between predicted and actual modal matrices is low (~0.000019-0.000025), confirming the consistency of modal predictions.

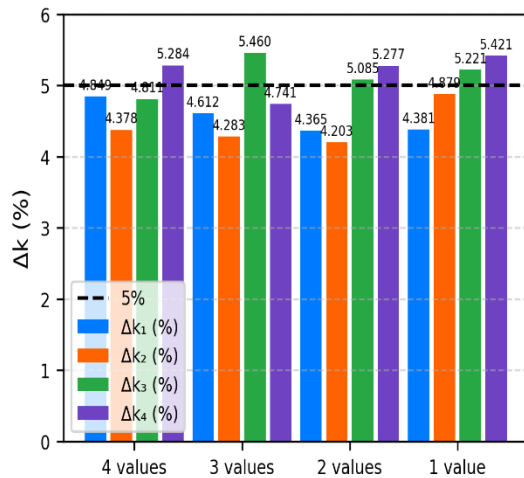


Figure 4. Δ_{ki} values for each case, with a reference line at 5% to indicate proximity to the expected value.

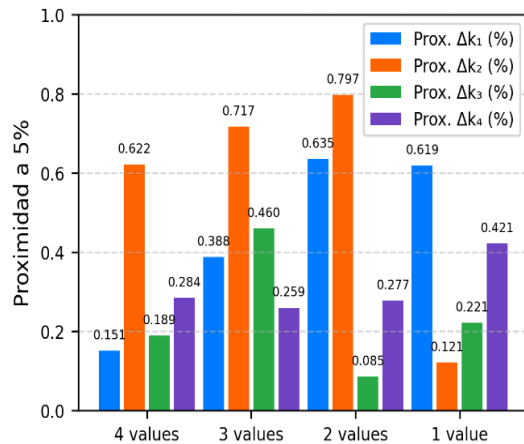


Figure 5. Proximity of each Δ_{ki} to the 5% target, highlighting the derivations across cases.

3. MODAL MATRIX VALIDATION

To validate the FDD method, the modal matrices of the undamaged structure obtained via eigenvalue analysis Φ_d and Φ_{FDD} were compared. Figure(6) shows the results,

with MAC values close to 1.0, confirming the accuracy of FDD in an ideal no-noise case. For the damaged system, Φ_{dFDD} was validated against Φ_d also showing high correlation.

4. MODAL ANALYSIS VALIDATION

Validation of Φ_{FDD} against Φ_d for the undamaged system (Figure 6) showed MAC values of 1.0000 (modes 1, 3, 4) and 0.9999 (mode 2), indicating near-perfect correlation. For the damaged system, validation of Φ_{dFDD} against Φ_d (Figure 7) showed MAC values of 1.0000 for all modes, confirming FDD accuracy in an ideal no-noise case.

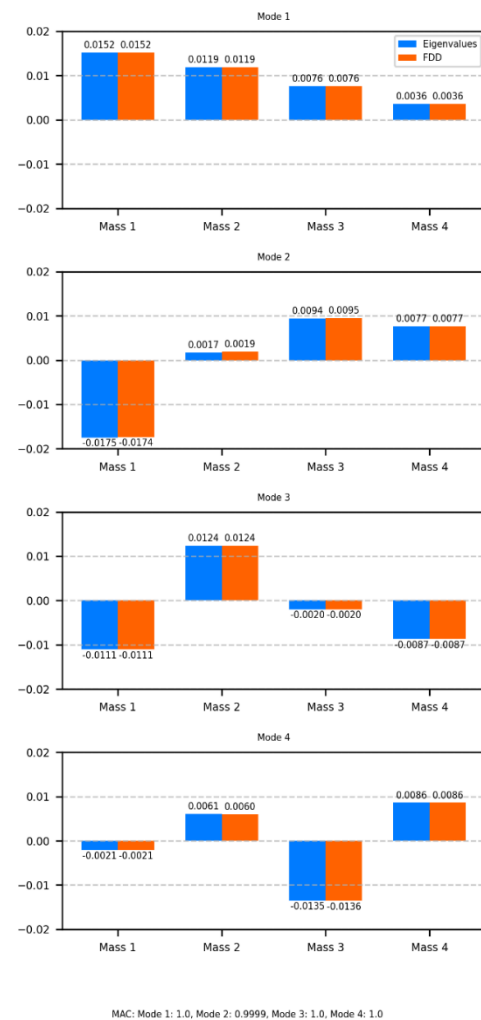


Figure 6. Modal shapes (Eigenvalues vs FDD)- Undamaged System.

These exceptional correlation levels not only establish the baseline reliability of the

extracted modal shapes under deterministic conditions, but also validate the numerical framework prior to introducing environmental noise or structural uncertainties.

5. DAMAGED MODAL MATRIX AND NEURAL NETWORKS PREDICTIONS

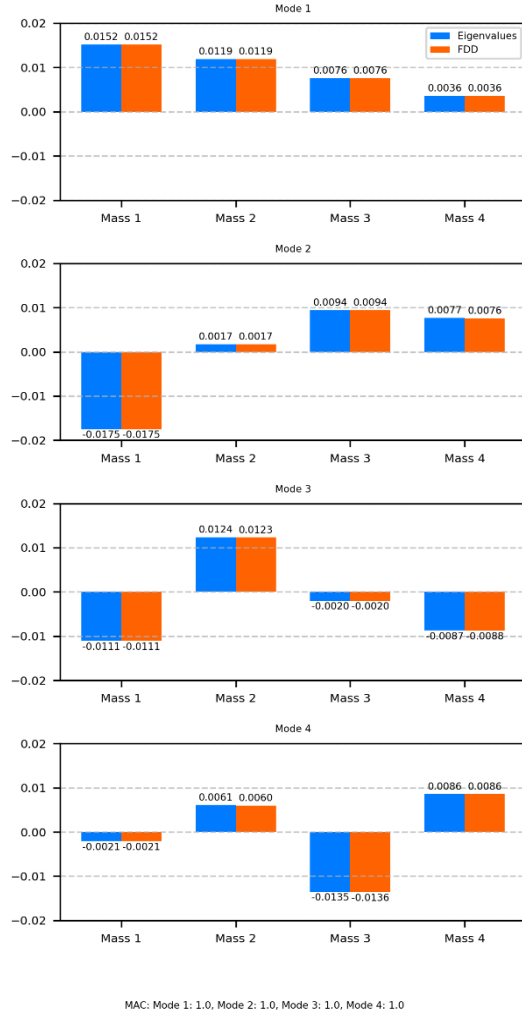


Figure 7. Modal shapes (Eigenvalues vs FDD)- Damaged System

For the damaged system with:

$$\begin{aligned} k_1 &= 760000 \text{ N/m} \\ k_2 &= 1520000 \text{ N/m} \\ k_3 &= 2280000 \text{ N/m} \\ k_4 &= 3040000 \text{ N/m} \end{aligned}$$

the eigenvalue problem $(K_d - \omega^2)\Phi = 0$ was solved, and FDD was applied to obtain the modal matrices Φ_d and Φ_{dFDD} respectively. The first row of Φ_{dFDD} , $\Phi_{dpartial} = [0.0152, -0.0175, -0.0111, -0.0021]$, was used as input for the

neural network in four cases: using all 4 values, 3 values $[0.0152, -0.0175, -0.0111]$, 2 values $[0.0152, -0.0175]$, and 1 value $[0.0152]$. The neural network predictions for Φ_d and stiffness coefficients k_2, k_3, k_4 are compared with actual values in figure (7) and figure (8) summarizes prediction errors, while figure(9) details the predicted modal and stiffness matrices for each case. Figure (8) shows the training loss of the neural network for each case.

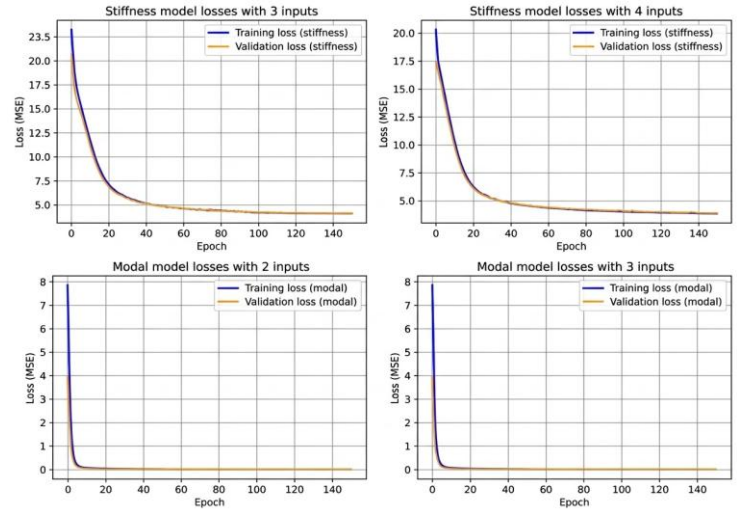


Figure 8. Neural network training loss for the 4-value and 1-value input cases.

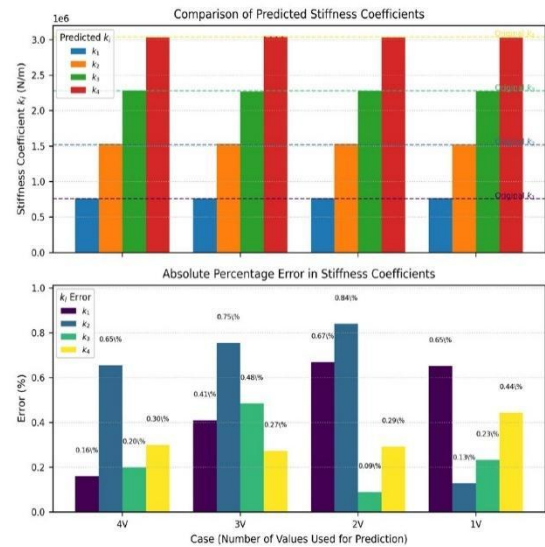


Figure 9. Predicted modal and stiffness matrices with stiffness coefficients for each case.

5.1 Neural Network Prediction.

The network predicted Φ_d and stiffness coefficients k_1, k_2, k_3, k_4 with low MAE

(~0.000019-0.000025 for the modal matrix) in all cases. Relative errors in k_1 range from 0.16% to 0.67%, in k_2 from 0.13% to 0.84%, in k_3 from 0.09% to 0.48%, and in k_4 from 0.27% to 0.44%. Accuracy decreases slightly with fewer input values, but the predicted modal and stiffness matrices (Figure 7 and Figure 9) show high agreement with actual values, especially for the modal matrix.

6. CONCLUSIONS

The proposed method accurately predicts modal and stiffness matrices from partial data, with low relative errors in k_i . The mass matrix was kept constant in this study, but future work should explore variations in M to model more realistic structural changes. Accuracy improves with more input data, but even a single value yields acceptable predictions, making it suitable for structural monitoring applications with limited sensors.

Furthermore, evaluating the method's performance on different structural configurations, including irregular structures and three-dimensional models, would be valuable. This would verify its use in more complex cases. Incorporating noise in training to simulate real-world conditions and training the network with modal matrices obtained entirely from Time History Analysis, along with experimental validation, are also recommended to strengthen the use of neural networks.

Acknowledgments.

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Conflicts of interest

The authors declare no conflict of interest.

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**Medical-Biological
Science**

114-II-PO CORRELATION BETWEEN BOADICEA MODEL ESTIMATES AND NEXT-GENERATION SEQUENCING RESULTS: A STUDY IN MEXICAN WOMEN AT RISK FOR BREAST AND OVARIAN CANCER

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Abstract: In Mexico, breast cancer (BC) and ovarian cancer (OC) are the leading causes of cancer related death in women. The BOADICEA model estimates the risk of carrying pathogenic variants associated with BC and OC, facilitating the prioritization of genetic testing and clinical decisions; however, its validity has not yet been evaluated in the Mexican population. In the present study, the risk estimates by BOADICEA in Mexican women will be correlated with their genetic variants identified through next-generation sequencing (NGS). A total of 194 patients have been evaluated. Pathogenic variants were identified in 38% of cases, variants of uncertain significance in 33%, and no variants in 28%. The most frequently affected genes were BRCA1, BRCA2, and CHEK2. BOADICEA estimated an average risk of 17.17 in patients with cancer and 8.34 in those without cancer. Considering the recommended risk threshold (ten), 18% false negatives were observed, suggesting that parameter adjustments may be needed for our population.

Keywords: genetic variants, genetic risk in cancer, prediction model.

1. INTRODUCTION

According to the World Health Organization (WHO), cancer is defined as abnormal and uncontrolled cell growth in any organ or tissue of the human body that can invade surrounding tissues and spread to other organs (metastasis) [1, 2].

Breast cancer (BC) and ovarian cancer (OC) are two types of cancer who affected the most women around the world. Currently, BC is the most frequently diagnosed cancer worldwide, surpassing lung cancer, and accounts for 1 in 8 cancer diagnoses. In Mexico, BC is the second most common cancer overall, after prostate cancer. Among women, however, it is the leading cancer type, representing 25% of all cases [3-6].

OC ranks seventh among malignant tumors and eighth as a cause of cancer-related death in women worldwide. Moreover, it is one of the most common gynecological cancers and the third leading cause of death among them (13). In Mexico, OC is the sixth leading cause of cancer-related death in women [7].

Both BC and OC are heterogeneous diseases comprising multiple molecular subtypes. Genomic characterization enables prognosis, risk stratification, which in turn could allow the allocation of targeted therapies or surgical

interventions, thus improving clinical outcomes in BC and/or OC patients [8].

Most cases are sporadic; however, 5–10% of BC and OC occur in patients with germline predisposition variants [9, 10]. A germline variant refers to a change in one or more nucleotides in the DNA sequence of a reproductive cell (egg or sperm), which is transmitted to the offspring and incorporated into the DNA of every cell in the body. These variants are inherited from parent to child [11].

Patients with a predisposition to BC and OC present a phenotype defined as hereditary breast and ovarian cancer syndrome (HBOC). Clinically, HBOC is defined by family history criteria, while molecular confirmation relies on the identification of pathogenic germline variants (Genetic alteration that increase cancer risk [12–15]) in genes such as ATM, CDH1, CHEK2, PALB2, PTEN, STK11, RAD51C, BRIP1, BARD1, MRE11A, MLH1, MSH2, MSH6, and TP53 [16, 17].

The early detection of pathogenic variants (PV) associated with breast and ovarian cancer through genetic testing is essential but remains limited in certain contexts.

When sequencing tools are not available, predictive mathematical models that estimate the probability of carrying pathogenic variants become highly valuable. These models can identify high-risk patients, guide individualized clinical decisions, serve as early detection strategies, and help prioritize patients for genetic testing [20].

The first mathematical model developed to predict familial BC risk, based mainly on family history and BRCA1/2 genotypes, was created by Antoniou and colleagues at the University of Cambridge, UK, in 2002 [15].

In 2004, this model was expanded to integrate additional factors, leading to the development of BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), which estimates

both disease incidence and the probability of carrying pathogenic variants for BC and/or OC.

Although the BOADICEA model has gained relevance and is recommended in international oncology guidelines, its application has not yet been validated in Mexican women.

This study aims to evaluate the utility of the BOADICEA model in Mexican women by correlating estimated risk (predicted carriers) with observed data obtained through Next-Generation Sequencing (NGS).

This study will provide key insights into risk characteristics in the Mexican population.

The findings could support the incorporation of the BOADICEA model in clinical practice, fully or under specific conditions, as a reliable tool to identify candidates most likely to benefit from genetic testing, thereby enhancing prevention and clinical management in the Mexican context.

Additionally, it will establish a framework to incorporate patient data over time, strengthen analyses, and eventually develop a regional predictive mathematical model.

2. MATERIALS AND METHODS

Study design: observational, ambispective, and cross-sectional.

The general workflow to assess the correlation between the estimated probability of carrying pathogenic variants predicted by the BOADICEA model (expected data) and the variants identified through massive parallel sequencing (observed data), in Mexican women at risk of breast and/or ovarian cancer involved selecting a study population that met the inclusion criteria (Table 1).

At least the minimum sample size estimated by the Epi Info® online program was achieved, which indicated that 137 participants were required to detect at least one germline alteration. A database was created with the genetic variants identified by massive parallel

sequencing (observed data). In parallel, a second database was generated with the probabilities estimated by the BOADICEA predictive model (expected data). Finally, the correlation between expected and observed data was evaluated.

Table 1. Eligibility criteria.

<i>Inclusion</i>	<i>Exclusion</i>
Mexican women at risk of BC and/or OC who have parallel next-generation sequencing results for the genes BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51C, RAD51D, and BRIP1, with clinical information available and complete according to Table 2.	-Women at risk of BC and/or OC with a nationality other than Mexican. -Mexican women at risk of BC and/or OC without parallel next-generation sequencing results for the genes BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51C, RAD51D, BARD1, and BRIP1. -Mexican women at risk of BC and/or OC without available clinical information.

2.1. Identification of Genetic Variants (Observed Data)

Variants were identified in the laboratory using parallel massive sequencing across multiple gene panels and analyzed with the bioinformatics tools SOPHIA GENETICS (<https://www.sophiagenetics.com/>), Franklin by Genoox (<https://franklin.genoox.com/>), and the ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/>).

All identified variants have been recorded in a Microsoft Access database since 2016, comprising Mexican patients with hereditary cancer.

Table 2. Data required for BOADICEA risk calculation

Criteria and values

Sex: Male or Female
Country: United Kingdom, Australia, Canada, USA, Denmark, Estonia, Finland, France, Iceland, Netherlands, New Zealand, Norway, Slovenia, Spain, Sweden, or other
Date of Birth: Day, month, and year
Height: Cm
Weight: Kg
Alcohol Intake: Type (glass of wine, pint or bottle of beer, mixed drink, shot), quantity (number), and frequency (daily, weekly, or monthly)
Age at Menarche: Years
Use of Contraceptive Pills: Years (duration in years), No or Unknown
Amenorrhea: Yes (age in years), No or Unknown
Use of Hormone Replacement Therapy: Yes (duration in years and type: known estrogen-only therapy, known combined therapy, other, or unknown), No, or Unknown.
Children: Yes (number of children, sex, and year of birth), No, or Unknown
Mammography: Yes (breast density known: Yes or No, if known, provide BI-RADS result), No, or Unknown
Endometriosis: Yes, No, or Unknown
Tubal Ligation: Yes, No, or Unknown
Surgeries: Mastectomy and/or oophorectomy
Cancer Diagnosis: Breast, contralateral breast, ovary, and/or pancreas (age at diagnosis)
Knowledge of Polygenic Risk Score: Yes or No
Family History (Pedigree): Nuclear, first degree, second degree. If there is a history of cancer or cancer in the proband, include age at diagnosis (breast, contralateral breast, vary, pancreas or prostate), pathology (estrogen, receptor, progesterone receptors, HER2, cytokeratin 14, cytokeratin 5/6), and genetic test performed (BRCA1/2, PALB2, CHEK2, ATM, BARD1, RAD51C, RAD51D, BRIP1)

Based on these records and corresponding patient data, a structured database was generated including patients at risk for breast and/or ovarian cancer, affected gene, transcript, chromosome and exon, variant read depth, allele frequency, and variant classification (benign, likely benign, variant of

uncertain significance, likely pathogenic, or pathogenic).

2.2. Estimation of the risk of carrying pathogenic variants (Expected data)

Using the CanRisk platform, the probability of carrying pathogenic variants for BC and/or OC will be estimated in patients, considering their clinical data and family history (Table 2).

The expected database will include the probability of developing BC and/or OC at the current age, within 5 years, within 10 years, and up to 80 years. It will also contain the hereditary BC risk category according to the National Institute for Health and Care Excellence (NICE, UK), the probability that the patient carries a pathogenic variant in any of the genes associated with BC and OC, and the individual probability for each gene (BRCA1, BRCA2, PALB2, CHEK2, ATM, BRIP1, RAD51C, RAD51D, and BARD1).

2.3. Correlation analysis

To assess the discriminatory ability of the BOADICEA model in the population of Mexican women at risk of BC and OC, the calculated area under the curve (AUC), representing the weighted average of sensitivity (true positives) and specificity (true negatives). The AUC measures the model's ability to correctly classify both positive and negative cases. All analyses were conducted using the R programming language.

3. RESULTS AND DISCUSSION

A total of 194 Mexican patients were analyzed at the Genomic Diagnostics Laboratory of the National Institute of Genomic Medicine (INMEGEN). The mean age of participants was 50 years, ranging from 21 to 90 years.

Of the total cohort, 68% (132/194) had a cancer diagnosis at the time of the study. The remaining 32% (62/194) did not have cancer at the time of the study but had a family history of BC, OC, or pancreatic cancer (Figure 1).

Within the cancer group, the majority had BC (88%, 116/132), followed by those with BC and another cancer type (5%, 7/132), including endometrial cancer, astrocytoma, skin, renal, and thyroid cancers. Cases with both BC and OC were identified in 2% (2/132), OC alone in 2% (3/132), and a group classified as "other" represented 3% (4/132), including pancreatic, thyroid, and endometrial cancers (Figure 1).

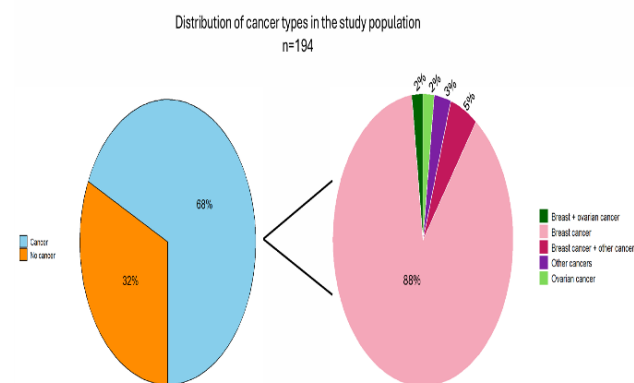


Figure 1. Distribution of cancer types among the study participants.

The 68% (132/194) had a cancer diagnosis at the time of the study. Breast cancer was the most prevalent (88%), followed by breast cancer with another type of cancer (5%), ovarian cancer (2%), and both breast and ovarian cancer (2%).

3.1 Variants Detected by NGS

In the genetic analysis of the 194 patients, 38% (74/194) harbored pathogenic or likely pathogenic variants, 33% (65/194) exhibited variants of uncertain significance (VUS), and 29% (51/194) showed no variants in the genes evaluated using any of the panels employed.

Distribution of variants detected by Next-Generation Sequencing

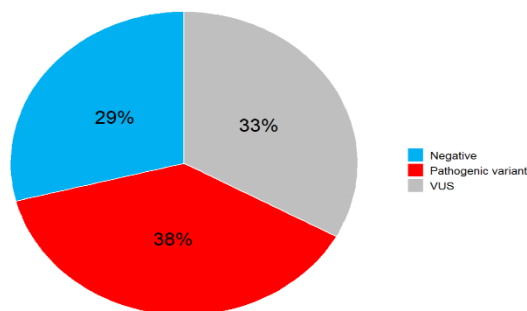


Figure 2. Proportion of patients with genetic variants (P, LP, VUS) or no variants detected (Neg).

Of the total cohort, 38% (74/194, red) of patients carried at least one pathogenic or likely pathogenic variant, followed by 33% (65/194, gray) with variants of uncertain clinical significance (VUS). No genetic variants were identified in 28% of the patients using the employed gene panels.

Among the individuals with P, LP, or VUS variants, the affected genes were identified. The genes with the highest representation of P and LP variants were BRCA1 (11%, 21/194), BRCA2 (7%, 13/194), CHEK2 (6%, 11/194), PALB2 (2%, 4/194), and CDKN2A (2%, 4/194), while the remaining genes exhibited a maximum of 1% pathogenic variants. The gene with the highest number of VUS was ATM (5%, 9/194) (Figure 3).

The red bars represent the proportion of individuals carrying pathogenic or likely pathogenic (VP) variants in each gene, while the gray bars indicate the proportion of individuals with variants of uncertain significance (VUS) in the same gene. BRCA1, BRCA2, and CHEK2 were the most frequently affected genes with P or LP variants in the study population, representing 11% (21/194), 7% (13/194), and 6% (11/194), respectively. The gene with the highest number of VUS was ATM (5%, 9/194). Patients without variants in the evaluated genes are not represented in this figure.

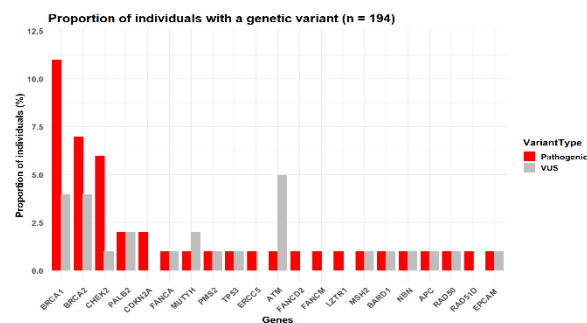


Figure 3. Proportion of patients with P, LP, or VUS variants by gene analyzed.

3.2 Variants Detected by BOADICEA

Of the 194 patients evaluated, 132/194 had a cancer diagnosis. In this group, the mean risk calculated using the BOADICEA model was 17.17 (range: 1.73–99.37), whereas in the 62/194 patients without cancer, the mean risk was 8.34 (range: 1.48–50.51).

According to the scientific literature, the established cutoff value for recommending genetic testing is 10 (39). Based on this threshold, 35% (68/194) of patients had a risk score equal to or greater than 10. Within this group, 53% (36/68) carried a pathogenic or likely pathogenic (P/LP) variant, meaning that approximately half of the high-risk patients harbored a clinically relevant variant, and can therefore be considered true positives. The remaining 47% (32/68) with a risk >10 did not have P/LP variants and are classified as false positives (Table 3, Figure 4a)

Conversely, 65% of patients (126/194) had a risk score below 10. In this subgroup, 28% (35/126) carried a pathogenic variant, representing false negatives, while 72% (91/126) had no variants or only VUS (Table 3, Figure 4a).

When the cutoff value was lowered to 5, 72% of patients (139/194) had a risk score equal to or above this threshold. Within this group, 42% (59/139) carried a pathogenic variant (true positives), while 58% (80/139) had no variants or only VUS (false positives). In contrast, 28% of patients (55/194) had a risk score below 5; of these, 22% (12/55) carried a pathogenic variant

(false negatives), and 78% (43/55) had no variants or only VUS (Table 3, Figure 4b).

Table 3. Distribution of BOADICEA estimated risk and identified genetic variants grouped according to two risk thresholds

<i>Risk estimation by BOADICEA</i>		<i>NGS análisis</i>	
Considering all genes included in the evaluated panels			
BOADICEA risk threshold	% of patients	P o LP variants	VUS or negative
≥ 10	35% (68/194)	53% (36/68)	47% (32/68)
<10	65% (126/194)	28% (35/126)	72% (91/126)
≥ 5	72% (139/194)	42% (59/139)	58% (80/139)
<5	28% (55/194)	22% (12/55)	78% (43/55)
BOADICEA risk estimation considering only <i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i> , <i>CHEK2</i> , <i>ATM</i> , <i>RAD51C</i> , <i>RAD51D</i> , <i>BRIP1</i> and <i>BARD1</i>			
BOADICEA risk threshold	% of patients	P o LP variants	VUS or negative
≥ 10	36% (48/135)	60% (29/48)	40% (19/48)
<10	64% (87/135)	23% (20/87)	77% (67/87)
≥ 5	70% (95/135)	46% (29/95)	54% (51/95)
<5	30% (40/135)	4% (2/40)	88% (38/40)

P: pathogenic; LP: likely pathogenic; VUS: variant of uncertain significance.

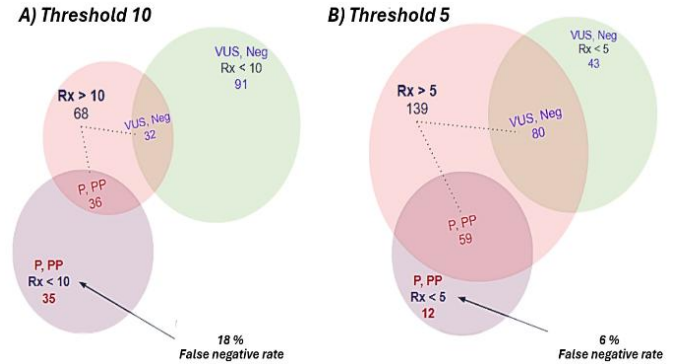


Figure 4. Relationship between BOADICEA-estimated risk and the presence of P, LP, or VUS variants in the study population.

Venn diagrams show the distribution of individuals according to the presence of pathogenic/likely pathogenic variants (P, LP) and cancer risk estimated by the BOADICEA model. (a) Comparison using a 10% risk threshold (Rx > 10% in grey; Rx < 10% in green). (b)

Comparison using a 5% risk threshold (Rx > 5% in grey; Rx < 5% in green). Pink circles represent individuals carrying P/LP variants. Black numbers indicate the total number of individuals in each intersection, while purple numbers correspond to individuals with variants of uncertain significance or negative results (VUS, Neg). This analysis evaluates the concordance between the genetic risk estimated by BOADICEA and the variant classification.

3.3 Area under the curve (AUC)

The Receiver Operating Characteristic (ROC) curve and its corresponding Area Under the Curve (AUC) are key metrics for assessing the discriminative performance of BOADICEA model. The ROC curve plots the true positive rate (sensitivity) against the false positive rate (specificity) across thresholds. The AUC summarizes the overall performance of the model into a single value, reflecting the model's ability to distinguish positive from negative cases.

In the scenario illustrated in Figure 5, the model achieves an AUC of 0.608, indicating a moderate ability to distinguish between positive and negative cases. While this performance is better than random chance (AUC = 0.5), it may be influenced by specific factors in the dataset: for instance, the NGS evaluation considered the number of variant copies, which BOADICEA does not account for, and certain genes such as BRCA1 have a high frequency in the Mexican population.

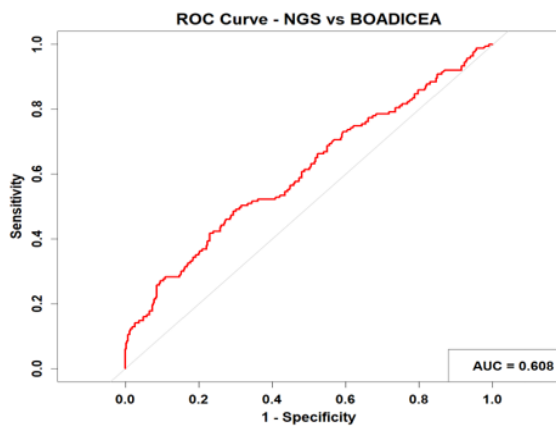


Figure 5. Receiver Operating Characteristic (ROC) curve for BOADICEA model.

The curve plots sensitivity versus specificity across different thresholds. The Area Under the Curve (AUC = 0.608) indicates the model's moderate ability to discriminate between positive and negative cases in relation to the observed in NGS.

4. PRELIMINARY CONCLUSIONS

This study analyzed 194 Mexican women at INMEGEN, revealing key insights into the genetic landscape of hereditary breast and ovarian cancer in this population. BRCA1 was the most frequently affected gene, with 11% of patients carrying pathogenic variants, including the exon 9-12 deletion, a known founder variant in Mexico. BRCA2 and CHEK2 contributed 7% and 6% of pathogenic/likely pathogenic variants, respectively, with recurrent variants such as CHEK2 L236P observed.

The BOADICEA model demonstrated a mean estimated risk of 17.17 in patients with cancer and 8.34 in those without. Using the recommended risk threshold of 10% resulted in 18% false negatives. Lowering the threshold to 5% reduced false negatives substantially but increased false positives, highlighting a trade-off between sensitivity and specificity.

The AUC observed suggests that there is room for improvement in enhancing the model's discriminative power. Overall, the findings suggest that BOADICEA can provide useful risk estimates for the Mexican population, but risk thresholds may require adjustment to optimize predictive performance. The results also underscore the importance of considering population-specific founder variants in genetic counseling and testing strategies.

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Conflicts of interest

The authors declare no conflict of interest.

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263-II-PP RATIONAL DESIGN OF NEW INHIBITORS ANTI-HER2 THROUGH COMPUTING APPROACHES

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Abstract: The study employs rational-in silico design strategies to develop novel selective inhibitors against one member of the Epidermal Grow Factor Receptors (EGFR): Human Epidermal Receptor 2 (HER2), overexpressed in breast cancer. A set of bioinformatics tools were integrated to generate a potential therapeutic agent, seeking to minimize the adverse effects associated with current treatments.

Keywords: HER2, rational design, antagonist therapeutic agents.

1. INTRODUCTION

Diseases are anomalous expressions that happened at cellular level due to misalignment on biomolecular machinery, both by errors at genetic material transcription needed for proteins production, or even till the overexpression of cellular components [1].

A reason given for the breast cancer clinical cases, for example, is founded at HER2 protein level, which is one member of the tyrosine kinase receptors family: Epidermal Grow Factor Receptors (EGFR) [2].

In this sense, as one of the most common physiological causes of cancer death in Mexican women [3], it has been reported that 15-20% of ductal carcinomas overexpress HER2 [4].

Additionally, it has been demonstrated that the persistent therapies resistance of breast cancer cells HER2-positive due to, among other oncogenic causes, HER2 T798M

mutation [5], causing failure in the treatment of HER2-positive breast cancer [2].

Thus, to address cancer issues, various strategies have been created for its treatment according to natural or mutational disease origin itself; receptor-inhibitors kind tyrosine kinases, by mentioning someone. From these inhibitors, exist two possible types: monoclonal antibodies (mAb), which functionality consists likewise a drug-nanocarrier associating on HER2 extramembrane domain, carrying to inhibition of the protein. On the other hand, there exist direct antagonist inhibitors, permeable to cell membrane, that get coupled to the receptor union site localized on its intracellular domain, serving as competitive inhibitors against ATP, a natural HER2 endogen substrate [6].

Due to HER2-action mode, a previous structural analysis conducted by our research group allowed us to characterize the orthosteric site of HER2, as well as additional cavities capable of accommodating ligands with competitive inhibitory activity against ATP [7].

Based on the principles lastly mentioned, the present work aims to describe the rational design of new molecules (Figure 1) as potential therapeutic antagonists targeting wild-type and mutant HER2-positive breast cancer.

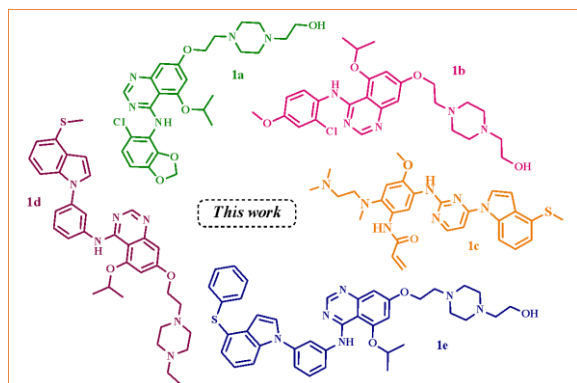


Figure 1. Molecules rationally designed in this work.

2. MATERIALS AND METHODS

2.1. Graphical visualizer

There were used visualizer PyMOL Molecular Graphics System, Version 2.6 Schrödinger, LLC. [8], and MOE (Molecular Operating Environment), Version 22 [9].

2.2. Structural models

The reference ligand models used for this objective were three: the co-crystallized ligand (**ccl**), founded in the empiric crystal model 7JXH (PDB) [10]; tak-285 [11], that is an inhibitor, currently probed for the treatment of breast cancer; and compound CAS 692055-34-8 [12], that is other model studied previously for the inhibition activity of receptor HER2 (Figure 2).

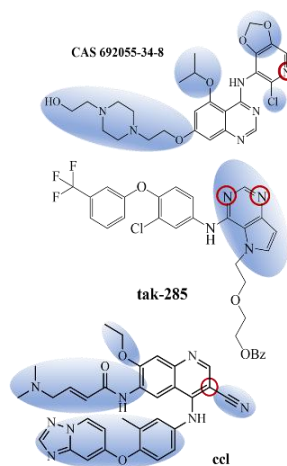


Figure 2. Reference ligand models

On the other hand, the inactive HER2 (*HER2_{in}*) -native and HER2 T798M mutant

conformations were taken as sheet the empiric crystal model 7JXH (PDB) [10].

2.3. ADMET properties determination

Following a virtual screening methodology, the structural modifications were tested in SwissADME online server [13], to predict physicochemical and toxicological properties. Thus, those molecular systems that had similar properties to those exhibited by **tak-285** could follow with the next probes.

2.4. Docking of reference and new compounds

A molecular docking technique was carried out, in order to determine the best energetic behavior, conformation, and direction of its substituents, according to the best pose acquired by tak-285 and **ccl** in the union site of HER2.

This exercise was done as a direct docking to the targeted residues T862, D863 and F864 (according to PDB numeration) using MOE package (Molecular Operating Environment V.22). Additionally, it was generated a blinded docking calculus using SwissDock (SD) online server, to support the recurrent binding site at which all the ligands tend to dock.

2.5. Molecular dynamic simulations

Molecular dynamic simulations were performed under explicit-solvent boundary conditions using the AMBER16 package [14] in conjunction with the ff14SB force field [15] and the TIP3P water model [16].

The total time for one simulation was 100 ns, carrying on three different experiments for each ligand. Thus, the most stable conformation of each system was determined from the means of these triplicated experiments.

2.6. Binding free energy calculation

To calculate the binding free energy (ΔG_{bind}) between wild type-HER2 or HER2-T798M mutant and the ligands, the MMGBSA/MMPBSA method was employed.

3. RESULTS AND DISCUSSION

3.1. Proposal design

From the structural models (Figure 2) were identified the bioisostere and isostere groups that could be replaced by or even combined with principal cores. For example, quinazoline and indole cores demonstrated to be principal actors for reaching the best reversible binding energies (ΔG) and the best binding modes. According to this, the molecular structural purposes shown in Figure 1 were designed.

The structural modifications were evaluated *in silico* through coordinate employed bioinformatic tools like pharmacophore modeling, ADMET properties, molecular docking (blinded and directed) and molecular dynamics simulation (Figure 3). We used as reference the predicted ADMET properties evaluated for lapatinib, a nowadays accepted therapeutic drug for breast cancer treatment, as well as the best affinity energy acquired from molecular docking between tak-285 and wild type-HER2 or HER2-T798M mutant.

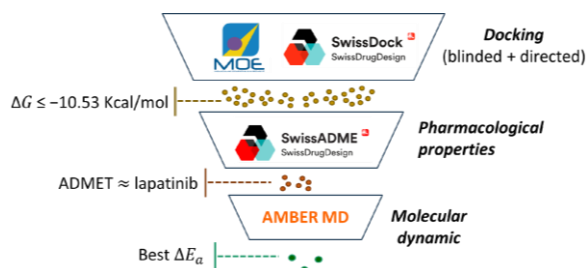


Figure 3. Rational design developed through different bioinformatic tools.

3.2. Molecular interactions

Observing the affinity capability and fashion binding of new derivatives through *HER2_{in}*-native, it was decided to evaluate at the same way, by docking, the response front to same receptor but on its mutated form. This means, front to HER2-T798M mutant.

This was carried out previously modifying wild type-HER2, stabilizing an amino acid change from threonine (T) to methionine (M) in position 798 base chain (PDB 7JXH).

For example, results found in molecular docking studies (directed and blinded, Figure

4), between ligand 1d and *HER2_{in}* receptor, using MOE package and server SD, showed a binding fashion near to that acquired by **ccl**, as well as a binding energy higher to **tak-285**.

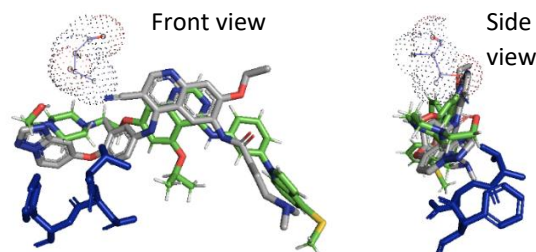


Figure 4. Ligand/receptor binding modes example given to 1d/*HER2_{in}* native. Green = 1d; grey = ccl (PDB 7JXH); blue = amino acid residues (T862, D863, F864); dotted spheres = T798M residue electronic density.

As Table 1 suggests, we could infer theoretically in first instance that 1d and 1e can be potential inhibitors for both *HER2_{in}* isoforms (native and mutated).

Table 1. Maximum binding energies (docking, ΔG = [Kcal/mol]): *HER2* receptor (native and mutated) against different ligands.

Ligands	HER2 receptor			
	Native		T798M	
	MOE	SD	MOE	SD
ccl	-11.22	-10.16	-9.70	-10.80
1a	-8.56	-10.78	-8.78	-8.99
1b	-8.92	-10.52	-9.62	-9.08
1c	-9.77	-10.27	-9.81	-9.09
1d	-10.66	-11.50	-10.21	-9.82
1e	-11.12	-11.49	-9.95	-10.32
tak-285	-9.60	-10.33	-8.10	-9.24

3.3. Molecular dynamics simulations

Afterwards identification of the best conformers of the new ligands, these were undertaken to a molecular dynamic simulation. This work sets out the study of the best ligand conformers with *HER2_{in}* receptor on its native and mutated (T798M) state. In this report the simulations for all ligands 1a-1e and tak-285 are registered.

From the resulting interactions and binding modes of the five new ligands with *HER2_{in}* -

native and mutated- receptor, it was observed, in general, the stability reached by the protein with each ligand on a mean time near to 80 ns -for a total simulation time of 100 ns-. Also, both *HER2_{in}*-native receptor molecular motions along the time were significantly reduced with ligands 1a and 1c (Figure 5a), and with derivatives 1a and 1b in the isoform *HER2_{in}*-T798M (Figure 5b), taking as reference tak-285 RMSD-profile.

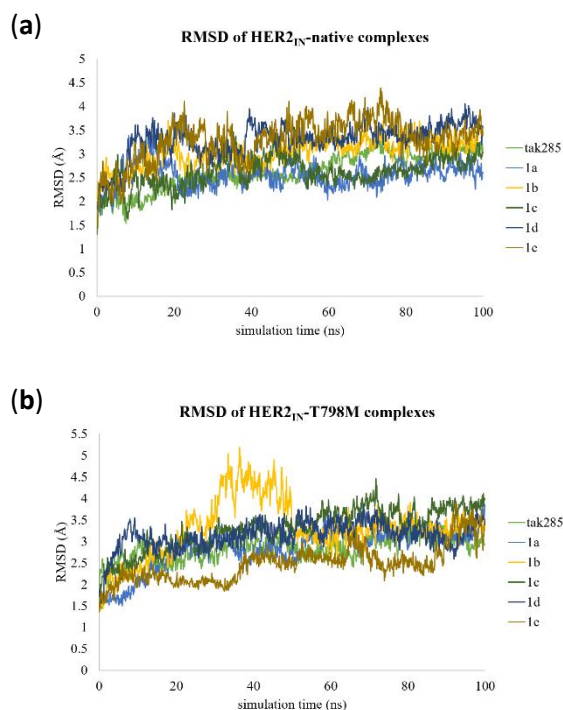


Figure 5. Geometrical parameters. Root means square deviation (RMSD) studies obtained for native (a) and mutated (b) isoforms of *HER2_{in}*-receptor molecular motions.

Even though we observed the molecular movements profiles of 1a-1c as the nearest to the reference ligand (tak-285), only when we analyze the complete simulation movies (data not given) of each system ligand-receptor -for native and mutated receptor forms-, and also have determined the energy affinity from the mean of some of the best ligand conformations obtained after simulations (Table 2), we could be able to discriminate ligands 1d and 1e as potential inhibition analogs for both *HER2* isoforms.

Table 2. Maximum binding energies ($\Delta G = [Kcal/mol]$): *HER2* receptor (native and mutated) against different ligands after molecular dynamic simulations.

Ligands	HER2 receptor	
	Native	T798M
1b	-39.1 ± 5.89	-
1c	-	-46.88 ± 0.65
1d	-56.57 ± 6.59	-56.78 ± 5.19
1e	-65.7 ± 7.91	-55.99 ± 8.3
tak-285	-52.91 ± 1.55	-20.71 ± 9.24

This result supports the theoretical capacity of ligand 1d, observed from the docking study (section 3.2 Molecular interactions), to have an acceptable degrade of response to establish a stable interaction with both native and mutated *HER2* receptors.

4. CONCLUSIONS

Despite of *HER2* is one of the most studied targets for the design of novel drugs against breast cancer, it is possible to generate new molecular systems for its treatment, even more considering the capability of this receptor to arise mutations.

Theoretical results found at current development of the project (Figure 1) suggest that compounds 1d and 1e exhibit favorable thermodynamic profiles as potential antagonists of both wild-type and mutant *HER2*. However, further experimental probes are going to be done as part of the present master's degree project (SECIHTI 4043367). For this, we are considering the chemical synthesis of systems 1d and 1e and their subsequent *in vitro* assessment on a panel of *HER2*-positive breast cancer cell lines to determine their inhibitory potential.

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Politécnico Nacional (National Polytechnic Institute).

Conflicts of interest

The authors declare no conflict of interest.

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283-II-PO PHARMACOPHORE MODELING FOCUSED ON DRUG REPOSITIONING WITH DUAL INHIBITORY ACTIVITY ON PI3K/MTOR FOR THE TREATMENT OF BREAST CANCER

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Abstract: In recent years, breast cancer (BC) therapy design has focused on overexpressed therapeutic targets, seeking to generate more selective therapies and reduce adverse effects. One of these targets is the PI3K-AKT-mTOR pathway, which is closely associated with cell proliferation, survival, cell invasion, migration, angiogenesis, and chemoresistance. The design and development of inhibitors of this pathway have yielded promising results, particularly dual inhibitors, which reduce the development of chemoresistance; however, adverse effects have limited their clinical use. In this work, a pharmacophore modeling approach based on tertiary structures of the therapeutic targets and co-crystallized dual inhibitory ligands was used. Pharmacophore maps targeting PI3K/mTOR were developed, refined and were used in a virtual screening with FDA-approved drug databases. Subsequently, molecular docking studies were performed to identify the main binding sites and the binding modes between the targets and the promising drugs. These studies allowed the identification of drugs that interacted with the catalytic site of PI3K and mTOR, of which, BIC was selected for *in vitro* evaluation. Cell proliferation assays were performed in BC cell lines MDA-MB-231 (triple negative) and MCF-7, (luminal), and MCF-10A, non-tumorigenic mammary cells, with BIC and the positive controls PI-103 (dual inhibitor) and buparlisib (pan-PI3Ki). A more pronounced antiproliferative effect was observed with BIC on BC cell lines (IC₅₀ MCF-

7: 30.6 μ M; IC₅₀ MDA: 116.6 μ M; as well as on non-cancerous cells MCF-10A IC₅₀: 151.3 μ M) at 72 h. The selectivity index showed that BIC has greater selectivity towards cancer cells than the reference compounds PI-103 and Buparlisib (4.9, 2.5 and 2.5 respectively).

Keywords: Breast cancer, Pharmacophore modelling, Drug repurpose

1. INTRODUCTION

Cancer is a group of diseases characterized by abnormal and rapid uncontrolled cell growth capable of initiating on any tissue [1]. It is known that cancer originates from cells that have been transformed into a cancerous phenotype due to accumulations of genetic, epigenetic and transcriptional alterations that lead to cellular senescence, increased proliferation, evasion of the immune system and decrease of growth suppressors, deregulation of cellular metabolism, resistance to cell death, among others [2].

Within the different types of cancer, the affected tissues with the highest incidence are lung, prostate, stomach, cervix, liver and breast tissue [1]; the latter being one of the most prevalent types of cancer globally [3]. Breast cancer can originate in cells of the lobules or epithelial cells of the ducts, which proliferate in an uncontrolled manner generating tumor masses that, depending on the intrinsic properties, can lead to the death of the patient [1]; it is considered a heterogeneous disease, due to differences between the types of cancer that range from location to changes in the profile of genetic expression [2].

Several classifications have been created according to several morphological and molecular criteria of the transformed cells. One of them is the molecular classification, which is based on differences in genetic expression and immunohistochemical profiles: Luminal A (ER+, PR $\geq$ 20%, HER2-, low Ki67), Luminal B (ER+, PR<20%, HER2+/-, high Ki67), HER2-enriched (ER-, PR-, HER2+, high Ki67) and Triple negative (ER-, PR-, HER2-, high Ki67), which allows defining the prognosis of the disease, as well as treatment options [3].

Nowadays, there are multiple treatment options, which can be nonspecific or directed towards a biological target of the tumor, such as the expression of a receptor type [4,5,6]. One of the main forms of treatment is chemotherapy, which consists of the administration of one or more cytotoxic chemical agents; although these therapies are considered effective in the treatment of breast cancer, new treatment agents have been sought that present a better risk-benefit ratio, are more selective towards transformed cells, increase the 5-year survival rate (5-year survival rate of current therapies is 84% and 1 year for advanced stages) or reduce/eliminate chemoresistance processes in addition to the multiple adverse effects [5,6]. One of the approaches to the design of new therapies are agents that act on overactivated signaling pathways in cancer cells, one of these is the PI3K-AKT-mTOR (PAM) pathway [7], a complex network of intracellular interactions with a fundamental role in essential cell activities such as cell growth, regulation of cell metabolism, proliferation, angiogenesis, cell cycle and apoptosis [7].

In breast cancer, the PAM pathway is often altered as a result of mutations in PI3K/AKT and loss of phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase (PTEN), a regulatory protein of this pathway, which generates overactivation and the development of the phenomena of deregulated metabolism, uncontrolled growth, evasion of programmed cell death

and phenomena of adaptation and resistance to treatment by these cells and therefore, a poor prognosis in patients due to the appearance of tachyphylaxis and allowing ER-cells to develop estrogen-independent growth forms [7,8,9]. Currently, there are multiple chemotherapeutic agents that target proteins in this signaling pathway that have shown promising results, such as Everolimus, a selective inhibitor of the regulatory subunits of mTORC1, which has shown an increase in the survival rate in patients in clinical studies [7]; however, these agents have multiple adverse effects and require use in combination therapy studies [10,11].

Drugs with Dual Inhibitory Activity. Due to the high homology between the active sites of PI3K and mTOR, in recent years there has been a search for compounds with simultaneous inhibitory activity against these two biological targets. This has arisen as a result of the need to eliminate the potential positive feedback loops, crosstalk, and chemoresistance present in inhibitors of this pathway already used in cancer therapy. From these compounds, it was observed that they are not only capable of inhibiting cell proliferation, but also promote apoptotic processes, exhibit greater potency, have demonstrated their ability to reduce the effects of chemoresistance, and can inhibit all catalytic forms of PI3K and mTORC1 and mTORC2 [9, 12]. Some examples of this class of compounds are Dactolisib and Samotolisib, candidates to be incorporated into the clinic, which present a desirable potency, solubility and adequate pharmacokinetic profiles; in preclinical and clinical studies, concomitant therapeutic regimens with other chemotherapeutic agents have been proposed as a result of their ability to enhance the effects of other chemotherapeutic agents [13].

However, none of the designed compounds with dual inhibitory capacity towards PI3K and mTOR have been approved to be used as treatment for cancer by regulatory agencies due to multiple reasons, ranging from their adverse effects, solubility and metabolic

instability. Therefore, multiple new strategies have been sought to allow the creation or identification of new molecules that can overcome these obstacles [9, 14]. Since breast cancer treatments usually have low selectivity and moderate to low efficacy, as well as the potential chemoresistance appearance to standard regimens, treatment schemes often lead to more aggressive therapies (switching from tamoxifen to aromatase inhibitors) [15]. Therefore, the search for new, more selective treatments with fewer adverse effects or a higher risk-benefit ratio has led pharmaceutical companies, health institutes, and research groups to search for and synthesize new molecules. However, these studies are costly and often take decades before the drug is released to market. Furthermore, *in silico* tools allow for massive screening of known drugs for repositioning strategies, which has multiple advantages, such as the use of fewer resources, a decrease in the cost of clinical research, synthesis and characterization, and a reduction in the time to market release from decades to years. The present study sought to identify compounds with the potential to be repositioned in the treatment of breast cancer through a multidisciplinary approach that would allow the selection of compounds that exhibit an antiproliferative effect mediated by the simultaneous inhibition of PI3K and mTOR.

2. MATERIALS AND METHODS

2.1. Development of a Pharmacophore Map Targeting mTOR and PI3K

The tridimensional (3D) structures characterized by NMR, X-ray diffraction, cryo-electron microscopy and those obtained by homology modeling of PI3K and mTOR proteins were searched, selected, and downloaded from the PDB database (<https://www.rcsb.org/>). Structures with PDB codes PI3K: 4L23, 7TZ7, 8EXL, 8SBC, 7K6M, 5UBR, 4WAF, 4JPS, 8EXO were selected. mTOR: 4JSX, 4JT5, 4JT6, 4JSP, since they presented a co-crystallized inhibitor, the lowest number of artifacts and unmodeled sequences and were treated in Biovia

Discovery Studio Visualizer v21.1.0 [16]. Subsequently, polar hydrogens and Kollman charges were added in the AutoDockTools v1.5.7 [17] to be used in the docking studies; in parallel, the files of the co-crystallized ligands were prepared employing AutoDockTools v1.5.7 [17] to create rotatable bonds between atoms, charge assignment and addition of polar hydrogens. Once the files were prepared, the protein complexes obtained from PDB were loaded into the LigandScout v4.4.9 software [18] and the interacting amino acids and the ligand were minimized, and the pharmacophore maps directed to PI3K and mTOR were generated.

2.2. Virtual Screening of the FDA Database

Using the generated pharmacophore maps, the FDA-approved drug database was downloaded and loaded into LigandScout 4.4.9 software [18] to perform a virtual screening and select drugs that exhibit a good fit-score and included within their structure the geometric spatial arrangement of at least 80% of the necessary molecular interactions reported in the pharmacophore maps.

2.3. Molecular Docking Studies of FDA approved Drugs

Once the candidates of the FDA-approved database that presented the best fit to the pharmacophore map were identified, AutoDockTools v1.5.7 [17] software was used to perform blind molecular docking tests (whole protein size interaction grid) as well as a directed molecular docking assay toward the alpha carbon of the amino acids PI3K: Met922; mTOR: Leu2185 on the 4JT6 and 4L23 structures (grid area: 70 Å³, spacing: 0.375 Å) due to the presence of a co-crystallized dual inhibitor (PI-103), in order to determine the ligand interactions and affinity toward the active sites respectively. Once the molecular docking results were obtained, the ligands with the best fit-score to the pharmacophore map and the greatest affinity towards PI3K and mTOR were selected, which were then subjected to a final filter by means of a bibliographic review in which those compounds that already have reported

inhibitory activity towards PI3K/mTOR, have previous studies as inhibitors of these targets or are currently used in antineoplastic therapies were discarded.

2.4. *In vitro* evaluation of drugs obtained by virtual screening

MCF7 (Luminal; ER+, PR+, HER2-) and MDA-MB-231 (Triple negative; ER-, PR-, HER2-) cell lines were used to evaluate the potential anticancer activity of the repositioned drugs and compared with the non-cancerous epithelial cell line MCF-10A.

2.5. Cell line culture

Cell lines were seeded in 100 mm x 20 mm Petri dishes and DMEM culture medium enriched with essential amino acids and fetal bovine serum (7% MCF7; 10% MDA-MD-231) and 1000 IU/mL streptomycin/penicillin was added, and incubated at 37 °C, 1 atm, 5% CO₂ [19, 20]. For the MCF-10A cell line, DMEM F-12 culture medium enriched with 334 µL of hydrocortisone stock solution (50 µg/mL), 100 IU/mL insulin, 1 µL of epidermal growth factor solution (1 µg/µL), 5% fetal bovine serum and 1000 IU/mL streptomycin/penicillin was added [21].

2.6. MTT Cell Viability Assay

Metabolic cell viability assays using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) were performed to ensure the anticancer activity of the compounds. Cells were disrupted using 1% trypsin-EDTA (0.53 mM). Once detached, they were centrifuged with culture medium at 3000 rpm for 10 min. The supernatant was decanted, and the cells were resuspended with 1 mL of medium. Cell counts were determined using an automated counter to collect a sample containing the number of cells required for seeding in 96-well plates. Cells were incubated for 24 h at 37 °C, 5% CO₂ to allow re-adhesion. After this time, positive controls (Dual: PI-103 and pan-PI3K: Buparlisib) and candidate drugs were administered at 316, 100, 31.6, 10, 3.16, 1, 0.316 and 0.1 µM in each well for 72 h [22]. Finally, 20 µL of MTT solution was added and incubated

for 3 h. At the end, the formazan crystals formed were solubilized in 100 µL of DMSO and the absorbance at 550 nm was recorded in an Elisa reader [22]. Once the IC₅₀ values were obtained, the Selectivity Index (SI) was calculated using the following formula $SI = IC_{50} \text{ Healthy cell line} / IC_{50} \text{ Cancerous cell line}$ [23].

2.7. Statistical Analysis

The data obtained was analyzed using GraphPad Prism v.10.2.3 [24]. Analysis of variance (one-way ANOVA) and Bonferroni post hoc test was used to assess the statistical significance at P<0.05. IC₅₀ values were calculated from the results of MTT using GraphPad Prism v.10.2.3 with the option of a nonlinear regression analysis of inhibitor concentration versus normalized response. Data are represented as the mean of three replicates of each concentration in sextuplicate ± standard deviation.

3. RESULTS AND DISCUSSION

The strategy employed in the search for dual inhibitors was an approach through the development of pharmacophore maps based on multiple crystal structures of PI3K and mTOR. The subsequent refinement allowed us to find common compounds identified by the majority of the maps. This strategy was based on the methodology used by Arooj et al. in 2013 [25], with the aim of achieving greater discriminatory capacity for compounds with biological activity. Thirteen crystal structures with good structural quality and active site integrity were used to develop the pharmacophore maps (Figure 1).

Analysis of the interacting amino acids with each map allowed the identification of common amino acids that match those reported in the literature. These include, in the case of PI3K, the hydrophobic amino acids Ile800, Ile848, Ile932, Met772, Met922, and Val850; hydrogen bond-forming amino acids Lys802 and at the backbone of Val851 as well as structural water molecules within the binding pocket [26]; and in the case of mTOR to the hydrophobic amino acids Ile2163,

Ile2237, Ile2356 and the hydrogen bond-forming at the backbone of the amino acid Val2240 [27].

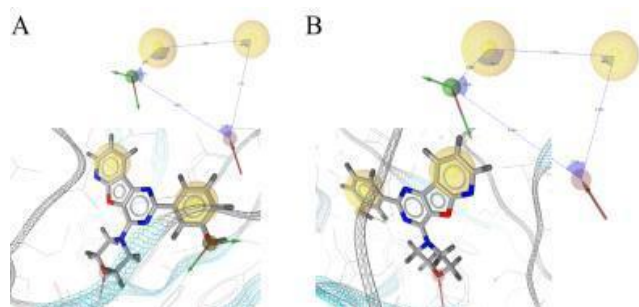


Figure 1. Example of structure-based pharmacophoric map targeting PI3K (A) and mTOR (B) obtained from crystals 4L23 and 4JT6, where hydrophobic regions are denoted as yellow spheres, hydrogen bond acceptors as red vectors and hydrogen bond donors as green vectors.

When screening the FDA database, an average of >200 compounds were found in each map that presented a pharmacophore fit-score greater than 40%. From these, a database was created to search for compounds that were identified by more than 50% of the maps and that were present in both proteins. After this refinement, 49 compounds were identified as potential candidates, from which discontinued compounds were eliminated, resulting in 20 compounds that were evaluated by molecular docking studies. By jointly analyzing the blind and targeted molecular docking studies, molecules were identified that exhibit affinity for both proteins based on binding energy values (Figure 2A and 2C), as is the case with Imatinib and Dasatinib (kinase inhibitors with reported interaction with PI3K). However other candidates were also identified, such as BIC (DB11799), a drug that has no history of chemotherapy use or interactions towards PI3K and/or mTOR, presenting ΔG values of -5.26 and -6.68 kcal/mol respectively and a binding mode >80% in both proteins comparatively with the co-crystallized dual inhibitor. By analyzing the binding mode in the protein pocket, it was observed that BIC meets the criteria analyzed by Takeda *et al.*, in 2016 [28] and by Poulsen *et al.*, in 2014 [29] by

acquiring a semi-flat conformation in the binding pocket thanks to its core of fused rings and interaction with the critical amino acids previously reported by the presence of functional groups capable of forming hydrogen bonds (Figure 2B and 2D).

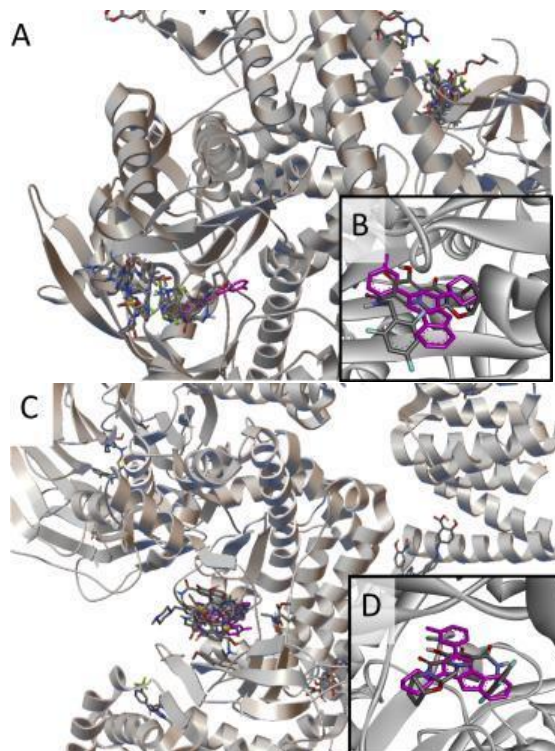


Figure 2. Main conformers obtained from each ligand evaluated in blind molecular docking assays towards PI3K (A) and mTOR (C), as well as the alignment of the ligand with the best fit to the pharmacophoric map and best results in molecular docking studies (BIC) towards PI3K (B) and mTOR (D) compared to the co-crystallized ligand PI-103 (pink).

Based on the results scored in the *in-silico* assays obtained from the structure-based pharmacophore maps and molecular docking, OPI (DB11632), BIC, BIM (DB00905), and DAQ (DBMET00290) were considered as potential candidates for repositioning (Table 1). BIC was acquired due to its affordability and promising results, as well as PI-103 and Buparlisib as positive controls for the biological evaluation of the antiproliferative effect based on the background found during the bibliographic review. *In vitro* results of cell viability evaluation of the PI-103 control showed an

IC₅₀ = 12.33 and 5.25 μ M for the MDA-MB-231 and MCF-7 cell lines, which is within the range of what was previously reported experimentally by other research groups [30,31]. Similarly, the IC₅₀ calculated for the compound Buparlisib was 25.62 and 8.25 μ M for the same cell lines. This difference in the IC₅₀ between the luminal and triple negative cell lines can be attributed to intrinsic characteristics in the activation state of the PAM pathway effector proteins, such as the mutational activation of the PI3KCA catalytic unit (MCF-7) or the overactivation of multidrug resistance mechanisms (MDA-MB-231) as proposed by Ker Yu et al. in 2008 [32].

Comparatively, the IC₅₀ for the MCF10A cell line highlights the low selectivity between cancer cells and non-cancer cells by both treatments, being relatively close to that obtained in MDA-MB-231 and MCF-7, which clarifies the search in recent years for other more selective compounds or less aggressive combinatorial therapeutic schemes in order to avoid the adverse effects that currently occur in therapeutic schemes that use them. When evaluating BIC, a decrease in viability was observed from a concentration of 100 μ M in the MDA-MB-231 and MCF-10A cell lines, and from 31.6 μ M in the MCF-7 cell line, which corresponds to what was expected from the results obtained in the positive controls; additionally, significant changes in cell morphology were observed in MDA-MB-231 treated with the compound at 100 μ M in addition to a reduction in cell confluence. And, although the mechanism of cell death cannot be elucidated with the current studies and results, these changes are possibly attributed to the triggering of an apoptotic event attributable to the presence of changes in cell size, blebbing, and pyknosis, as reported by Syed Abdul et al., in 2013 [33]. Comparing the IC₅₀ results obtained by BIC in the cell lines with the controls used in the study, the concentration required to obtain a reduction in cell viability is higher than that of the controls; however, it must be taken into consideration that the difference in IC₅₀

between the MCF-10A cell lines and the cancer cell lines generates a much broader treatment range than the controls comparatively (Table 2).

Table 1. Scoring of the dual inhibitory potential capacity score of the compounds obtained from the structure-based pharmacophoric maps relative to the PI-103 control

	Fit-Score	ΔG x 10				% Binding mode		Σ Score
		PI3K (B')	PI3K (F'')	mTO R (B')	mTO R (F'')			
						PI3K	mTO R	
PI-103	52.7	84.0	83.0	88.0	107.0	100.0	100.0	614.65
BIC	55.8	62.3	82.9	132.4	117.7	87.5	88.9	627.46
OPI	54.0	83.0	106.1	90.7	111.8	87.5	77.8	610.89
DAQ	53.8	57.8	75.9	82.9	114.1	75.0	77.8	537.25
BIM	50.1	N/A†	70.5	77.6	108.2	50.0	55.6	411.99

†Drug mainly targeted other sites on the surface of the protein

•: Average Fit-Score obtained from the screening of all structure-based maps

*B: Blind docking free energy calculation

**F: Focused docking free energy calculation

Table 2. IC₅₀ values of drugs per cell line evaluated after 72 h of exposure to the treatment.

	Concentration (μ M)		
	MDA-MB-231	MCF-7	MCF-10A
PI-103	12.33	5.25	12.91
Buparlisib	25.62	8.25	21.01
BIC	116.60	30.55	151.30

Therefore, it was decided to calculate the selectivity index of the compounds towards each cell line, and it was observed that BIC presented a ~2-fold greater selectivity towards luminal cancer cells than PI-103 and Buparlisib (4,952, 2,459, 2,546 respectively). If this behavior is comparable to what occurred in an organism, it indicates greater selectivity of the compound for cancer cells than non-

cancer cells and could mean a treatment with fewer adverse effects.

4. CONCLUSIONS

The development of structure-based pharmacophoric maps for the search for dual PI3K and mTOR inhibitory molecules, in conjunction with molecular docking studies, identified the compound BIC as a potential dual PI3K/mTOR inhibitor. *In vitro* cell viability assays determined its antiproliferative activity in breast cells, with a greater effect on cancer cells. This makes it an attractive candidate for the potential repositioning of this drug in breast cancer treatment; however, further studies are required to fully elucidate the mechanism and type by which the cell death is mediated.

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Conflicts of interest

The authors declare no conflict of interest.

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43-III-PO BETWEEN GENTRIFICATION AND TOURISTIFICATION: BIBLIOMETRIC ANALYSIS OF BUILT HERITAGE IN LATIN AMERICAN CONTEXTS

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Abstract: This research examines the intersection between transnational gentrification, touristification, and built heritage in the central neighborhoods of Mexico City. To this end, a systematic review of the literature and a bibliometric analysis were conducted using VOSviewer, based on an initial corpus of 1,900 references, which was refined in successive phases to form 65 documents published between 2014 and 2024. The co-authorship and co-occurrence analysis identified the main references in the field (Navarrete, Delgadillo, Hayes, López-Morales, Díaz-Parra, and Janoschka) and grouped the output into four thematic areas: real estate valuation and financialization, socio-cultural effects of displacement, public policies and heritage preservation, and touristification linked to digital platforms.

The results show that the literature emphasizes the relationship between transnational migration and urban revaluation processes, documents touristification as a catalyst for gentrification, and questions the role of state policies in socio-spatial exclusion. However, a significant gap was identified: the scarcity of studies that systematically and comparatively analyze the architectural and morphological transformations of built heritage (facadism, contemporary insertions, changes of use).

In conclusion, the bibliometric analysis shows that, although there is a consolidated body of work in the economic, social, and cultural spheres, research integrating GIS, architectural inventories, and longitudinal

analyses is needed to understand the material traces of transnational gentrification. The thesis from which this document emerges aims to fill this gap by providing empirical evidence on the architectural transformations of heritage in the central neighborhoods of Mexico City.

Keywords: Transnational gentrification, touristification, lifestyle migration, heritage, bibliometric analysis.

1. INTRODUCTION

In the 21st century, human mobility has taken on a markedly transnational dimension: in addition to traditional labor flows, there has been an emergence of movements motivated by the search for lifestyles such as climate, heritage, cultural environments, and new forms of temporary or semi-permanent residence (e.g., residential tourism and digital nomads). These movements, often led by populations with greater purchasing power from economies in the Global North[1], have transformed the logic of the city in ways that go beyond mere mobility: they are reconfiguring real estate markets, land use, and heritage conservation practices. In this context, the notion of lifestyle migration helps to understand actors and motivations that do not fit into the classic framework of labor migration[2]. The convergence of transnational migration, touristification, and the valorization of built heritage has driven specific forms of gentrification in the Global South[3], which we refer to in this document as transnational gentrification[4], where foreign actors (residents, retirees, digital

nomads, long-stay tourists) generate demand for housing and services geared toward higher-income consumption, transforming central neighborhoods and historic centers[5], [6]. These processes not only increase prices and encourage real estate speculation, but also materially modify heritage buildings (typological adaptations, facadism, contemporary insertions) and erode the community meanings associated with heritage.

In Latin America, touristification[7] is understood as the planned or deliberate adaptation of central areas for the enjoyment of visitors, which often acts as an accelerator of transnational gentrification[8], [9]. Public policies for heritage revitalization, tax incentives, and public-private partnerships have created favorable conditions for real estate revaluation and the entry of transnational capital. The emergence of digital platforms (such as Airbnb) and the emerging figure of the digital nomad intensify pressure on traditional residential supply and amplify the effects of displacement, both material and symbolic.

Based on a systematic review of the literature (institutional databases + open access search engines) and a bibliometric analysis with VOSviewer on an initial selection of 296 references, which was filtered down to a final selection of 74 relevant documents, the authors and central themes that guide the debate were identified: academic production focused on land economics (rent gap, financialization), sociocultural transformations (loss of identity, elitization), and the active role of the state in promoting touristification. The visualization of co-authorship and co-occurrence networks highlighted the centrality of authors such as Navarrete, Delgadillo, Hayes, López-Morales, Díaz-Parra, and Janoschka, which supported the selection and detailed analysis of the bibliographic corpus.

However, bibliometric analysis and critical reading reveal a significant gap in this thesis:

although there is abundant literature on socioeconomic and displacement effects, there are few studies that systematically and comparatively examine the specific architectural and morphological transformations of built heritage resulting from transnational gentrification (i.e., typological changes, façade interventions, contemporary insertions, and their relationship with heritage regulations). This gap justifies the research presented here, which proposes an approach that combines spatial, documentary, and ethnographic analysis to document how transnational mobility not only leaves material traces but also has adverse social effects on the central neighborhoods of Mexico City.

Finally, this research is based on the hypothesis that transnational migration is a distinctive and recent driver of the transformation of built cultural heritage in central neighborhoods: its demands, consumption practices, and purchasing power introduce logics of revaluation that not only displace populations but also reconfigure the form, use, and meaning of heritage. The following chapter describes in detail the methodology applied, including the bibliographic matrix used in the systematic review and the criteria applied in VOSviewer for its bibliometric analysis.

2. MATERIALS AND METHODS

The bibliometric analysis was designed to identify the most influential authors and conceptual nodes at the intersection of gentrification, touristification, and transnational migration in the global south. Starting with a collection of > 1,900 references (imported and organized in Mendeley), thematic and geographic filters were applied to form a subset of 296 records linked to Latin America. This set was processed in VOSviewer to produce maps of co-authorship and co-occurrence of terms that showed the centrality of authors such as Navarrete, Delgadillo, Hayes, López-Morales, Díaz-Parra, and Janoschka. As a result, a corpus of 74

documents was defined which, after applying chronological and empirical criteria, was finally reduced to 65 works (2014–2024) analyzed in depth. The systematization of these 65 documents was recorded in a bibliographic matrix with fields for author, year, type of document, methodological approach, variables/indicators, theories, methods, and key findings, which allowed for the identification of trends, recurring frameworks, and research gaps.

The systematic review followed a structured protocol inspired by methodological guidelines[10] and adapted to the needs of the study, which included the following steps:

1. Sources consulted and strategy: the review combined institutional databases and open access search engines to balance quality and regional coverage, as can be seen in detail in Figure 1. Queries were made in Spanish and English using Boolean operators (AND/OR) on terms such as “GENTRIFICATION,” “TOURISTIFICATION,” “TRANSNATIONAL MIGRATION,” and related synonyms (e.g., “URBAN HERITAGE,” “URBAN TRANSFORMATION”).

2. Volume and initial filtering (PRISMA[11] flow summarized): the search yielded > 1,900 references that were imported into Mendeley; after an initial thematic filter, 430 references remained, and after applying a geographic filter, the corpus was reduced to 296 references. Bibliometric analysis was applied to this set in VOSviewer, and based on the authors and clusters identified, a final corpus of 74 documents was defined (which was then refined for an in-depth analysis of 65 works published between 2014–2024).

3. Purpose of the bibliometric analysis: to identify central authors, thematic clusters, node terms (co-occurrence), and guide the final selection of the corpus for qualitative and empirical analysis[12]. The document explicitly stated that VOSviewer was used for co-authorship and keyword co-occurrence maps

and that the visualization allowed the most influential authors to be identified.

4. Bibliographic matrix: the selected corpus (65 documents for in-depth reading) was systematized in a bibliographic matrix with fields for: author(s), year, title, region/area of study, methodological approach, variables/indicators, theories/concepts and key findings. Filling in this matrix allowed us to code themes, compare methods, and detect gaps.

3. RESULTS AND DISCUSSION

This chapter presents and discusses the results derived from the bibliometric analysis applied to the corpus constructed during the systematic review. The objective is to reveal (a) who are the most central authors and groups at the intersection of the themes of gentrification, touristification, and transnational migration in Latin America; (b) what are the issues and thematic frameworks that have dominated scientific production; (c) what recurring findings the literature contributes; and (d) what lines of research or gaps emerge from the bibliometric mapping and the cross-referencing with the bibliographic matrix. The following statements are based on the results and visualizations generated with VOSviewer and on the systematization recorded in the bibliographic matrix.

3.1 Key authors

The co-authorship analysis and total link strength measurement performed with VOSviewer identified a group of authors who occupy a central position in the thematic network: Navarrete, Delgadillo, Hayes, López-Morales, Díaz-Parra, and Janoschka, as shown in Figure 2. These nodes stood out for their high visibility in the corpus and their connectivity with other authors and thematic clusters, positioning them as key references for understanding discussions on transnational gentrification and touristification in Latin American contexts.

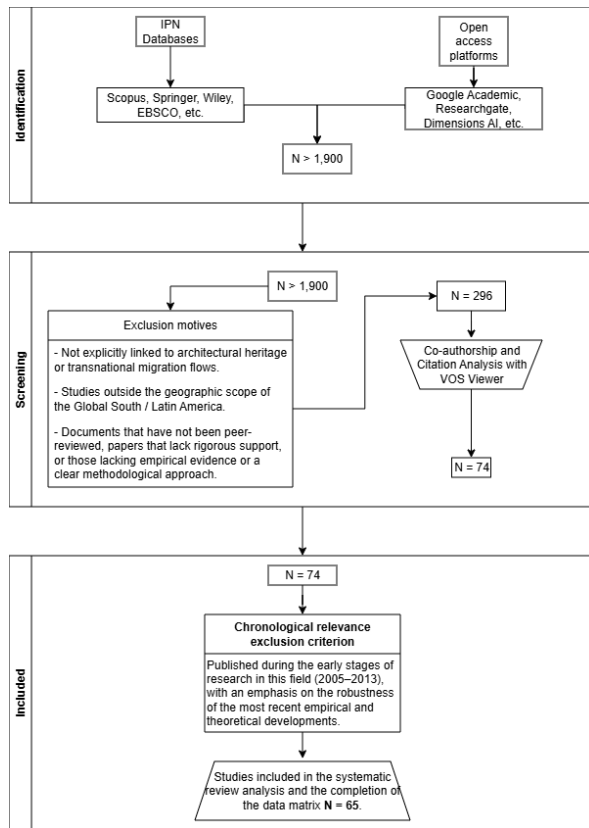


Figure 1. Flowchart of the literature review using bibliometric analysis. Source: Own elaboration.

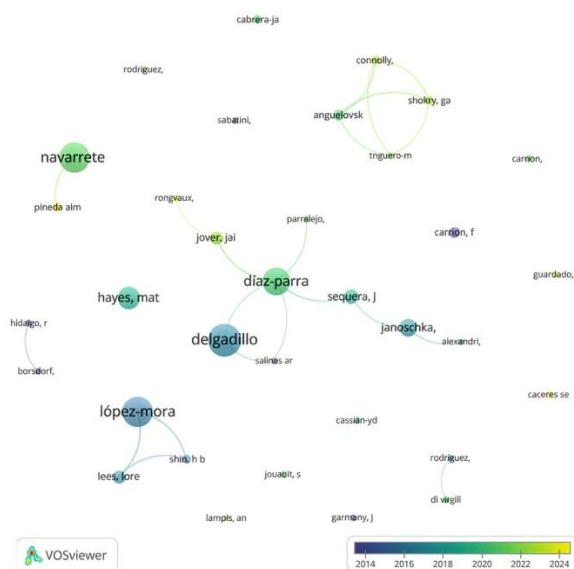


Figure 2. Co-authorship map of the leading authors and publication timelines regarding gentrification, touristification, and transnational migration. Own elaboration based on VOSviewer.

3.2 Collaborative structures and thematic segmentation

The co-authorship maps showed relatively dense networks around academic groups that combine critical approaches (studies on urban neoliberalism and financialization) with more empirical and case-based research (analysis of real estate markets and ethnographic studies of lifestyle migration). The cluster segmentation derived from the VOSviewer algorithm produced coherent groupings that, in interpretive terms, can be distinguished into at least four major thematic clusters: economic-financial, socio-cultural, heritage-architectural, and public policy/state. These groupings were validated against the bibliographic matrix to ensure thematic coherence (Figure 3).

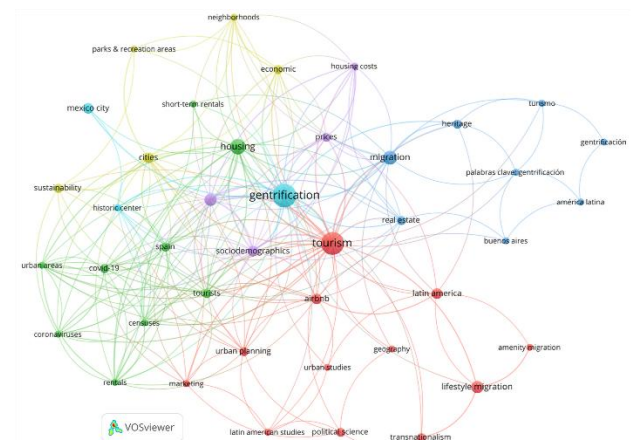


Figure 3. Map of the main co-occurring terms identified in the 65 documents analyzed. Own elaboration based on VOSviewer.

3.3 Main issues addressed in the literature

Based on the co-occurrence of terms and the synthesis in the bibliographic matrix, the following predominant issues were identified in Figure 4:

Autor	Main focus of the issue	Key Findings
Deigadillo	Urban restructuring; Gentrification; Financialization of urban development; Social resistance; Role of public policy; Public space; Heritage; Selective modernization.	Socioeconomic and socio-spatial inequalities; Population displacement; Rising housing and land prices; Speculative development; Commodification of housing; Public space policies.
Navarrete	Urban and heritage transformations influenced by globalization, tourism, and new forms of mobility and work.	Transnational gentrification; touristification; displacement and sociocultural exclusion due to rising costs, real estate speculation, urban and architectural transformations of heritage sites, and the erosion of local identity and heritage authenticity.
Hayes	Urban transformation processes and transnational gentrification; Financialization of housing; Transnational investment; Mobility of privileged populations and urban asset appreciation.	Rising housing and land prices; displacement and marginalization of low-income residents and informal vendors; urban gentrification enclaves such as "Gringolandia"; reproduction of colonial social relations; geographic arbitrage.
López-Morales	It focuses on the dynamics of land rent and gentrification processes through government interventions, investment in public infrastructure, regulatory changes, income gaps, and the relevance and applicability of theories developed in the Global North.	An increase in land values driven by public and private investment, as well as regulatory changes, which creates rent differentials captured by the real estate sector. This leads to gentrification, displacement, exclusion from the housing market, transformation of the urban fabric, loss of heritage, and social conflicts, as well as the role of the state in facilitating these processes.
Díaz-Parra	Explore the debates surrounding the appropriateness of the term, the reluctance of Latin American scholars to adopt it, and the need to use the concept in a clearer and more critical way to understand urban restructuring and the displacement of vulnerable populations.	It argues that the concept of "gentrification," although debated due to its potential for academic colonialism, is useful for analyzing urban transformations in Spain and Latin America, especially in historic centers that have been revitalized through government investment in tourism and heritage.
Janoschka	It analyzes urban transformations in Latin America and Spain, focusing on gentrification, displacement, and dispossession, and critically evaluating the application of concepts from the "Global North." It also examines housing policies, urban violence, and social resistance.	It identifies as key effects the displacement of low-income populations to marginalized outlying areas due to gentrification and housing policies, which exacerbate segregation, injustice, and urban violence. It highlights the transformation of the real estate market and the emergence of community resistance, although such resistance is often limited in its ability to challenge the root causes.

Figure 4. Summary table of the main issues studied by the key authors and their main findings. Own elaboration.

Real estate valuation and rent gap/urban financialization. Much of the literature analyzes economic processes that explain land revaluation, capital inflows, and the conversion of urban uses to higher-value offerings (high-income residential, tourist accommodations). This axis draws on classic theoretical frameworks (rent gap [13], [14], [15]) and contemporary debates on the financialization of land [16].

Socio-cultural effects: displacement, loss of identity, and gentrification. The literature documents how the influx of residents/consumers with greater purchasing power and touristification alter the social composition, reduce functional diversity, and erode community practices and meanings. Qualitative and ethnographic studies have been key to capturing these dynamics.

Public policies, selective heritage preservation, and public-private partnerships. Several studies analyze the role of the state in promoting or modulating valuation processes (rehabilitation programs, tax incentives, revitalization plans) and how these measures, even when justified in terms of conservation, end up favoring dynamics of touristification and displacement.

Touristification and digital platforms. The influence of platforms (e.g., short-term

rentals) and touristification as a vector accelerating urban transformations is recognized, although quantitative studies on the exact weight of these platforms are still limited.

Heritage dimension: tensions between conservation and architectural transformation. A growing number of studies discuss how heritage preservation (formal and informal) interacts with real estate revaluation[17], [18], [19]; however (and this is central to the thesis) there is a lack of systematic analysis of the specific architectural transformations (e.g., facadism, contemporary insertions, typological reconversion) linked to these processes.

3.4 Recurring findings in the corpus

When synthesizing the most influential works and articles by thematic cluster, frequently recurring findings emerge as we can get in Figure 5:

Autor	Areas of Research.
Deigadillo	Further research is needed on the evolution of the concept of gentrification in Latin America, the financialization of urban development, and social resistance to these processes. It is also necessary to examine in greater depth the impact of the pandemic on inequality, the application of the term "urban regeneration," the long-term effects of policies regarding public space and heritage, the role of business policies, and to develop methodologies for studying displacement.
Navarrete	Conduct further research into the regulation and impact of digital platforms (such as Airbnb) on gentrification and the role of the state in mitigating their negative effects. Gain a better understanding of transnational gentrification and luxury tourism in Latin American heritage cities by analyzing their specific consequences. Explore the usefulness of concepts such as "whitewashing" to incorporate racial dimensions. It is crucial to investigate the sustainability of the global model of heritage appropriation and its long-term effects on authenticity, local identity, and new inequalities, even in medium-sized cities.
Hayes	We must explore the long-term future and the resurgence of transnational gentrification in the post-pandemic era, delving deeper into the right to the city and global justice. It is essential to investigate the unequal consequences of migration in the Global South, the power dynamics and colonial legacies in urban planning, and the disconnect between perceptions of migrants and their actual role in displacement. We need to analyze the long-term effects of North-South migration linked to global capitalism and better understand the comprehensive consequences of financialization and privileged mobility in specific cities such as Cuenca.
López-Morales	Research is needed on land rent and the rent gap from a global comparative perspective, focusing on the Global South and East and developing new theoretical frameworks. It is crucial to analyze state-led gentrification (SLG) in Latin America, the effectiveness of mitigating public policies (such as taxes), the consequences and methodologies for studying and preventing exclusionary displacement, and the forms and impacts of social resistance.
Díaz-Parra	There is a need for more in-depth comparative studies on gentrification in Mexico, Spain, and the Global South, analyzing government investment in tourism and cultural heritage in historic districts. It is crucial to continue the critical debate on the applicability of the Anglo-Saxon concept of gentrification (taking academic colonialism into account) and its social consequences. Further research is also needed on the primacy of government intervention as a driving force behind these processes in Spain and Latin America, taking into account heritage protection and social resistance.
Janoschka	Research is needed to understand why progressive social housing models failed in Ecuador and to examine the limitations of popular resistance in the face of neoliberal logic and urban violence. With regard to gentrification in Latin America and Spain, it is crucial to delve deeper into its specific characteristics (as compared to the Anglo-Saxon world), including the various mechanisms of displacement, forms of resistance, and the role of institutions, symbolic violence, and formalization. Furthermore, we must continue to analyze the connection between neoliberal policies, urban revanchism, and gentrification, and how these processes lead to dispossession and affect the right to the city.

Figure 5. Summary table of the main lines of research proposed by the authors studied. Own elaboration.

The combination of foreign demand (lifestyle migrants, retirees, digital nomads) and valorization policies creates conditions conducive to transnational gentrification, with direct effects on prices and land use. Studies by Hayes and colleagues illustrate in depth the logic of lifestyle migration and its relationship to revaluation processes [20-24].

Touristification acts as a catalyst—and sometimes as the main cause—of functional changes in central neighborhoods: conversion of residential units to tourist accommodations, proliferation of visitor-oriented businesses, and transformation of cultural offerings. These findings appear in the empirical literature on Latin American heritage cities[25-32].

Critical frameworks point out that heritage “revitalization” policies tend to favor capital inflows and socio-spatial exclusion when they do not incorporate redistributive or housing protection measures. Critical authors such as Janoschka, Alexandri, Casgrain, Sequera, Ramos and Vives-Miró [33-38] provide theoretical arguments on how neoliberal urbanism produces dispossession and social dislocation.

Methodologically, there is a plurality of approaches: from econometric studies and market analysis to ethnographies and architectural analysis; this plurality enriches the evidence but also makes direct comparisons difficult. The combined use of bibliometrics and a documentary matrix helped to organize and relate these traditions.

3.5 Gaps and lines of research requiring further attention

The intersection between bibliometric maps and the bibliographic matrix allows us to identify significant gaps that justify the contribution in the following lines of research:

1. Architectural and morphological transformations of heritage (main gap). Although there is abundant literature on socioeconomic effects, there are few studies that analyze physical interventions in heritage (types of intervention, frequency, relationship with municipal regulations) in a comparative and detailed manner. This methodological and empirical deficit justifies the thesis's focus on documenting and classifying these transformations.

2. High-resolution longitudinal and spatial analysis. There is a lack of work that articulates spatial time series (GIS) with data on transnational occupation and detailed architectural inventories. Bibliometric mapping shows few studies that robustly integrate these sources.

3. Impact of digital platforms on specific heritage dynamics. Although their role is recognized, quantitative studies are needed to measure their impact on the urban form and material structure of heritage.

4. Evaluation of policies aimed at reconciling conservation and urban justice. There is little evaluative evidence (before/after) on the real effectiveness of heritage protection instruments when implemented in conjunction with tourism development measures. This suggests the need for evaluative and comparative studies.

5. Articulation between bibliometrics and fieldwork. Few studies use bibliometric findings to design empirical samples that directly contrast conceptual nodes with evidence in the field; the present study demonstrates the usefulness of such integration.

3.6 Interpretative discussion: theoretical and practical implications

From a theoretical perspective, the results confirm that the field is dominated by two complementary frameworks: (a) economic theories on markets and financialization (rent gap, capital gentrification), and (b) critical and cultural approaches that emphasize identities, practices, and politics. The integration of both frameworks (recognized by authors such as Lees, López-Morales, and Janoschka) is necessary to understand both the causes and the material and symbolic consequences of the phenomenon.

In practical terms, the gaps identified point to research and policy priorities: measuring and regulating the impact of touristification on built heritage; designing conservation

instruments that consider the right to housing; and developing architectural indicators to monitor morphological transformations at the block and building scale. By focusing on architectural documentation and GIS-ethnography integration, the thesis seeks to provide empirical evidence for these decisions.

Bibliometric analysis made it possible to map the academic landscape on transnational gentrification and touristification in the Global South, identify key authors and clusters, synthesize the dominant issues and findings, and—fundamentally—highlight research gaps relevant to the thesis, especially the systematic study of architectural transformations of built heritage. These results guide both the empirical phase (selection of cases, indicators, and methods) and the expected theoretical contribution of the work.

4. CONCLUSIONS

This study, focusing on the intersection between transnational gentrification, touristification, and built heritage, conducted a systematic review and bibliometric analysis to map the state of knowledge and identify relevant gaps. Based on the analyzed corpus, the following conclusions are formulated, which summarize the most relevant findings and their academic and practical implications:

1. Academic production on transnational gentrification is highly concentrated around key figures (Navarrete, Delgadillo, Hayes, López-Morales, Díaz-Parra and Janoschka) whose collaborative networks highlight the growing importance of lifestyle migration (nomads or retirees) as a critical driver of real estate revaluation, underscoring the need to incorporate migration variables into urban market analysis.
2. While dominant theoretical frameworks successfully combine economic and socio-cultural approaches, there is a persistent lack of studies integrating high-resolution spatial

time series (GIS), architectural inventories and transnational occupation data to transition from descriptive profiles to robust causal explanations of material heritage transformations.

3. Touristification and digital platforms act as critical catalysts for gentrification, yet empirical studies measuring their direct impact on the material form of built heritage remain scarce. This highlights a prominent thematic gap regarding systematic and comparative analyses of physical architectural transformations, which this paper directly addresses.

4. Combining VOSviewer bibliometrics with a coded matrix is an effective procedure for prioritizing literature and designing fieldwork. By integrating detailed architectural documentation, qualitative GIS and empirical samples, this research offers a replicable methodological contribution that bridges the gap between conceptual nodes and material, block-level evidence.

5. Heritage revitalization often facilitates socio-spatial exclusion without redistributive housing protections, signaling an urgent need for policies that reconcile conservation with urban justice. Future research must prioritize post-intervention evaluations, comparative studies of heritage cities and longitudinal monitoring of digital platforms' impacts on urban morphology.

Taken together, the conclusions confirm that transnational gentrification and touristification transform not only the social and economic aspects of the urban landscape, but also its physical aspects, and that the existing literature needs to move toward studies that measure and classify these physical transformations. The bibliometric approach applied in this study offers a solid starting point for guiding such empirical research and for the thesis to provide systematic and replicable evidence on the architectural traces of these processes.

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Conflicts of interest

The authors declare no conflict of interest.

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167-III-PO REGIONAL ANALYSIS OF EDUCATION IN MEXICO AND ITS IMPACT ON WAGES

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Abstract: This research quantitatively measures the effect of basic, intermediate, and higher education levels on wage income across Mexico's eight economic regions. To this end, a Mincer equation is estimated using Ordinary Least Squares (OLS), based on data from the National Survey of Household Income and Expenditures (ENIGH) [1-4], and applying the Heckman correction to control for potential selection bias. The results demonstrate that, in some regions, basic education has a greater marginal impact on wages compared to intermediate and higher levels, indicating a decreasing rate of return as educational attainment increases. These findings highlight the need to design educational policies focused on developing skills relevant to the labor market, particularly in lagging regions, as well as labor policies that promote wage improvement and regional equity.

Keywords: Educational level; Wage income; Economic regions.

1. INTRODUCTION

Various labor market theories, particularly human capital theory, establish a positive relationship between education and earnings, assuming that higher levels of schooling increase individuals' productivity and, consequently, their labor remuneration.

However, recent evidence for Mexico shows that educational returns are not homogeneous. According to the Mexican Institute for Competitiveness [5], young people with a higher education degree earn only 14% more than those with upper

secondary education at the beginning of their professional careers; nevertheless, this difference can increase up to 78% throughout their working life.

Mexico, due to its vast territorial diversity, could be seen as an advantage—having greater biodiversity, being a raw materials exporter, and a tourist country—but also as a disadvantage, since in the country's economic regions, wages depend heterogeneously on various factors such as schooling, age, experience, productive activity, and location, among others [6].

For this reason, it is important to analyze the relationship between educational attainment and earnings to determine how profitable higher, upper secondary, and basic education levels are according to each region.

The objective of this research is to analyze and measure the effect of different educational levels—basic, upper secondary, and higher—on wage income, incorporating variables such as age, work experience, productive activity, and the region of residence, within the framework of Mexico's economic regions. The hypothesis is that the impact of the first two levels of education, basic and upper secondary, on individuals' wage income is greater than that of higher education, but that this effect varies across the country's regions, thus demonstrating the nonlinearity of returns to education.

2. MATERIALS AND METHODS

To achieve the research objective, this study applies a quantitative, observational, and non-

experimental approach based on secondary data from the National Household Income and Expenditure Survey (ENIGH) for the years 1992, 2000, 2010, and 2022 [1-4]. The database contains information on household characteristics, labor conditions, income, and educational attainment.

The estimation is performed using STATA through a multiple linear regression model with cross-sectional data. The sample includes household heads between 15 and 70 years old, who worked at least 20 hours per week and whose economic activity belongs to the primary, secondary, or tertiary sectors.

The dependent variable is the natural logarithm of labor income, while the explanatory variables include educational attainment, age, gender, working hours, economic activity, locality size, and geographic region.

Educational attainment is classified into three levels: basic, high school, and higher education.

Economic activity is identified according to the North American Industry Classification System (SCIAN) [7], and grouped into three sectors: primary, secondary, and tertiary.

The size of locality is incorporated as a binary variable, taking the value of 1 for urban areas (localities with more than 2,500 inhabitants) and 0 for rural areas.

Geographic location is analyzed through the classification of Mexico's eight economic regions. The regional division was constructed using the state identification codes available in the ENIGH, following the economic regionalization approach proposed by Bassols Batalla [8], which considers the socioeconomic and productive characteristics of Mexican territories.

Since ENIGH does not provide direct information on labor experience, potential experience is estimated following the traditional Mincer approach [9]:

$$Exp = Age - (Years\ of\ formal\ education + 6)$$

Given the specification of the traditional Mincer equation [9], estimated by OLS, the following semi-logarithmic equation refers to a specific equation as Eq. (1):

$$\ln Y = \alpha + \sum_{k=1}^m \beta_k D_k + \gamma_1 exp + \gamma_2 exp^2 + hrs + sexo + edad + \sum_{a=1}^m \beta_a D_a + \varepsilon \quad \text{Eq. (1)}$$

To avoid the inconsistency in the biased estimators produced when running the model using OLS, caused by endogeneity in sample selection, the Heckman correction will be applied. In its first stage, a probit model is employed [10], specifying the probability that the individual has a wage income above the average as Eq. (2):

$$P(Z = 1) = P(\lambda'W + u > 0) = \phi(\delta W / \sigma) \quad \text{Eq. (2)}$$

Where Z takes the value of 1 if the respondent has an income above the mean and 0 otherwise; W represents the explanatory variables that influence the probability of obtaining higher-than-average income; and u is the error term.

The coefficient λ captures the effect of self-selection bias, and when this coefficient is significant, the sample ceases to be random, thereby allowing the estimators to be consistent. In the second stage, the Mincer equation is estimated through OLS, including λ (the inverse Mills ratio) as an independent variable, obtaining the following Eq. (3):

$$\ln Y = \alpha'X + \rho\lambda + \omega \quad \text{Eq. (3)}$$

ρ is the correlation coefficient between the probabilities of obtaining wage income above the mean and the original income function; X is the vector of the previously considered variables; and ω is the error term.

2.1. Analysis of the Results by Regions

The estimations allow identifying the effects of the variables on income determination, particularly how the three educational levels generate differentiated impacts across the country's eight economic regions.

Table 1. Heckman correction. Dependent variable (treatment): wage income above the average.

Independent	2022	2010	2000	1992
	Coefficientes	Coefficientes	Coefficientes	Coefficientes
Constant	-2.253174	-3.110448	-2.374089	-2.418295
Basic	0.421093	0.451193	0.630468	0.546702
Medium	0.586260	0.806301	1.009653	1.194551
Higher	1.234878	1.533209	1.750677	1.822775
Secondary	0.525308	0.525348	0.845306	0.613964
Tertiary	0.366405	0.526808	0.682820	0.514531
Age (19-23)	0.432532	1.135800	0.178555	0.350736
Age (24-29)	0.647173	1.180183	0.308921	0.592502
Age (30-39)	0.856437	1.434141	0.528038	0.854407
Age (40-49)	1.185582	1.773690	0.925723	1.247753
Age (50-59)	1.406436	1.972608	1.265921	1.452658
Age (60-70)	1.365681	2.097102	1.353576	1.566379
Exp	-0.002537	0.007735	0.017396	-0.015408
exp2	-0.000200	-0.000320	-0.000614	-0.000005***
Hours	0.003546	0.002482	-0.002890	0.000813
Urban	0.384143	0.407604	0.682097	0.807637
Pseudo R ²	0.1075	0.1450	0.2031	0.1963

Significance level at 99% for P(z)

*** P(z) not statistically significant

The model shows that, in all the years analyzed, higher education exerts the greatest positive impact on the probability of earning wages above the mean, compared with the other educational levels. Likewise, activities in the secondary sector stand out significantly, as manufacturing and other industrial activities have represented a substantial share of the country's economic production. The only exception appears in 2010, when the tertiary sector displays a slightly higher probability, attributable to its steady growth, although this increase may not be reflected in 2022 because of the 2019 pandemic.

With respect to age, the ranges showing the highest probability of earning above-average income correspond to individuals aged 50-59 and 60-70. This finding is consistent with the theory suggesting that at the start of a working life, incomes tend to be lower, and as age and experience increase, the probability of obtaining higher earnings rises. By contrast,

the variables of experience, its squared term, and weekly working hours show a lower probability of yielding above-average incomes.

In the second stage, to obtain more consistent estimators, the inverse Mills ratio (λ) is incorporated as an independent variable in the Mincer equation. Additionally, the gender variable is included, ages are grouped into a general variable called "age," and the variable of weekly working hours is omitted, since its results were not significant in the OLS regression.

OLS results indicate that marginal returns to education decrease as the level of schooling increases. While basic education (β_1) shows higher returns compared to medium (β_2) and higher education (β_3), higher education is associated with the highest absolute income, illustrating the concept of diminishing returns to education.

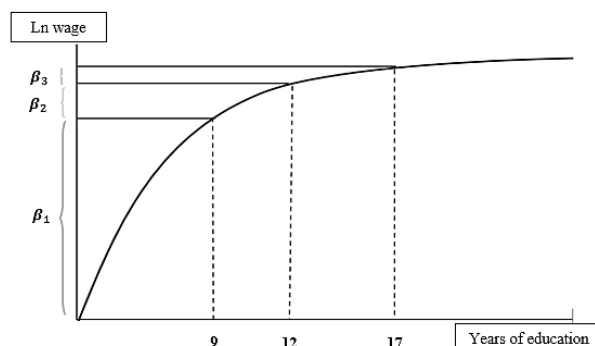


Figure 1. Relationship between Wages and Education.

The reduction in wage returns associated with education can be explained by several factors. First, the stagnation of real wages in recent years has limited the increase in earnings derived from higher educational attainment.

Likewise, the expansion of the supply of workers with upper secondary and higher education has generated greater availability of qualified human capital, reducing wage differentials across educational levels. This difference becomes more pronounced mainly at the postgraduate level, where individuals

with master's and doctoral degrees obtain higher relative returns.

3. RESULTS AND DISCUSSION

The results confirm the relevance of human capital theory, which establishes that education increases labor productivity and earnings [11-13]. However, the findings also show that returns to education are heterogeneous across Mexico's economic regions, indicating that the value of human capital depends not only on individual characteristics but also on the productive structure and labor market conditions of each territory.

The results reveal that higher education generates the greatest absolute income levels; however, its marginal effect decreases compared with lower educational levels. This evidence is consistent with the literature on developing economies, where the expansion of educational attainment has increased the supply of qualified workers, while the creation of high-productivity employment has not grown at the same pace. Therefore, the economic returns of education depend on the capacity of regional economies to absorb and reward qualified labor.

Regional differences are particularly evident in marginalized areas, such as the South Pacific and the Gulf of Mexico, where higher education has a greater relative effect on wages due to the scarcity of qualified workers. Nevertheless, structural limitations, including lower productivity activities, educational disadvantages, and limited formal employment opportunities, restrict the translation of schooling into higher earnings. Conversely, industrialized regions, such as the North and South-Central regions, show stronger returns due to their manufacturing base, industrial parks, and export-oriented activities.

The sectoral results reinforce this interpretation. The secondary sector presents higher wage effects in regions specialized in

manufacturing, industry, and energy activities, where greater capital intensity and technological requirements increase the demand for skilled labor. In contrast, in regions such as the South Pacific and Yucatán Peninsula, tertiary activities, particularly tourism, represent important sources of income, although their impact depends on the degree of specialization and formalization of employment.

The negative effect associated with experience differs from the traditional Mincerian expectation of a positive relationship between experience and wages. This result may reflect labor market characteristics in developing economies, where experience accumulated in informal or low-productivity occupations does not necessarily translate into higher remuneration.

Urbanization also contributes to explaining wage differences, as cities concentrate infrastructure, investment, and employment opportunities. This finding is consistent with the New Economic Geography approach, which highlights the role of agglomeration economies in generating productivity advantages and higher wages.

Finally, the gender variable shows that differences in labor market outcomes persist even after controlling for educational attainment and other individual characteristics. This result is consistent with labor market segmentation theories, which indicate that occupational distribution and sectoral concentration influence wage outcomes. Although education improves employment opportunities, women's concentration in lower-paid sectors and their limited participation in high-wage activities may reduce the economic returns associated with schooling.

Overall, the results indicate that education is a key factor for improving income; however, its effectiveness depends on regional productive conditions, employment quality, and the

capacity of local economies to generate higher-value-added jobs.

4. CONCLUSIONS

In accordance with the proposed approach and in order to test the hypothesis, continuous variables such as the natural logarithm of wages, age, experience, and hours worked were used, along with treatment variables for gender, educational levels, economic sector, and geographic zone, obtained from the ENIGH microdata for the years 1992, 2000, 2010, and 2022, analyzed at the regional level.

This approach allowed us to confirm the stated hypothesis, as the results show that basic education has the greatest impact on wages, particularly in the North and Central-West regions, exception of 2022. In that year, the impact of basic education was higher across the entire country, reflecting the economic dynamics influenced by the pandemic.

In contrast, in the South-Central and Gulf regions, medium and higher education stand out. In the South Pacific and Yucatán Peninsula regions, higher education is the most significant. However, these two regions, particularly the South Pacific, exhibit the highest illiteracy rates and have fewer institutions offering higher education. These results indicate that in certain regions of the country, achieving higher income requires greater educational specialization, whereas in other regions, this is less critical.

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Conflicts of interest

The author declare no conflict of interest.

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239-III-PV TECHNOLOGICAL INTELLIGENCE MODEL FOR THE CREATION OF A CIRCULAR ECOSYSTEM IN THE ADMINISTRATIVE SERVICES SECTOR IN MEXICO

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Abstract: Technological globalization is a process of economic, social, and cultural interconnection accompanied by technical advances in countries, industries, and companies facing sustainability challenges. In Mexico, the administrative services sector lacks a framework that integrates digital technologies for the effective functioning of the ecosystem of actors. The objective of this research was to propose a Technological Intelligence Model for the creation of a Circular Ecosystem in the Administrative Services Sector in Mexico. The theoretical assumption is that the Technological Intelligence Model fosters the creation of a Circular Ecosystem within the Administrative Services Sector. The research began with a documentary review of the characteristics and performance of the Administrative Services Sector in the economy. Subsequently, a literature review of the elements of Technological Intelligence was conducted, and the factors related to the creation of the Circular Ecosystem were identified. The research method employed was qualitative, non-experimental, with a descriptive scope, and using a cross-sectional study for data collection. Documentary research techniques were used to collect data and analyze the characteristics of the categories and their respective dimensions. The results highlight how key components of Technological Intelligence facilitate the creation of the Circular Ecosystem.

Keywords: Technological Intelligence Model, Circular Ecosystem, Administrative Services Sector.

1. INTRODUCTION

The contemporary social, economic, industrial, business, and technological landscape is defined by multiple phenomena and processes such as globalization and internationalization, which exert both exogenous and endogenous impacts on countries, economic sectors, and organizations [1]. Within the current system of plurality, business constitutes a fundamental arena of human activity, heavily influenced by emerging digital technologies for information and communication [2]. The vertiginous transformations of the current technological field and the circular ecosystem have modern roots in the global conflict that took place between 1939 and 1945. This period led to the emergence of the VUCA concept within the US military. It is an acronym coined to describe volatile, uncertain, complex, and ambiguous environments that challenge the reliability of forecasts in all sectors of human activity, based on the foundational theories of Warren Bennis and Burt Nanu [3]. Moreover, recent decades saw the rise of the BANI framework, a term proposed by Jamais Cascio approximately in 2018 to characterize the concept of the current transition toward a brittle, anxious, non-linear, and incomprehensible world that undermines the stability of contemporary social ecosystems and systems [4].

Schwab [5] coined the term Fourth Industrial Revolution (4IR) or Industry 4.0 in to address the presence of smart industries and modern technologies amidst radical, abrupt, and profound changes within social structures, economic systems, and business environments in a holistic manner. These ecosystems are perceived as crucial sources of innovation and serve as pillars of entrepreneurial thinking through collective action [6]. Within this context, the circular economy offers a systematic approach to optimize and rationalize resources, serving as a key success factor in transitioning from linearity to circularity through coordinated alignment among all actors and stakeholders [7]. Currently, the quality of the administrative services sector remains essential to enhance trust in institutions and organizations due to digital transformations in business [8]. However, in Mexico, the endogenous administrative system has historically evolved in a disorganized manner [9].

The problem identified was that actors in the Administrative Services Sector in Mexico lack a logical representation that encompasses and integrates the key elements of Technological Intelligence with the main factors that enable the transition from linearity to circularity across the institutional and organizational entities of the Circular Ecosystem of this sector. Therefore, the objective of this research was to propose a Technological Intelligence Model for the creation of a Circular Ecosystem in the Administrative Services Sector in Mexico. The theoretical assumption is that the Technological Intelligence Model fosters the creation of a Circular Ecosystem within this sector.

Technological Intelligence improves organizational performance and drives a country's economic development under external requirements from emerging organizational transformations, as well as internal necessities in performance or efficiency [10]. Concurrently, a Circular Ecosystem combines the circular economy with the business environment to produce,

deliver and capture sustained value across modern entities within the market [11].

2. MATERIALS AND METHODS

The methodology on which this research is based was developed according to the core object and subject of study to systematically address the identified problem, fulfill the objectives, answer the questions, and validate the theoretical assumption.

As maintained by Castillo [12], the research method was structured as the set of methodical procedures in three stages according to the reference framework of the problem. Furthermore, the methodological process is aligned with the type and design of the study which are built upon problem elements [13], which were previously described.

2.1. Type and design of the research

As stated by Rojas-Soriano [14], the methodological approach was designed according to the theoretical framework of the research, the complexity of the phenomena under study, the institutional possibilities, and the characteristics of the research group:

- The research adopted a qualitative approach because the phenomena were characterized by the following two analysis categories: 1) Technological Intelligence Model (TInM), and 2) Circular Ecosystem (CE).
- The research was non-experimental, since deductive reasoning was used, starting from universal knowledge and moving toward specific knowledge.
- The research was descriptive in scope, as it described the characteristics of the phenomenon under study to gain a deeper understanding of its nature.
- The research was conducted using a cross-sectional study, as the data were collected at a single point in time during the research.

2.2. Research method

Based on Castillo [12] and on Pineda and Torres [13], Figure 1 illustrates the process of the method used.

The research method began with the problem statement, which was identified through the problematization. It corresponded to the planning with methodological considerations with the problem elements, its reference framework, justification and theoretical assumption. The execution of the research work began with a documentary review to contextualize the characteristics of the Administrative Services Sector, its actors, and components in the economy both at international and national level, considering its background and main data [12-14].

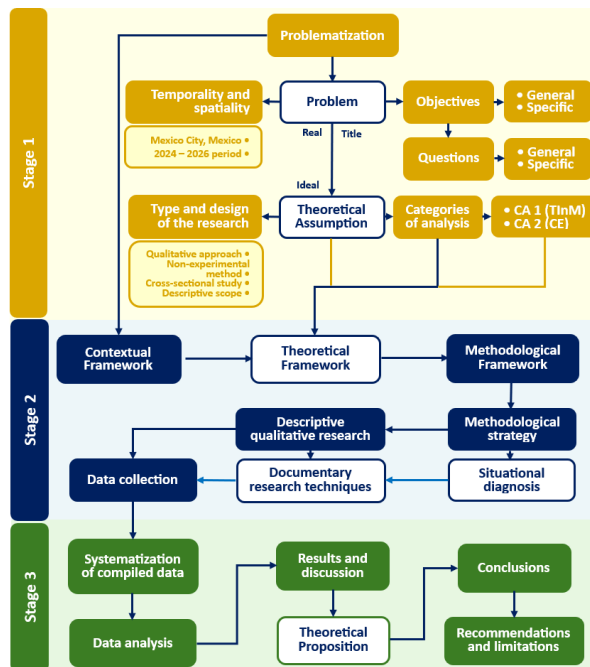


Figure 1. Research method.

Subsequently, a literature review was conducted to analyze the elements of Technological Intelligence for structuring the Model, and the factors associated with the creation of the Circular Ecosystem were identified. Documentary research techniques were used to collect data [13]. At its culmination, the research consisted of the systematization of compiled data and the discussion of the results to structure the proposal.

2.3. Stages of the research

The stages of the research are implicit in the three phases of the research method [12-14]:

- **Stage 1.** This involved planning the research protocol based on the problem statement as a starting point for the study in methodological considerations.
- **Stage 2.** This involved executing the study, where data were collected through documentary research techniques for analysis. Compiled data were analyzed according to the content of the literature reviewed and the context of the research.
- **Stage 3.** This involved discussing the results, structuring the proposal, and presenting the findings to the experts.

3. RESULTS AND DISCUSSION

The analysis of the results was based on data collected within the methodological framework, which provided information for the situational diagnosis, using documentary research techniques to consult formal sources, obtain data, analyze them, and discuss them.

The Global Competitiveness Report of Browne and Geiger [15] from the World Economic Forum (WEF) [15, 16] shows the distribution of the world economy by country and sector, along with their capacity to achieve sustained levels of growth, as illustrated in Figure 2.

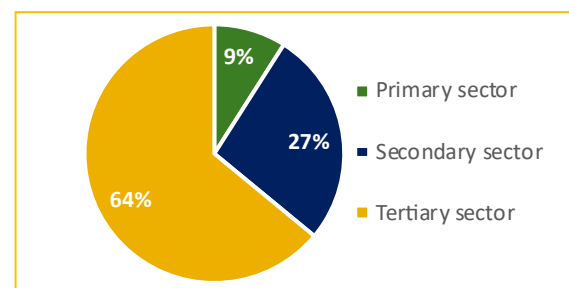


Figure 2. Distribution of the world economy.

The tertiary or service sector has the highest percentage contribution to global Gross Domestic Product (GDP) in a sample of 112 countries, including Mexico. This international economic structure reflects economic activity based on the resources available in each region and country, classified as developing

and developed economies. The service sector, as the predominant sector, shows dependence on technological innovation and competitiveness.

In the third quarter of 2025, Mexico's GDP grew by 0.6% compared to the second quarter of the same year, with the services sector showing the greatest growth. Compared to the third quarter of 2024, Mexico's GDP in 2025 grew by 1.2% annually, with the services sector in second place [17], as shown in Table 1.

Table 1. Distribution of the Mexican economy.

Sectors	2Q/2025	3Q/2024
Primary	-2.4	2.6
Secondary	0.7	-0.3
Tertiary	0.8	1.8
Total GDP	0.6	1.2

Mexico is a developing economy that is transitioning from primary and secondary activities toward strengthening the service sector. While the tertiary sector accounts for between 45% and 50% of GDP, this figure exceeds 70% in developed countries. However, the service sector is becoming the main source of economic growth in Mexico. This economic structure remains crucial for sustained endogenous and exogenous competitiveness, especially when considering total revenue from the supply of goods and services, total employed personnel, and total expenditure on the consumption of goods and services.

The three sectors of the Mexican economy, such as agriculture, manufacturing, and services, specifically administration, held distinct shares of the national GDP in 2023, with corresponding estimates for 2025, projections for 2030, and average annual growth rates [18-23], as illustrated in Figure 3.

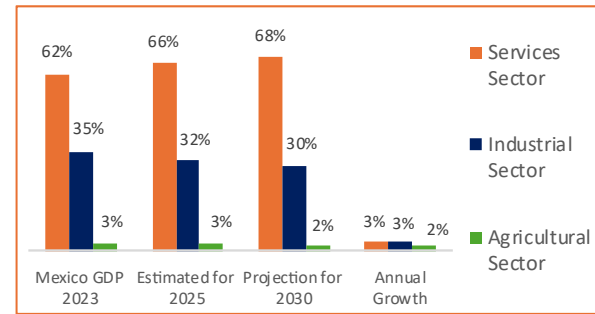


Figure 3. Distribution of Mexican sectors.

The tertiary sector, where administrative services are classified according to the North American Industry Classification System (NAICS), shows stable and sustained growth, representing the largest share of Mexico's GDP. This reflects a country transitioning from an industrialized, manufacturing, and export-oriented economy toward one focused on tertiarization and technological innovation.

The report on technology and innovation by the United Nations Conference on Trade and Development (UNCTAD) [24] outlines the elements and factors of Technological Intelligence (TI) in 2023, along with projections for 2033, as illustrated in Figures 4 and 5.

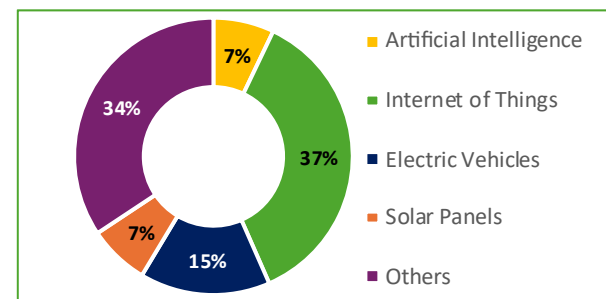


Figure 4. Composition of TI in 2023.

Technological Intelligence (TI) is a systematic process to obtain, analyze, and disseminate data on scientific and technological trends, enabling strategic decision-making and both endogenous and exogenous evaluations in technological innovation projects.

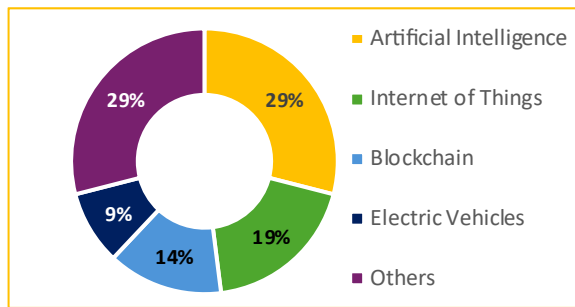


Figure 5. Projections of TI for 2025.

Currently, the Internet of Things (IoT) predominates among the elements and factors of TI for training intelligent models. However, by 2033, Artificial Intelligence (AI) will become the primary technological tool in models capable of learning, reasoning, perceiving, and solving problems related to a specific object of study.

Revenue from the use of AI software grew by approximately USD 10 billion over a 10-year period, driven by an increase in global market value, technological adoption, and organizational utilization [25], as detailed in Table 2.

Table 2. Growth of AI.

Year	Income	Value	Adoption	Use
2020	22.59	45	30%	40%
2021	34.87	65	35%	42%
2022	51.27	140	35%	45%
2023	70.04	279	35%	48%
2024	94.41	400	40%	50%
2025	126	1810	63%	55%

Note: Revenue and market value of AI are expressed in billions of US dollars.

The market expands rapidly with the rise of digital technologies for AI processes and the TI model, becoming an economic pillar driven by technological innovation. This expansion is closely integrated with the business environment, where exponential changes are beginning to replace linear ones.

The implementation of the TI model, supported by both digital technologies and tools such as the IoT and AI across eight specific areas, yielded a positive assessment, improved efficiency, and significant cost reduction for the business environment,

fostering a circular and sustainable ecosystem [26], as shown in Table 3.

Table 3. TI indicators for a circular ecosystem.

Area	Impact	Improv	Cost Red.
Environmental monitoring	6	24%	40%
Energy efficiency	10	20%	7%
Resource management	8	19%	31%
Smart infrastructure	6	34%	22%
Waste reduction	6	35%	28%
Network optimization	6	34%	18%
Green finance	7	36%	37%
Circular economy	7	21%	33%

Note: Impact is measured on a scale of 1-10, efficiency improvement and cost reduction are expressed in percentage terms.

The data in the table represent metrics on the benefits of developing a TI model in specific areas to achieve sustainable and circular growth in the face of exponential changes in different sectors, industries, environments, and ecosystems. Furthermore, these data are transformed into key signals of the technological landscape, which integrate with systems and subsystems to leverage sustainable opportunities in innovation and management. This approach is highly relevant for administrative services, which remain pervasive across all sectors of economic and human activity.

Mexico's business ecosystem is mostly made up of micro, small, and medium-sized economic units, which contribute 52% of GDP, generate 72% of employment, and constitute 99% of companies [18-20], as illustrated in Figures 6 and 7.

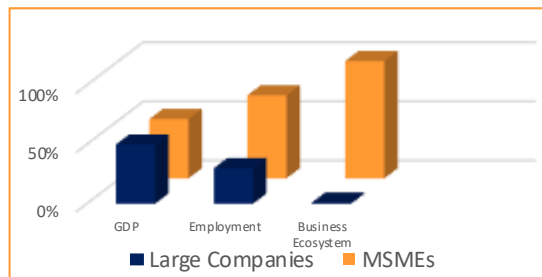


Figure 6. Overview of the Business Ecosystem.

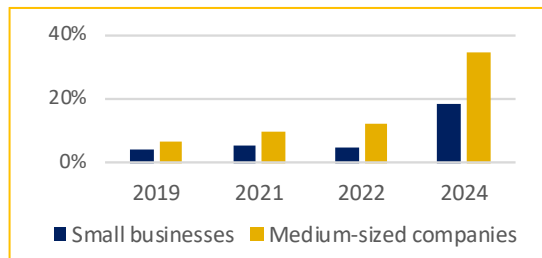


Figure 7. Integration of TI into the Mexican Business Ecosystem.

The business ecosystem made up of distinct types of organizations is broadly classified into two subsections. The first comprises Micro, Small, and Medium Enterprises (MSMEs), which make up approximately 99% of the business entities, 72% of employment, and 52% of GDP. Conversely, large companies represent less than 1%, although they are the ones that report the highest productivity and contribution to the economy despite having fewer employees. Within this ecosystem, Small and Medium-sized Enterprises (SMEs), which represent approximately 4.8% of the actors, are the key segment with high development potential for creating formal, productive, and scalable companies in a sustained manner in the circular and digital economy.

The key elements and resources of the current linear business environment are determining factors for the creation of the Circular Ecosystem (CE) [20-23], as shown in Figures 8 and 9.

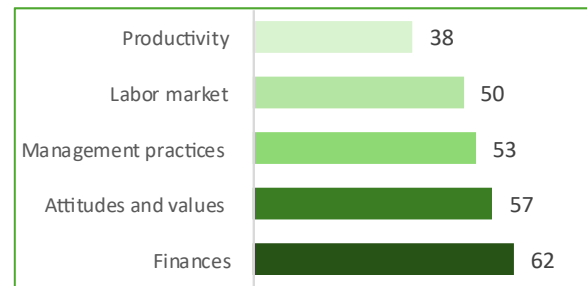


Figure 8. Business Efficiency for the CE.

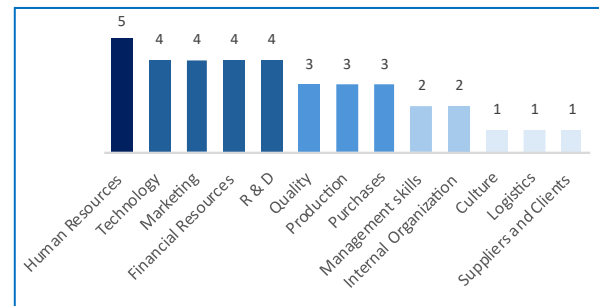


Figure 9. Key resources for CE.

Business efficiency leads to the optimization of key resources, which is jointly reflected in determining factors in environmental, economic, social, and technological aspects that enable the transition toward circularity in the service sector, which serves as a cornerstone of the tertiary economy, and more specifically within administrative services, as they provide cross-cutting support to other industries.

4. CONCLUSIONS

The research showed that Technological Intelligence is a three-stage process involving the collection, analysis, and dissemination of data. This cycle provides strategic information for intelligent decision-making in specific sectors of the economy and the business ecosystem, which currently converge in what is known as the circular digital economy. The application of the Technological Intelligence process is based on its key elements and components, which are dominated by technological tools such as the Internet of Things and Artificial Intelligence.

Digital technologies in Technological Intelligence are crucial for the creation of the Circular Ecosystem because the current

technology market is experiencing exponential growth with an impact on specific areas of the linear business environment, requiring a transition to a circular business ecosystem based on business efficiency and the optimization of key resources for positive assessment in the fulfillment of long-term organizational objectives.

The Technological Intelligence Model is based on the five dimensions of this analysis category, which are implicit in the Technological Intelligence process. The dimensions are technology watch, prospecting and analysis, knowledge management, decision-making, and evaluation and feedback. Furthermore, the determining factors for the creation of the Circular Ecosystem are based on the four dimensions of this analysis category. These are environmental, economic, social, and technological aspects or criteria.

The proposal focuses on the administrative services sector because it provides cross-cutting support for other industries, has a greater share of GDP, and has a direct social impact. In addition, the actions for its implementation demand fewer physical resources for the transition from a linear toward a circular ecosystem, achieving better replicability across other sectors.

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Conflicts of interest

The authors declare no conflicts of interest.

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274-III-PO DIGITAL TOURISM PROMOTION STRATEGY ´S PROPOSAL FOR SAN AGUSTÍN DE LAS CUEVAS NEIGHBORHOOD IN MEXICO CITY

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Abstract: Information and Communication Technologies (ICT) play a crucial role in promoting tourist destinations and have made it possible to transcend the barrier of physical distance. In a competitive tourism market, cities use these tools to reach different audiences in an economical and personalized way.

Mexico City has a wide range of tourist attractions, with neighborhoods full of mysticism and charm. To the south of the city, the San Agustín de las Cuevas neighborhood, part of the Tlalpan Historic Center, was once classified as a magical neighborhood due to its heritage, natural, ecological, historical, and cultural characteristics. The Municipality´s Office's government program recognizes tourism as a strategic focus, but it does not include the use of ICT as required by current trends.

A diagnosis of digital tourism promotion at the local level is proposed for this neighborhood, focusing on the actions currently being taken to promote the preservation of the cultural attractions of the San Agustín de las Cuevas neighborhood.

The theoretical section analyzes concepts such as promotion, digital marketing, content marketing, and neighborhoods as urban tourist spaces. A qualitative methodology is

adopted, with an ethnographic research method and a descriptive scope.

Based on the assessment carried out, the "Tlalpan Vibrates" campaign is planned in the neighborhood through the region's potential for disconnection and discovery of the undiscovered. They advocate for the promotion of religious, archaeological, and indigenous tourism.

Keywords: promotion, neighborhoods, ICT, digital marketing, heritage.

1. INTRODUCTION

With the rapid advancement of Information and Communication Technologies (ICT), companies have reinvented their procedures in such a way that they now have a significant impact on the entire value chain, transforming customer experience. According to the Mexican newspaper "El Economista", by 2023, 67% of the world's population (5.4 billion people) will be connected to the Internet; specifically in Mexico, by 2024, an estimated 100.2 million people—equivalent to 81.2% of the population aged 6 and older—will be using the Internet [1].

These statistics give an idea of the scope of ICT in the contemporary world. Tourism companies are not exempt from these changes, as destinations seek visibility and positioning through competitive tools using

ICT. A clear example of this is tourism promotion, as ICT has made it possible to transcend the barrier of physical distance in communicating content and messages to latitudes that were previously unthinkable to reach. This phenomenon has made it possible to introduce Mexican culture to the world through its cities and its wide range of tourist attractions.

Tourism promotion efforts are concentrated in areas and towns with a proliferation of world-renowned attractions and tourist infrastructure that attract large numbers of visitors, and Mexico City is no exception.

However, the city is home to neighborhoods full of mysticism and charm. In the south of Mexico City, the San Agustín de las Cuevas neighborhood, part of the historic center of the Tlalpan district, was once classified as a magical neighborhood due to its heritage, natural, ecological, historical, and cultural characteristics.

Neighborhoods located in heritage cities or cities of great historical importance are usually well preserved and valued by public institutions [2].

The Municipality Office's 2024-2027 Government Program includes tourism as a strategic focus, promoting sustainable tourism development in downtown Tlalpan, increasing tourism offerings, and ensuring an inclusive experience for visitors, as well as positioning it as a key destination for domestic and international visitors [3]. However, it does not include the use of ICTs as required by current trends.

This presents an opportunity to influence and propose the readjustment and/or creation of a digital tourism promotion strategy at the local level that enables the preservation and dissemination of its cultural attractions, prioritizing community participation and links with local actors and businesses for the sake of its development and autonomy. To this end, it will be appropriate to carry out an assessment to understand the context of tourism

promotion in which the neighborhood is inserted, as well as the content that is disseminated on social networks and digital platforms.

Although promotion continues to be one of the fundamental pillars for improving processes and decision-making in tourism marketing, a new form of promotion for destinations is currently emerging with the use of digital tools and platforms: digital tourism marketing. Digital marketing tends to be more cost-effective than traditional marketing, as production and distribution costs are lower.

To maximize the reach of digital platforms, it is essential to integrate a relevant content strategy tailored to the type of audience and content of each platform and/or social network. To this end, content marketing is an essential tool that seeks to appeal to the emotional component of users through persuasive and experiential leads.

"Content marketing is a marketing approach that involves creating, selecting, distributing, and amplifying content that is interesting, relevant, and useful to a clearly defined audience to generate conversations about the content" [4].

The research will shed light on the promotion of digital tourism and dissemination actions and policies carried out by the local council in question, and how they influence the preservation of local cultural attractions and their visibility. The analysis and adoption of the correct use of Information and Communication Technologies (ICT) play a fundamental role in the development of strategies to strengthen and consolidate tourism to make promotion, governance, and communication processes more efficient.

In terms of the contributions of this study to the understanding of the tourism phenomenon, the results are part of a larger research project, which will plan a tourism promotion strategy for the neighborhood. This strategy will allow the neighborhood to adapt to changes and innovative trends using digital

technologies for tourism promotion. At the same time, understanding tourist trends and behaviors is crucial for designing competitive strategies.

2. MATERIALS AND METHODS

This research takes a qualitative approach, as it aims to achieve a broader and deeper perspective on a social phenomenon.

The research method is ethnographic, as it “the intended purpose is to provide an analytical and interpretive description of the culture, ways of life, and social structure of the group under study” [5]. In this case, digital tourism promotion was studied from the perspective of the neighborhood as a tourist destination.

This research has a descriptive search, since, according to Hernández-Sampieri et al. [6], this reach seeks to “specify the properties, characteristics, and profiles of people, groups, communities, processes, objects, or any other phenomenon that is subject to analysis” (p. 92). The research carried out a diagnosis of digital tourism promotion as the main category, based on the study and description of this in a specific context and community, in this case the San Agustín de las Cuevas neighborhood, Historic Center of Tlalpan, in Mexico City.

A cross-sectional time frame is established for the research because instruments will be used to collect data only once for subsequent analysis. Among the non-probability sampling types, convenience sampling is adopted by choosing a segment of the population that is accessible within a given period.

The documentary research technique used was content analysis of official documents and digital platforms. These platforms include official social media accounts and the Tlalpan Municipality’s Office website.

In the fieldwork, a series of interviews were conducted with a group of informants considered key to the research, with the aim of obtaining information from experts in the context. First, public officials from the General Directorate of Environment, Sustainable

Development, and Economic Development (DGMADSFE) were selected, as they are closely involved with tourism and cultural functions in the Municipality’s Office.

In a second phase, interviews were conducted with those in charge of the Art and Culture Route in Tlalpan, as part of the local network of entrepreneurs, an experience and local initiative designed to promote culture and tourism, which in turn promotes the neighborhood in question.

Based on both sources of data, the results were triangulated to compare the information collected. By cross-referencing data from various sources, a complete and more reliable picture of the subject of study is obtained.

3. RESULTS AND DISCUSSION

This article is part of the progress of the master’s Thesis research: “Proposal for a digital tourism promotion strategy for the San Agustín de las Cuevas neighborhood in Mexico City,” during the period 2024-2026, and is therefore not yet complete. Therefore, the following analysis, as part of the diagnosis in the San Agustín de las Cuevas neighborhood of Mexico City, represents the initial results of the research.

The Tlalpan Municipality’s Office has its official institutional website, which brings together content related to the internal work of the Municipality’s Office, as well as announcements and programs being planned by the Municipality’s Office, communication, procedures and services, and its main contacts.

On this website, there is a section entitled “What to do in Tlalpan?” which highlights some of the main attractions to be found in the borough. At first glance, this section relates to tourism and the tourist attractions that the borough council wants to show users who visit its website. However, the information presented is insufficient, as it is essential to cover a greater number of attractions and not limit the neighborhood to those that are most

frequently visited. Above all, the Historic Center has attributes, magic, and characteristics that make it an unmissable neighborhood in Mexico City [7].

In this Magical Neighborhood, we can find scenes full of contrasts, ranging from pre-Hispanic vestiges, colonial art, and 19th-century facades to modern shopping and service centers. Along its avenues and streets, we find sites that evoke the colonial era and independent Mexico and take us into modernity. It offers us a range of landscapes, colors, smells, and flavors, all captured in its great diversity of places to visit and enjoy, which form part of the cultural heritage of this district [8].

The Tlalpan Municipality's Office website also features a call to action on the social media platforms where they have a presence: Facebook, Instagram, and Twitter. In addition to these, they also have accounts on TikTok and YouTube.

Key informants interviewed stated that the Social Communication department is responsible for disseminating and publishing content on the Municipality's Office's official social media accounts. These accounts mainly feature informative and educational content for the people of Tlalpan about upcoming events at the Municipality's Office and how residents can collaborate to make the most of them.

The same is true of tourism-related posts. There is a wealth of informative content about the main traditional festivals that take place. However, there is a lack of emotional and/or educational content related, for example, to the care and preservation of heritage attractions that converge in the historic center of the Municipality's Office.

"Tlalpan was declared a Historic Monument Zone on December 5, 1986. Its architecture and urban layout reflect elements from different periods of Mexican history; however, the area largely retains its original 18th-century grid

layout, as well as buildings of historical interest and architectural value" [9].

These attractions themselves create a reason to visit, drawing people to the neighborhood. All types of cultural assets are cared for and preserved so that people can enjoy, learn about, and appreciate them. Raising awareness and educating both residents and visitors to the San Agustín de las Cuevas neighborhood can greatly contribute to the preservation of historical heritage.

"Global heritage communication is conceived as the cultural and communicative management that serves as a bridge between heritage resources and society, with the aim of promoting responsible, beneficial, appealing, and effective use that combines the preservation of cultural assets with their full enjoyment by the public" [10].

Furthermore, through coherent planning, social networks and digital tools can contribute effectively to communicating and disseminating the importance of protecting historical heritage, first at the local level, to create collective awareness and spread it to every person who visits the neighborhood.

Municipality's Office is promoting tourism with the "Tlalpan Vibra" campaign, which owes its name and essence to the vibrant lands of Tlalpan due to the presence of volcanic activity in the territory and the opportunity it offers visitors to disconnect from the hustle and bustle of a city as dynamic as Mexico City. Regarding this campaign, the mayor mentions that:

"Tlalpan has it all: from archaeological remains such as Cuicuilco, mountain areas such as Pico del Águila, to natural parks, volcanoes, museums, and vibrant traditional cuisine. After the Historic Center, Tlalpan is the most beautiful part of the city; it looks like a village with cobbled streets, alleys with Nahuatl names, and a lively community life" [11].

As part of this campaign, the Deputy Director General of Tourism for the Municipality's

Office states that content is being planned for social media in the form of short videos. In addition, a series of brochures were produced to help promote tourism for the campaign. The content presented in these brochures refers to a group of colonial buildings and mansions located in the Historic Center which, thanks to their good state of preservation, are attracting great interest from visitors.

The campaign also promotes Indigenous tourism and cultural tourism, with routes through the historic center, patron saint festivals, and food fairs. The brochures also feature a Route of the Towns of Tlalpan, which combines history, customs, patron saint festivals, and unique viewpoints.

These routes through the historic center of Tlalpan include a tour of some of the main attractions, such as the main square, the Temple of San Agustín, the Chapel of Calvario, and the Oratory of Amaxcalco; the Temple of the Immaculate Conception, the Old Hacienda of Tlalpan, the Casa Chata, the Old Mint, the House of the Count of Regla, the House of Viceroy Antonio de Mendoza and of the insurgent Pedro Ascencio, the House of the Marquis of Vivanco, and the Frissac House, as well as the houses with portals, the municipal building, and the La Paz market [11].

The Tourist Tram route also starts from the historic center, with a capacity of 24 people per trip. The tourist tram is an effective local experience, as it takes visitors on a tour of the indigenous villages, the Cuicuilco Archaeological Zone, Fuentes Brotantes Park, and other attractions, where priority is given to the economic benefits of local service providers, encouraging tourists to spend their money in these businesses [12].

The Municipality's Office is also promoting religious tourism, as there is a strong presence of religious institutions in the region, especially in the historic center, including the Pontifical University. "The Tlalpan Center area is also known as the Vaticanito because of the large number of religious congregations there" [12].

In relation to the testimonies of the network of local entrepreneurs, Tlalpan is also home to the local private initiative "Ruta de Arte y Cultura" (Art and Culture Route), which is a local experience and initiative that takes visitors on different tours of incredible places where art is produced in Mexico City. The route consists of four main tours in different areas of the city: Roma-Condessa, Historic Center, Coyoacán-San Ángel, and Tlalpan. Each route covers a series of cultural spaces, including galleries, sculpture, painting, and engraving workshops, photography exhibitions, music centers, etc. In addition, each visit is accompanied by complimentary mezcal, beer, and snacks to make the experience truly idyllic [13].

Without a doubt, this project seeks to transform the way society relates to art, encouraging visitors to immerse themselves in this route through different artistic expressions. In Tlalpan, as this is an initiative that starts locally for cultural, tourist, and recreational offerings in Mexico City, it helps reduce the burden on other similar historic centers, particularly San Ángel and Coyoacán, with which it shares a past as a neighboring colonial town and a present as a historic center and magical neighborhood.

This assessment found that, in general, several actions and campaigns are being planned around tourism promotion, mainly by the Municipality's Office as the official institution responsible for positioning this neighborhood as a unique and magical experience in the greater Mexico City area. However, the benefits and competitive advantages offered using ICTs in tourism promotion are not being exploited.

4. CONCLUSIONS

The San Agustín de las Cuevas neighborhood, the historic center of the Tlalpan Municipality's Office, has an exceptional historical, cultural, and architectural heritage, recognized as a Historic Monument Zone since 1986. However, its current tourism promotion is limited and focuses on the best-known

attractions, leaving aside the richness of the Historic Center and other spaces with heritage value. The information available on the municipality's website and social media is insufficient and lacks depth, especially in terms of emotional and educational content that promotes the preservation and appreciation of heritage.

Although the Municipality's Office has a strong presence on social media, the predominant focus is informational and promotional, failing to take advantage of the potential of digital tools to educate, raise awareness, and generate consciousness about the importance of protecting heritage. Tourism content is limited to providing information, without exploring innovative formats or narratives that connect emotionally with the public.

Nowadays, there are some cool initiatives, like the Tourist Tram, the "Art and Culture Route," and the "Tlalpan Vibra" campaign, which aim to diversify tourism and spread the economic benefits among local service providers. These initiatives show that there's interest in positioning Tlalpan as a cultural and indigenous destination. However, greater dissemination and coordination with digital strategies are needed to integrate heritage preservation with tourist enjoyment and actively involve the local community and visitors in its care.

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Conflicts of interest

The authors declare no conflict of interest.

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IV

Interdisciplinary

**217-IV-PO EFFECT OF CHITOSAN: TPP RATIO ON THE FORMATION OF DNA
NANOENCAPSULATES**

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Abstract:

The application of exogenous nucleic acids (DNA and RNA) in agriculture represents an innovative technology for gene regulation and crop protection. One of the main challenges is to prevent the degradation of these molecules under environmental conditions. In this context, the development of nanomaterials is an essential step for the protection, storage, and delivery of genetic material. In this project, DNA nanoencapsulates were developed using chitosan as the main biopolymer and sodium triphosphate (TPP) as the cross-linking agent, with the object of generating stable structures capable of protecting and transporting genetic material for potential application in agriculture. Empty and DNA-loaded nanoparticles were prepared in three different chitosan:TPP ratios. Their DNA retention capacity, evidence of cross-linking validating the chitosan:TPP interaction, particle size, and spherical formation of the nanoencapsulates were evaluated. The results show that all ratios generate spherical encapsulates with an approximate size of 4 μm capable of fully encapsulating the DNA. FTIR analysis showed that the 4:1 ratio has the lowest yield due to the absence of displacement or low absorbance at wavelengths key to nanoparticle formation, such as 1548 cm^{-1} to 1535 cm^{-1} and 1407 cm^{-1} to 1385 cm^{-1} , compared to the 1:1 and 2:1 ratios.

Keywords: Nanoencapsulation, Chitosan:TPP, iRNA, Exogenous DNA, Exogenous RNA.

1. INTRODUCTION

Currently, gene silencing through RNA interference (RNAi) is emerging as a powerful and innovative tool in agriculture, promising to protect commercially important crops from pests, bacteria, viruses, and fungi in an environmentally friendly, safe, and targeted manner [1-3]. To date, RNAi has been successfully applied to crops such as corn, tobacco, tomatoes, cucumbers, citrus fruits, peppers, rice, and squash, effectively reducing the expression of selected genes [5-11]. For example, Gan et al. (2010) demonstrated that spray application of exogenous RNA containing a fragment of the CP (capsid protein) gene of the sugarcane mosaic virus (SCMV) inhibited SCMV infection in maize Namgial et al., (2019) performed a process called "RNA-based vaccination" in which they vaccinated tomato (*Solanum lycopersicum*) with dsRNA specific for tomato leaf curl virus (ToLCV), demonstrating that the application of dsRNA conferred approximately 55% protection against ToLCV.

Despite of its promising functionality, there is a list of challenges to overcome before this technology can be applied on a large scale. One of the main challenges is protecting nucleic acids from environmental conditions that can degrade them. Factors such as temperature, pH, and degradation by enzymes such as DNases and RNases could impair their functionality [1-3]. The lifespan of a nucleic acid exposed to the elements due to environmental conditions is short, ranging

from minutes to a few hours [15]. This reduces its period of effectiveness. Therefore, finding a protective vehicle is key to its application in the field.

The research for vehicles has focused mainly on nanomaterials, whose characteristics must meet the requirements of storage, protection, biocompatibility, and allow for the controlled release of genetic material [16]. So far, materials such as LDH (layer double hydroxide), carbon dots, vesicles, protein capsules, and chitosan nanoencapsulation have been proposed as promising vehicles for nucleic acid storage [17].

Chitosan nanoparticles with sodium tripolyphosphate (TPP) have interesting properties for the nanoencapsulation of nucleic [17,18]. The encapsulation method is simple, fast, and relatively inexpensive [20]. So far, they have been found to provide high protection to RNA under environmental conditions [19]. Therefore, the nanoencapsulation of nucleic acids with chitosan and TPP has become a viable alternative for protecting genetic material from environmental conditions.

In this study, the effect of DNA nanoencapsulation using three different ratios of chitosan:TPP (1:1, 2:1, and 4:1) during the encapsulation process was analyzed.

2. MATERIALS AND METHODS

2.1. Materials

The medium molecular weight chitosan and sodium tripolyphosphate (TPP) used were obtained from Sigma-Aldrich® Merck.

2.2 Amplification of DNA sequence of interest

The DNA sequence of interest was obtained using conventional PCR. Thermo Scientific DreamTaq® Polymerase was used according to the manufacturer's instructions. PCR was performed in a T100 thermocycler (Bio-Rad, USA) under the following conditions: (1) Initial denaturation at 95 °C for 1 min, (2) 34 cycles of denaturation at 95 °C for 30 s, annealing at 55

°C for 30 s, extension at 72 °C for 30 s, and (3) a final extension at 72 °C for 10 min. The product was then analyzed by electrophoresis in a 1% agarose gel at 75V for 45 min using Thermo Scientific GeneRuler 1kb+ as a molecular weight marker.

2.3 Synthesis of nanoencapsulates

Prior to DNA encapsulation, a 0.1% (w/v) chitosan solution was prepared in sterile deionized water together with 1% acetic acid. Next, its pH was adjusted to 4.8 and it was kept under magnetic stirring for 24 hours to promote complete protonation and dissolution. A 0.1% (w/v) TPP solution was also prepared. Subsequently, empty nanoencapsulates (NV) were prepared as a control, and DNA nanoencapsulates (ND) were prepared at different ratios (1:1, 2:1, 4:1) of chitosan:TPP, respectively, together with their corresponding replicates.

The nanoencapsulation consisted of three stages. First, the previously synthesized DNA was added to the TPP solution, adjusting the final concentration to 10 ng/μl depending on the volume required.

Second, the TPP-DNA mixture was incorporated in a controlled manner into the chitosan solution under magnetic stirring. Finally, the formed nanoparticles were incubated at 600 rpm for 30 min to promote their encapsulation.

2.4 Electrophoresis

To evaluate the encapsulation capacity, agarose gel electrophoresis was performed at 1%. Under the following parameters: 80V, for 35 min. To determine the effectiveness of encapsulation, samples of the nanoparticles and the supernatant were placed, as well as a sample of unencapsulated DNA as a control. Sybr Gold was used to stain the samples and GeneRuler 1kb+ as a molecular weight marker.

2.5 FTIR analysis

To compare the effect of different ratios of chitosan:TPP on the synthesis of the

nanoencapsulates, Fourier Transform Infrared Spectroscopy (FTIR) analysis was performed using Vertex 70X equipment. The samples were taken at a resolution of 60 readings every 4 cm^{-1} at a wavelength range of 4000 cm^{-1} to 400 cm^{-1} . The results were analyzed in Origin 2016 software using the AverageSpectra function to average the spectra of the replicates.

2.5 Microscopy

A ZEISS Primo Star microscope equipped with an AxioCam ERc 5s camera was used. The images were then analyzed using Image J software (<https://imagej.net/ij>) and the data was normalized using a $100\text{ }\mu\text{m}$ scale.

3. RESULTS AND DISCUSSION

3.1 DNA Encapsulation

To verify the effectiveness of DNA encapsulation, 1% agarose gel electrophoresis was performed. The samples were analyzed together with their respective supernatants to observe the presence of unencapsulated DNA. The agarose gel confirmed the complete encapsulation of DNA in the different proportions tested. Fig. 1 shows the retention of nanoparticles at the top of the gel due to the immobilization of the nanomaterial. This corresponds to what was previously reported by Mudo et al., (2022). While the supernatant shows no presence of DNA, indicating complete encapsulation, the presence of nanoparticles is still observed in the supernatant of the 4:1 ratio (Figure 1, c).

3.2 FTIR analysis

FTIR spectroscopy analysis identified the chemical interactions between the components of the encapsulates in each proportion (Figure 2), validating the cross-linking between chitosan and TPP.

Figure 2 shows a shift in the wavelengths from 1548 cm^{-1} to 1535 cm^{-1} and from 1407 cm^{-1} to 1385 cm^{-1} , as well as a decrease in their ABS, which, according to reports, indicates the interaction of the amino groups of chitosan

with the phosphate groups of TPP [20,22]. Meanwhile, for those generated by the 4:1 ratios, this shift is subtle, presenting the same wavelengths at 1407 cm^{-1} and 1548 cm^{-1} as the chitosan without interaction.

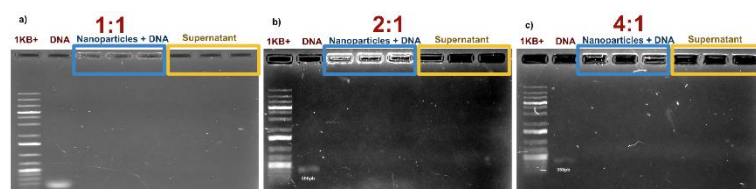
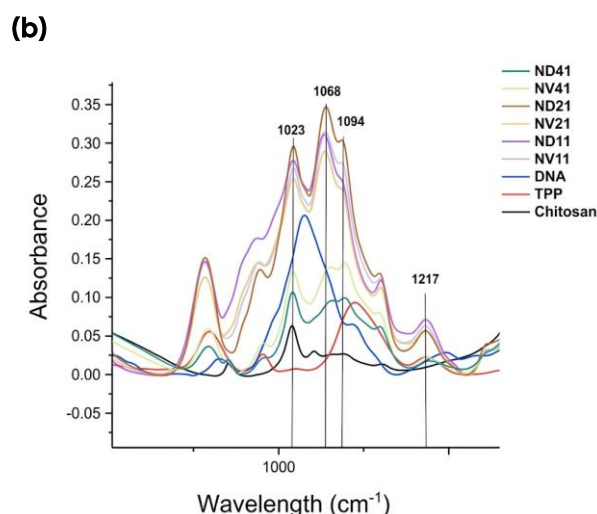
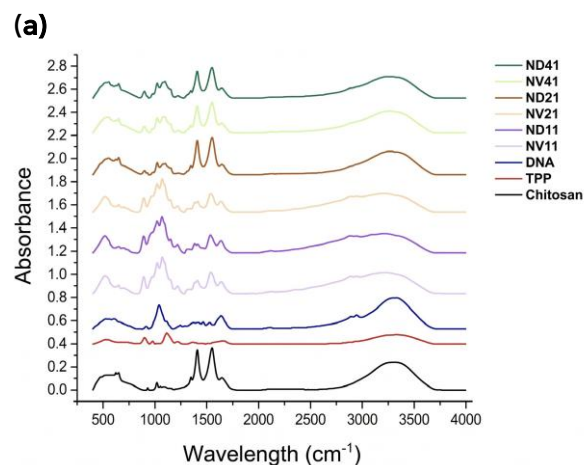


Figure 1. Analysis of DNA nanoencapsulates. Nanoencapsulates at different ratios (1:1, 2:1, 4:1) loaded with DNA (ND) together with their supernatant and unencapsulated DNA were stained with Sybr Gold, placed in a 1% agarose gel, and run at 80V for 35 min. (a) ND11, (b) ND21 (c) ND41.



(c)

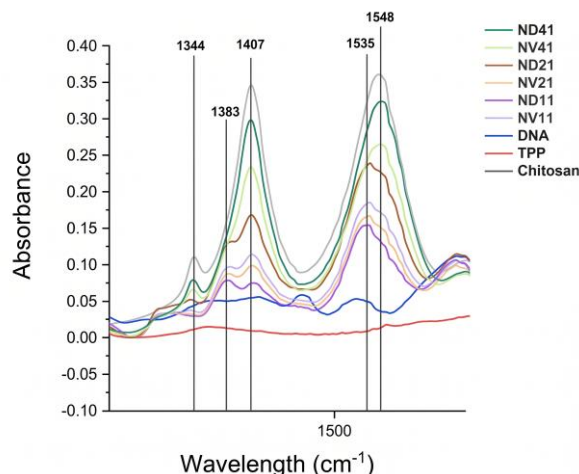


Figure 2. FTIR analysis of chitosan:TPP nanoencapsulates at different ratios with and without DNA. (a) The graph shows a comparison of the spectra of nanoencapsulates at different chitosan:TPP ratios (1:1, 2:1, and 4:1) empty (NV) and with DNA (ND), (b) The graph shows a close-up of the spectra at a wavelength of 1000 cm^{-1} to 2000 cm^{-1} , focusing on the peaks representing chitosan. (c) The graph shows a close-up of the spectra at a wavelength of 500 cm^{-1} to 2000 cm^{-1} , focusing on the peaks representing sodium tripolyphosphate (TPP).

Finally, there are differences in the ABS peaks at a wavelength of 1217 cm^{-1} . As the concentration of TPP decreases in the different proportions, the intensity of this peak decreases. It is suggested that the appearance of new bands around 1210 cm^{-1} corresponds to the P=O stretching of the phosphate group of TPP generated by the interaction [22].

Considering the above points together with the results of the FTIR analysis, it can be inferred that the 1:1 and 2:1 ratios show greater chitosan:TPP interaction, demonstrating the correct generation of nanoencapsulates. Meanwhile, the 4:1 ratio shows signs of encapsulation to a lesser extent.

3.3 Microscopy analysis

The nanoencapsulates were observed under a microscope at 100x magnification, where the presence of mostly spherical nanoencapsulates was confirmed (Figure 3).

With the help of Image J software, the approximate size of the nanoencapsulates was determined to be between 100 nm and 200 nm in diameter for empty nanoencapsulates and 150 nm on average for DNA nanoencapsulates. For 1:1 ratios, there is an increase in size in DNA encapsulates of almost double; on the contrary, for 2:1 and 4:1 ratios, their size decreases slightly in DNA-loaded nanoparticles. The size obtained for the nanoencapsulates corresponds to that previously reported by Dhandapani et al., (2019) and Yan et al., (2021), whose nanoencapsulates are similar in size.

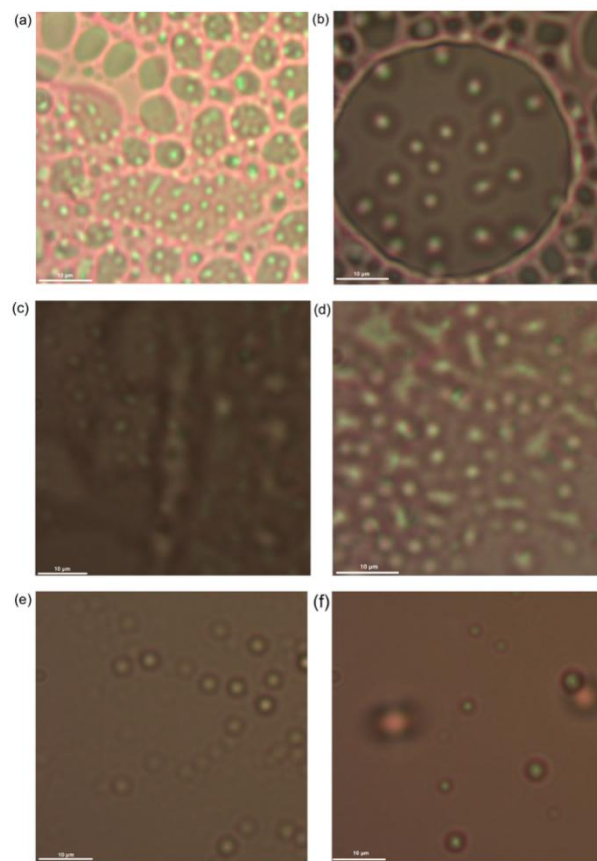


Figure 3. Chitosan:TPP nanoencapsulates with and without DNA at 100x magnification. The images show empty nanoencapsulates (NV) and those loaded with DNA (DC) obtained at different chitosan:TPP ratios (1:1, 2:1, and 4:1) using a 100x objective and a scale of 10 μm (a) NV11, (b) DC11, (c) NV21, (d) DC21, (e) NV41, (f) DC41.

4. CONCLUSIONS

The results show that the effect of the chitosan:TPP ratio on the formation of DNA nanoencapsulates significantly influences the yield and size of the nanoparticles obtained. The 1:1 and 2:1 ratios yielded the highest results compared to the 4:1 ratio. This demonstrates that the TPP concentration is the limiting factor for the generation of nanoencapsulates. However, despite the differences in yield obtained, it was found that the different ratios manage to completely encapsulate the DNA concentration, forming spherical nanoencapsulates of around 150 nm in diameter according to the ratio. This is in line with the size suitable for its applicability in plants.

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Conflicts of interest

The authors declare no conflict of interest.

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358-IV-PP COMPUTATIONAL MODELING OF HAPTEN FORMATION BY THE NITROSO METABOLITE OF SULFAMETHOXAZOLE ON HUMAN SERUM ALBUMIN IN DRUG HYPERSENSITIVITY REACTIONS

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Abstract: Drug hypersensitivity reactions (DHRs) are clinically significant adverse events that can affect up to one-third of the population. Among culprit drugs, sulfonamide antibiotics, notably sulfamethoxazole (SMX), are frequent triggers. Although SMX has been in use since the 1930s, key structural details of the immunogenic species that break tolerance remain unresolved. Current evidence indicates that hepatic biotransformation yields the nitroso derivative (SMX-NO), a highly reactive intermediate that covalently binds proteins, particularly human serum albumin (HSA), to generate haptens that drive T-cell-mediated (type IV) DHRs. Here, we used an *in silico* approach to design and validate physicochemically consistent parameters for SMX-NO and to model its covalent conjugation to HSA at experimentally implicated lysines (K199 and K137). Density-functional theory-optimized geometries used in SwissParam-assisted parametrizations, complemented with reported experimental vibrational frequencies, enabled explicit-solvent molecular dynamics (MD) simulations in NPT ensembles for the hapten candidates. The resulting hapten models (HSA-SMX-NO-K199 and -K137) remained stable over 100 ns, with limited RMSD fluctuations consistent with modest but measurable conformational rearrangements in HSA. We provide a validated

structural framework for HSA-SMX-NO haptenation modelling, filling the gap left by the lack of crystallographic structures for these haptens, and establish a blueprint for rational *in silico* design of anti-hapten antibodies or binders for treatment, diagnosis, and for mechanistic explorations of DHRs.

Keywords: Drug hypersensitivity; Sulfamethoxazole; Hapten; Human serum albumin (HSA); Molecular dynamics (MD)

1. INTRODUCTION

Drug hypersensitivity reactions (DHRs) represent atypical, non-dose-dependent adverse events (type B) with an immunologic basis that can escalate to severe cutaneous adverse reactions (SCARs) [1]. DHRs are clinically significant adverse events that may affect up to one-third of the population, with 8–10% of cases requiring hospitalization for severe immune-mediated responses. Consequently, incidence rates in hospitalized settings are substantial, and the associated economic and clinical burdens are considerable. [2]. Antibiotics, especially β -lactams and sulfonamides, anticonvulsants, and antivirals, are the most implicated agents. Mechanistically, three non-exclusive models explain how small molecules breach immune tolerance: the hapten/pro-hapten concept

(covalent protein modification), the pharmacological-interaction (p-i) concept (non-covalent TCR/HLA binding), and peptide-repertoire alteration via drug-HLA interactions (e.g., abacavir with HLA-B*57:01) [3]. SMX remains a canonical system to study haptentation: hepatic CYP2C9 metabolism produces hydroxylamine (SMX-NHOH), which auto-oxidizes to SMX-NO, a reactive species that adducts HSA at exposed lysines and, less frequently, cysteine or tyrosine [4]. Despite extensive biochemical characterization and detection of specific HSA haptens in limited patient samples, no crystallographic structures of SMX-derived hapten-protein complexes or anti-hapten antibodies exist. This knowledge gap limits rational diagnostic reagent development and mechanistic modeling of T-cell recognition. We therefore built physics-based structural models of human serum albumin (HSA) haptentated by the nitroso metabolite of sulfamethoxazole (SMX-NO) at lysines K199 and K137, with site selection guided by solvent accessibility and prior literature. The models were validated by molecular dynamics (MD) and are intended as a reusable platform for downstream docking to anti-hapten antibodies (Abs) or single-chain variable fragments (scFv) and for hypothesis generation in DHRs.

2. MATERIALS AND METHODS

Structural templates and small-molecule inputs: The HSA template was taken from PDB ID 1E78 (2.6 Å resolution) [5]. The 3D structure of SMX was obtained from DrugBank (DB01015) and geometry-optimized at the DFT level (PBE/DZVP) using deMon2K v6.0.1 [6]. A nitroso derivative (SMX-NO) was constructed and similarly optimized. SwissParam provided initial CHARMM-compatible topologies and parameters, which were complemented with literature-derived constants, i.e. infrared stretching bands for the -N=N- bond [7]. A covalent linkage between the ϵ -amino group of lysine and the amino-substituted aromatic system of SMX-NO was modeled as an azo-like connection; force constant was obtained by vibrational frequency analysis (633.96

kcal/mol/Å²). Atomic charges were adjusted to preserve electroneutrality for CHARMM [8] compatibility.

Hapten construction and system assembly: Two hapten models were built (HSA-SMX-NO-K199 [hapten A] and HSA-SMX-NO-K137 [hapten B]) using psfgen. Systems were solvated with ~38,000 TIP3 water molecules (box dimensions ~98.8 × 121.5 × 104.7 Å) and neutralized with Na⁺/Cl⁻ to 0.1 M.

Equilibration and MD production: Simulations were run in NAMD 2.12 [9] with the CHARMM27 force field [8]. Protocol: (1) 3,000-step minimization of solvent/ions with protein fixed; (2) 30,000-step NVT heating from 0.15 to 298.15 K at 1 K/200 fs (protein fixed); (3) 3,000-step full-system minimization; (4) 100-ps heating to 310.15 K; and (5) 100-ps NPT MD at 310 K, 1 atm. Production MD ran 100 ns with 2-fs steps using SHAKE for X-H bonds, PME electrostatics, a 10 Å cutoff for non-bonding interactions (12 Å pairlist, 8 Å switching), and Langevin thermostat/barostat.

Site selection metrics: Solvent accessible surface area (SASA) was computed for peptides encompassing reported SMX-NO modification sites using the program VMD [10]. We considered per-peptide SASA and residue-normalized SASA to prioritize exposure. In vivo detectability (patient serum evidence) was used as an additional criterion.

Analysis: Backbone and ligand heavy-atom RMSD were tracked during MD. Energy minimization convergence was monitored to confirm parametrization consistency. Comparative overlays against unmodified HSA quantified conformational impact.

3. RESULTS AND DISCUSSION

Human serum albumin design

Human serum albumin (HSA) has 162 structural models in the PDB; from these we selected ID 1E78, which has a resolution (above the average) of 2.6 Å and is not co-crystallized with other molecules, as is the case for most entries.

In addition, this structure was crystallized to study drug binding.

According to Tailor et al. [4], there are eleven lysine sites in HSA subject to modification by SMX-NO *in vitro*. These modification sites are visualized in Figure 1. Additionally, solvent-accessible surface area (SASA) calculations were performed considering these amino acids analyzed *in vivo* in sera from patients with sulfamethoxazole hypersensitivity.

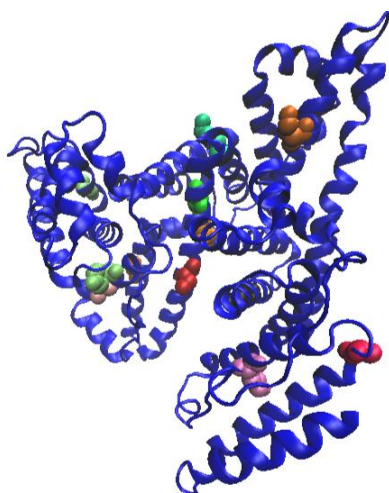


Figure 1. Location of amino acids found modified by nitroso-sulfamethoxazole *in vitro* in Human Serum Albumin (PDB model 1E78).

As shown in Table 1, from SASA values we found that not all the modification sites are equally exposed to the protein surface, therefore, different preference to haptenize is expected. We chose K199 and K137 to test two configurations. While K199 is much less exposed given its average SASA of 29.3 Å², it has been detected as a haptenization site *in vivo* and is lining a binding site favorable to several known ligands [4]. K137 is one of the haptenization sites investigated *in vitro* which is more exposed, as can be observed in Figure 2, with a larger average SASA equal to 46.1 Å². This greater solvent exposure could allow improved binding and recognition by receptors or antibodies.

Table 1. Peptides and selection criteria for hapten modeling

Lysine No.	Peptide	SASA (Å ²)	Average SASA (Å ²)
12	F <u>K</u> DLGEENFK	498.8	43.7
137	<u>K</u> YLYEIAR	336.1	46.1
159	RHPYFYAPELLFFA <u>K</u> R	594.5	52.5
190	LDELRDEG <u>K</u> ASSAK	792.0	58.2
195	ASSA <u>K</u> QR*	280.5	40.1
199	L <u>K</u> CASLQK*	341.1	29.3
212	AF <u>K</u> AWAVAR	358.6	54.2
351	LA <u>K</u> TYETTLEK	533.7	27.0
432	NLG <u>K</u> VGSK	306.1	31.6
525	<u>K</u> QTALVELVK*	194.3	33.5
541	AT <u>K</u> EQLK	591.2	89.2

aa, amino acid; SASA, solvent-accessible surface area; *, Lysine residues identified by *in vivo* analysis.

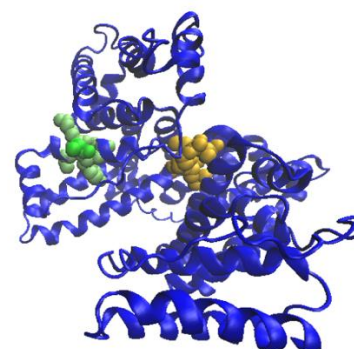


Figure 2. Human serum albumin highlighting K199 (yellow) and K137 (green).

It is worth noting that, in addition to the literature background, visual inspections, and SASA evaluation used to choose the sites, we considered computational scFv recognition assays (data not shown). There are, however, other potential modification sites that can be

evaluated using computational methods; an exhaustive assessment of all possible modification sites in HSA, although beyond the scope of the present work, would be feasible using the parameter set developed in the present work (described in the following section), as it would be transferable to any lysine residue.

Nitroso-sulfamethoxazole design

The three-dimensional structure of sulfamethoxazole (SMX) was obtained from DrugBank under ID DB01015, Figure 3a). This initial structure was optimized using the previously described DFT-level methodology. A model of its azo-alkyl derivative was likewise generated and optimized to be used in the parametrization (Figure 3b), as this compound analogous to the final Lys-N=N-SMX hapten resulting from the haptenization reaction. It should be emphasized that SMX-NO reacts with and binds covalently to HSA forming the azo-alkyl hapten that is the subject of study in this work.

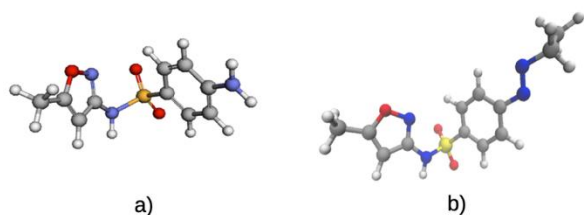


Figure 3. Initial structure models of (a) sulfamethoxazole (SMX) and (b) its azo-alkyl derivative used to parametrize SMX-HSA adduct.

SwissParam [11] was used to obtain parameters for the CHARMM force field that would allow, through molecular-mechanics calculations, optimization of the structure of the SMX-HSA hapten, as well as evaluation of structural effects on the protein. As described in the Methods section, the parameters generated by the SwissParam server were refined using experimental information reported in the literature, because the parameters needed to describe SMX or its metabolite are not included in the CHARMM force field. The refinement included rescaling of atom charges to generate a modified lysine residue incorporating the SMX structure bonded by the azo linkage, conserving the electroneutrality of the new

residue. These topology and parameter definitions were used to create two hapten models (called A and B), modifying the previously selected lysine sites K199 and K137, respectively. Once the haptens of interest were obtained and following the equilibration protocol for the modified protein structure in a periodic box with explicit water molecules and ions, we analyzed RMSD variation over the course of the dynamics. As shown in Figure 4 for hapten A, the linkage remained stable with very few fluctuations in the Lys-SMX structure, demonstrating that the calculated parameters enabled an appropriate attachment of the nitroso metabolite of sulfamethoxazole to lysine 199 of HSA. Given that the same parameters designed for site K199 are applicable to binding at other lysines, hapten B (site K137) was confirmed to display behavior similar to that observed in this analysis.

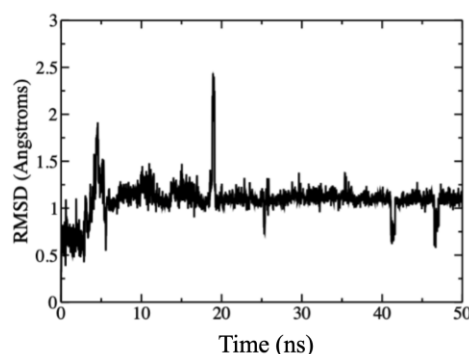


Figure 4. RMSD time evolution for SMX bound to HSA in hapten A.

The RMSD plot shows some fluctuations corresponding to transient torsions in the structure, indicating that the parameters also permit a certain degree of flexibility in the SMX-NO structure even when bound to the protein. A jump in RMSD of ~ 0.5 Å was observed at approximately 5 ns of simulation and remained constant for the rest of the run, suggesting that SMX-NO adopts a structure different from the initial free form when bound to HSA.

According to the literature, the production of anti-hapten Abs with the desired specificity depends critically on hapten design. Key points for haptens include preserving the chemical structure and spatial conformation of the

compound, as well as the appropriate selection of the carrier protein and conjugation method. For this reason, special attention was given to antigen design, i.e., HSA modified by nitroso-sulfamethoxazole. In this context, we successfully modeled the nitroso metabolite to bind any lysine of human serum albumin; thus, we constructed the model of hapten A and the model of hapten B, as shown in Figure 5.

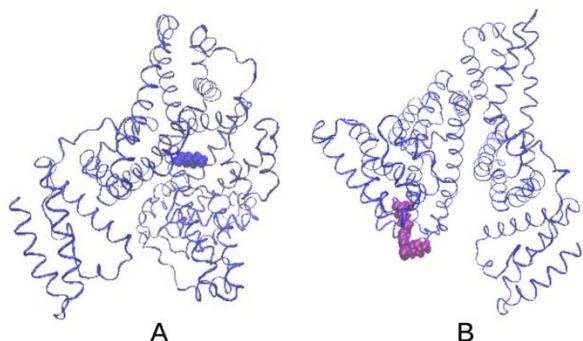


Figure 5. Hapten A, HSA-SMX-NO-Lys199, and Hapten B, HSA-SMX-NO-Lys137. The modified lysine residues are shown as spheres.

Once the haptens were obtained, energy minimizations, equilibrations, and production simulations were carried out for both haptens, along with solvation by adding water molecules and charge stabilization by adding ions, as described in the Materials and Methods section. Figure 6 shows the energy-minimization stage, where the expected behavior upon relaxing the protein structure is observed. Around step ~200, an energy value close to the minimum is reached, indicating that the structure has attained its maximally relaxed state. This also confirms the correct performance of the proposed parameters for SMX-NO bound to HSA. These parameters ensure that the lower the energy obtained for the modified lysine residue, the closer its structure will be to the optimized structure at the DFT level of theory.

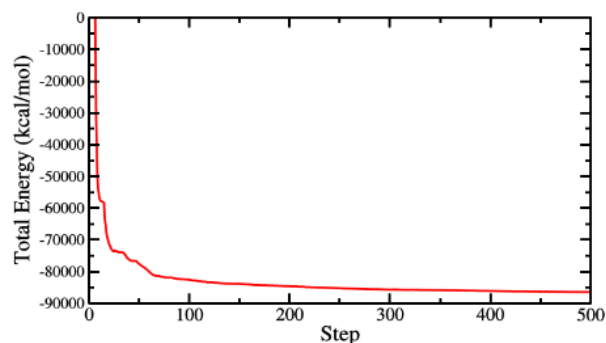


Figure 6. Energy minimization stage for hapten A model immersed in a box with ~38,000 water molecules and 0.1 M of Na⁺ and Cl⁻ ions.

In Figures 7 and 8, a structural comparison of HSA for the two haptens A and B is shown to evaluate the effect on the protein structure upon modification by SMX-NO. The RMSD for hapten A is 2.48 Å, whereas for hapten B it is 2.87 Å. Taken together, the data indicate a conformational change attributable to covalent modification of lysine residues by the nitroso metabolite, with effects that extend beyond the local site and may alter how the protein is recognized by other molecules, including immune receptors.

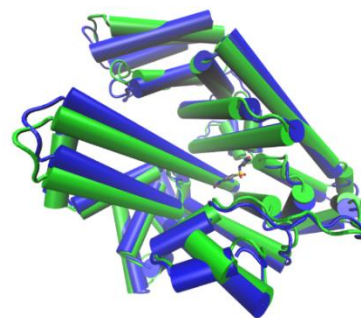


Figure 7. Comparison of human serum albumin (green) versus hapten A (blue).

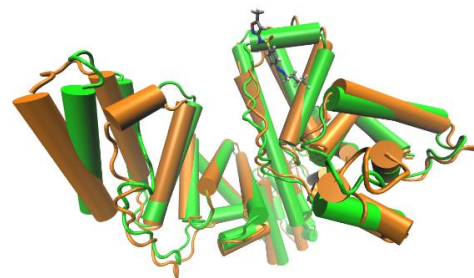


Figure 8. Comparison of human serum albumin (green) versus hapten B (orange).

Based on the results shown, we conclude that the parameters used to model the binding of

the nitroso metabolite of sulfamethoxazole to two HSA binding sites (lysines 199 and 137) are suitable to carry out studies of scFv recognition.

4. CONCLUSIONS

We present a validated computational framework to model HSA haptenation by the nitroso metabolite of sulfamethoxazole. To our knowledge this is the first computational atomistic model that accounts for the covalent binding of the sulfamethoxazole-nitroso metabolite to the Human Serum Albumin protein at two different lysine sites. CHARMM-compatible topology and parameter definitions for SMX-HSA haptens applicable to different molecular mechanics calculations, including Molecular Dynamics, were obtained. These enabled stable, explicit-solvent MD of covalent hapten at K199 and K137, producing structural hypotheses for downstream immunological interrogation. These models fill a critical structural knowledge gap in SMX-associated DHRs and should facilitate rational design of diagnostic anti-hapten Abs/scFv's and mechanistic studies of T-cell recognition. Extending this approach across additional sites and carriers, and benchmarking against experimental peptide elution and functional assays, will further refine our understanding of drug-induced haptenation.

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Conflicts of interest

The authors declare no conflict of interest

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**446-IV-PO ORGANISATIONAL VIABILITY FOR WATER AND TOURISM MANAGEMENT IN
MAGDALENA ATLITIC**

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Abstract: The challenges of today's world, where natural resources are increasingly impacted by human activity, demand special attention. In 2021, UN Tourism declared the need to move away from overtourism towards a regenerative approach that promotes ecosystem restoration, community inclusion, and resilience in the face of climate change. Rural communities with a tourism vocation have emerged as key actors in achieving this regenerative perspective. The rural community of *La Magdalena Atlitlic*, located in Mexico City, faces significant difficulties as a result of urban expansion and overtourism.

This study develops a diagnosis from a systemic perspective, applying the Viable System Model (VSM) with the aim of assessing the organisational viability of the system under study. Combined with fieldwork and the measurement of organisational entropy, the current situation of the actors involved was identified. The findings reveal weak feedback between system functions such as operations, regulation, and control, as well as the absence of a shared vision oriented towards regenerative tourism and water stewardship among macro-environmental actors.

The application of the VSM made it possible to visualise the tensions and opportunities within the system and to propose a desired structure that integrates the five subsystems of the model, guiding decision-making towards a fairer and more sustainable management of the territory.

Keywords: Regenerative tourism, water management, Systems Thinking, entropy.

1. INTRODUCTION

Overtourism [1], characterised by encouraging a high influx of visitors, enabling extractive practices of natural resources, and the superficiality with which activities are conducted in tourist destinations [2], has become a systemic problem in areas with a tourism vocation, and has even severely affected places that are not traditionally tourist sites.

This structural consequence, in which tourism directly impacts and alters the environment, has been a subject of study for several decades [3], particularly in relation to water as a natural resource. Tourism dynamics have been shown to be among the main drivers of water use worldwide [4], [5].

In addition, the global water crisis is unfolding at a faster pace in cities whose populations exceed their carrying capacity [6]. In a densely populated city such as Mexico City, with a projected population of 12.2 million in 2025 [7], the growing demand for water requires a regenerative and sustainable approach to its management.

Some data indicate that in Mexico only 43% of the population has access to safely managed drinking water services, while in 2023 as much as 57% of the country's water sources were lost due to inefficient irrigation systems [8], largely derived from agricultural activity.

These figures highlight the complexity and challenges involved in achieving efficient water management in the metropolis. Despite the efforts made by the scientific community to expose the problem, and the regulations implemented over recent decades to curb excessive consumption, it remains a systemic issue, particularly in tourist areas.

This research develops a diagnosis from a systemic perspective, applying the Viable System Model (VSM) with the aim of evaluating the organisational viability of social tourism enterprises in the rural community of *La Magdalena Atlitlic* (LMA) and their relationship with water management. The model seeks to help organise and strengthen these enterprises, so that overtourism practices do not harm the community but rather sustain it over time and contribute to improving local realities.

1.1. SYSTEM UNDER STUDY

Mexico City is divided into sixteen boroughs, each with its own distinctive cultural and socio-economic diversity. The community of LMA is located within the borough of *La Magdalena Contreras* (Figure 1), situated in the south-western part of the city. This borough stands out for its environmental value and is home to the protected natural area known as *Los Dinamos* National Park.

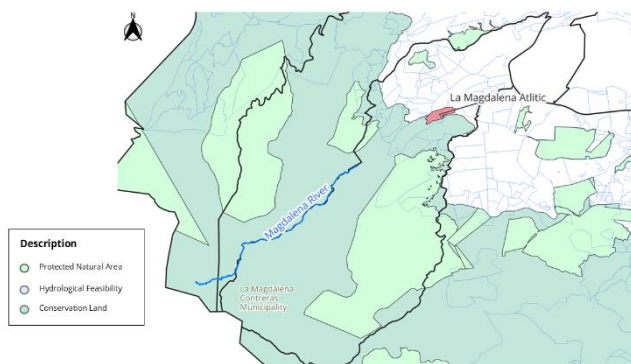


Figure 1. La Magdalena Contreras Map. Source: author's own work.

As shown in Figure 1, the borough covers a wide conservation area, composed mainly of mountain forest, and is also home to the last living river of the metropolis. The Magdalena

River is a vital water body, as it provides a source of drinking water for the nearby urban area and constitutes a zone of high environmental value and rich biodiversity.

The conservation of the Magdalena River is essential to mitigate the ecological imbalances of the area, which have repercussions across the whole of Mexico City. Other challenges include the overexploitation of aquifers, inefficiencies in water distribution, and inadequate infrastructure for wastewater treatment.

It is important to emphasise that these challenges in water management become more acute in rural areas with a tourism vocation, where infrastructure is more limited and water demand can fluctuate significantly due to the variability in the flow of tourists and visitors.

Tourism activities in LMA include mountain biking, rock climbing, hiking (interpretative or its variants), abseiling, and zip-lining. In some nearby areas, community members have adapted rustic facilities for the incorporation of *temazcales* (traditional saunas) and sport fishing in trout farms.

This range of tourism products and services reflects a wide variety of activities, yet it is important to emphasise that most of them are carried out by local residents of the borough, responding both to the characteristics of the environment and to the material and immaterial capacities of its people.

The involvement of the rural community of LMA in the design, operation, and maintenance of these enterprises that provide tourism products and services offers a dimension of identity within the system under study. It represents a form of local self-management that generates income and, in most cases, seeks to preserve the ecological and cultural environment.

2. METHODS

With the growing pressure on natural resources, it becomes essential to adopt integrated approaches to water management.

In this regard, the implementation of systemic methodologies in complex human activity problems offers pathways for improving reality within real contexts, where water as a resource is affected from multiple angles.

2.1. Approach

The interactions and decision-making processes among the actors involved in a system may vary depending on the nature of their relationships and the degree of agreement that exists between them. According to Jackson [9], problem situations or contexts can be categorised into three types, based on the participants' perspectives and the nature of the system, as shown in Table 1.

Table 1. 'Ideal-type' grid of problem contexts

Classification	Description
Unitary	All participants share beliefs, values, and interests, which facilitates decision-making through consensus.
Pluralist	Although differences exist, the actors are able to reach agreements in order to achieve the objectives of the system.
Coercive	It is characterised by conflictual relationships and the absence of shared interests, where one group imposes its will on the others, reaching agreements through domination rather than collaboration.

Source: Adapted from Jackson [10].

2.2. Viable System Model

The VSM [11] is a framework based on the principles of cybernetics that assists in diagnosing complex organisations, enabling them to remain alive and adaptable in a changing environment. Through this model, leaders and entrepreneurs in LMA can learn to identify what is not functioning within their 'organisation' and how to address it.

According to Beer [12], a viable organisation must comprise five subsystems (Table 2).

Table 2. Subsystems of the VSM

System	Functions	Description
S1	Operations	Basic units with their respective management. Primary units.
S2	Coordination	Attenuation of oscillations.
S3 & S3*	Control and Audit	- Operational management of a group of subsystems. - Audit and monitoring channel.
S4	Intelligence	Long-term management with the environment.
S5	Policy	Identity and values of the organisation.

Each subsystem fulfils a specific function and maintains mutual relationships with the others, contributing to the alignment with the objectives of the system under study in order to achieve viability and improve reality. From this perspective, sustainability represents a horizon to be reached, whose construction requires the participation of the actors involved.

Complementing the Systems Approach and with the aim of gaining a deeper understanding of the relationships and dynamics within LMA, qualitative techniques were integrated into the diagnostic process. These included observational guides, semi-structured interviews, and participatory research workshops. These tools made it possible to identify the actors involved and to map the social enterprises.

2.3. Entropy

To assess organisational entropy, the proposal of Martínez Berumen et al. [13] was adapted through five scenarios derived from each of the five subsystems of the VSM. For this purpose, Shannon's entropy formula was applied, as shown in Eq. (1), to calculate the level of disorder within the system under study.

$$S = - \sum_{i=1}^N p_i \ln(p_i) \quad \text{Eq. (1)}$$

Where S is the entropy of the system under study; p_i is the probability of scenario i ($S1$ al $S5$), assigned on the basis of the diagnosis and the application of qualitative techniques; and $N = 5$.

3. RESULTS AND DISCUSSION

Through the methodological application, various components and key actors were identified, as represented in Figure 2.

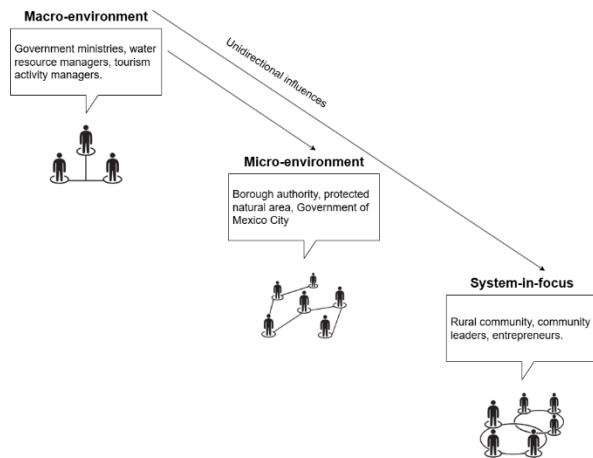


Figure 2. Unidirectional hierarchical interdependence. Source: author's own work.

The actors involved in the system under study were identified at three levels: 1. **Macro-environment:** government ministries, water resource managers, and tourism managers;

2. **Micro-environment:** the borough, the protected natural area, and the Government of Mexico City; and 3. **System-in-focus:** the rural community, community leaders, and entrepreneurs.

The type of situation and relationships identified reflect a complex system fluctuating between the pluralist and coercive, where macro-environment actors impose structures and decisions that are then implemented and operationalised by the micro-environment, directly influencing the system-in-focus. This underscores the presence of a vertical asymmetry and the absence of systemic recursion, which limits the response capacity and self-management of the system-in-focus.

Identifying the actors involved and their positioning within the system made it possible to map the VSM (Figure 3).

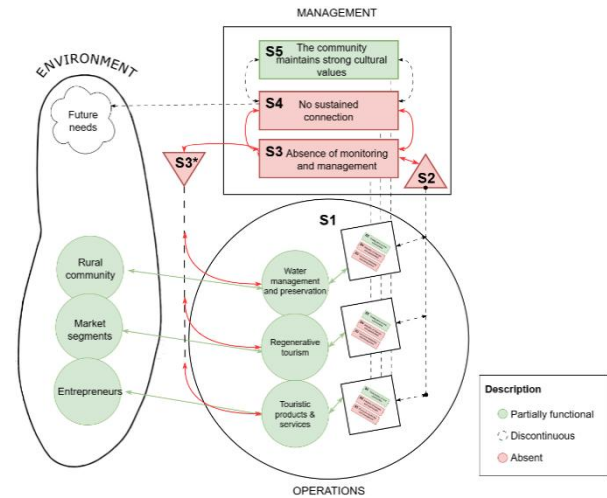


Figure 3. Viable System Model of the system under study. Source: author's own work.

The diagnosis revealed a system in which the viability of the LMA community is compromised due to the discontinuity and functional absence of key system components. The operational units ($S1$), in relation to water management, regenerative tourism, and the development of tourism products, display a certain level of activity. However, this functionality is only partial, owing to limited resources and the absence of a shared governance platform.

In contrast, the coordination ($S2$), control ($S3$), and intelligence ($S4$) functions are absent, which restricts the adaptive capacity of the system. The lack of a coordinating role among $S1$ units generates a misalignment of efforts. The absence of control and audit mechanisms ($S3$ & $S3^*$) prevents effective feedback and evidence-based decision-making, weakening the system's capacity to learn and self-correct.

Likewise, the absence of $S4$ limits the adaptive capacity of the system as a whole, since there is no environmental assessment or trend analysis that would allow anticipation of critical scenarios, such as water scarcity or severe ecological deterioration.

Another subsystem that functions only partially is S5, as it reveals an active connection with the cultural values of the LMA community, which is fundamental for social resilience. Nevertheless, these structures are not formally recognised, preventing the projection of a shared strategic vision through mechanisms that preserve such values in the face of the pressures of overtourism and urbanisation.

This diagnosis was complemented by the estimation of organisational entropy, for which five scenarios corresponding to the five VSM subsystems were considered. Each scenario was assigned a probability p_i proportional to the level of risk identified in the diagnosis (with $\sum p_i = 1$). These probabilities were then substituted into Eq. (1) to estimate the entropy S of the system. Table 3 summarises the scenarios, the values of p_i and the individual contributions used.

Table 3. Scenarios of entropy

System	Risk scenario	Assigned probability	Contribution $-p_i \ln(p_i)$
S1	Risk in the supply and integration of tourism services.	0.10	0.2303
S2	Lack of agreements within the LMA community.	0.40	0.3665
S3 & S3*	Absence of evaluation and feedback mechanisms.	0.20	0.3219
S4	Disconnection from the institutional and external	0.20	0.3219

	environment.		
	Absence of a shared vision regarding regenerative tourism and water.		
S5		0.10	0.2303
	Total	1.00	1.4709

Source: author's own work

An organisational entropy value of $S = 1.4709$ was obtained. Considering the five scenarios (S1-S5), the theoretical maximum entropy corresponds to Eq. (2), $S_{\max} = 1.6094$, which is reached when an equiprobable distribution is assigned across the scenarios ($p_i = 1/N$).

$$S_{\max} = \ln(5) \quad \text{Eq. (2)}$$

The value obtained represents 91.4% of the maximum possible entropy. According to Martínez-Berumen et al. [13], a value greater than $\frac{3}{4} \ln K$ corresponds to a high level of organisational disorder. For the five scenarios considered in this study, this threshold corresponds to 1.2071. Therefore, $S = 1.4709$ places the system under study within this category.

This level of entropy indicates that organisational disorder is distributed across several system functions, which is consistent with the diagnosis obtained through the VSM. This is particularly evident in the coordination (S2), the control and audit (S3 & S3*) and the intelligence (S4), whose individual contributions to entropy sum to 1.0103 and represent approximately 68.7% of the total value obtained.

The lack of communication between S3 & S3* constrains evaluation, monitoring and feedback processes, while the absence of S4 restricts the system's capacity to identify changes in the environment and anticipate scenarios related to water scarcity, ecological degradation and pressure from overtourism.

These results are consistent with previous studies on organisational entropy, such as that of Ursacescu and Cioc [14], who applied Shannon entropy to organisational processes and observed that states approaching maximum entropy are associated with higher levels of uncertainty and a lower degree of organisation, whereas reductions in entropy increase system predictability.

These studies make it possible to interpret relative proximity to maximum entropy as an indicator of organisational pathology. For example, although S1 and S5 exhibit relatively more stable functioning, their contribution is insufficient to offset the entropy observed at the other levels, thereby reflecting the need to strengthen internal cohesion and the system's relationship with its environment in accordance with the reality under study.

4. CONCLUSIONS

The diagnosis carried out shows that, despite the efforts of the LMA community to sustain the operation of social tourism enterprises and preserve its cultural identity, organisational viability and homeostasis are compromised. The application of the VSM made it possible to demonstrate the absence and limited functioning of several of its subsystems.

This situation results in a lack of effective feedback and a limited capacity to make decisions, including the ability to anticipate critical scenarios related to water and the pressures of overtourism. This is confirmed by the organisational entropy, which yielded a value close to the maximum possible, concentrated in the most strategic subsystems (S2, S3 & S3*, and S4). Meanwhile, operations and identity maintain a certain degree of stability, but their contribution is not sufficient to counteract the weaknesses identified in the system.

Likewise, the application of the VSM in a rural community context also presents limitations. Unlike a formal organisation or one with a rigid organisational structure, a community is characterised by social, cultural and

institutional relationships in which functions, responsibilities and decision-making mechanisms are not always clearly defined.

Consequently, the implementation of the VSM through community workshops is not always appropriate, particularly when there are limitations in the willingness of the community to participate actively in this type of process. Recent studies applying the VSM in rural communities have also indicated that cultural differences, participation and communication capacities, as well as power asymmetries among actors, can influence the way in which self-governance capacities are identified and developed [15]

To address this, it is necessary to strengthen the system's internal cohesion through clearer coordination mechanisms, communication and control processes that generate reliable feedback, and an intelligence subsystem capable of linking the community with external actors involved in tourism dynamics and water management.

The consolidation of these functions would help to improve sustainability and even promote regeneration as a new approach for social enterprises offering tourism products and services. This would lay the foundations for fairer and more resilient water management, consistent with the principles of regenerative tourism, the needs of the territory, and the reality of the LMA community.

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Conflicts of interest

The authors declare no conflict of interest.

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459-IV-PO EFFECT OF THE SEQUENTIAL APPLICATION OF PHOTOCATALYSIS AND A LIGNINOLYTIC FUNGI ON SULFAMETHOXAZOLE REMOVAL FROM WATER

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Abstract: Sulfamethoxazole (SMX) is a persistent sulphonamide antibiotic poorly removed in wastewater treatment. This study evaluated graphitic carbon nitride (g-C₃N₄) photocatalysis and its combination with *Phanerochaete chrysosporium*. The catalyst, characterized by FTIR and XDR, showed a band gap of 2.66 eV and achieved nearly 40% SMX removal (20 mgL⁻¹ SMX) after 180 min under visible light. Biological treatments with free and immobilized mycelium further transformed SMX but generated secondary metabolites. Combined processes enhanced SMX degradation but did not achieve complete mineralization, indicating the need for integrated strategies to eliminate transformation products.

Keywords: Coupled treatment, Photocatalysis, Mycoremediation, Emerging pollutants, Biodegradation.

1. INTRODUCTION

Sulfamethoxazole (SMX) is a sulphonamide antibiotic widely applied in animal feed to enhance livestock production. Due to incomplete metabolism and high environmental mobility, SMX is frequently detected in ground and surface waters [1].

In wastewater treatment plants, SMX removal shows no correlation with standard indicators such as suspended solids, chemical oxygen demand, or biochemical oxygen demand. In activated sludge systems, SMX exhibits low

sorption to primary sludge. Whereas stabilization ponds achieve 72.7% removal through combined biodegradation and photodegradation [2].

Advanced Oxidation Processes (AOPs), including photocatalysis, generate hydroxyl radicals capable of oxidizing organic contaminants into less toxic compounds [1]. Graphitic carbon nitride (g-C₃N₄), with a bandgap of 2.7 eV, enables visible-light photocatalysis and achieves 95% degradation of 0.05 mM rhodamine B under sunlight, offering an advantage over UV-dependent catalyst such as TiO₂ [3].

Fungi also contribute to pharmaceutical degradation through extracellular and intracellular enzymes with broad specificity. Their hyphal structure facilitates compound absorption and immobilization, making mycoremediation a sustainable and environmentally favourable approach. *Phanerochaete chrysosporium* (*P. chrysosporium*) has demonstrated the ability to degrade antibiotics, psychiatric drugs, anti-inflammatories and antiepileptics [4].

The integration of biological treatments with photocatalysis has been proposed as a synergistic strategy. This study evaluates the performance of whole *P. chrysosporium* cells in enhancing SMX removal efficiency.

2. MATERIALS AND METHODS

Reagents and media were used without further purification. SMX was obtained from Sigma-Aldrich, sodium alginate (reagent grade) from Meyer, and CaCl_2 (technical grade) from DDC. The commercial cereal All bran (Kellogg's) and bacteriological agar (BD Bioxon) were used as growth media.

2.1. Photocatalytic treatment

The carbon nitride catalyst was synthesized as described in [5] and characterized by DRX (Bruker D8 Advance diffractometer with $\text{Cu K}\alpha$ radiation $\lambda = 1.5406 \text{ \AA}$ at a scan rate of $0.02^\circ \text{ s}^{-1}$ over a 2θ range of $10\text{--}40^\circ$) and FTIR (PerkinElmer spectrum 400 equipped with an attenuated total reflectance accessory). Photocatalytic degradation of SMX was evaluated using 200 mL of a 20 mg L^{-1} SMX solution with 200 mg of catalyst under a 50 W LED chip lamp ($\lambda = 400 \text{ nm}$). The reaction was conducted in a glass reactor under magnetic stirring. Post-treatment solutions were stored at 4°C prior to biological assays.

2.2. Biological treatment

P. chrysosporium ATCC 48747 was cultivated for 7 days at 28°C on cereal solid media (20 g L^{-1} All bran in 17 g L^{-1} agar).

2.2.1 Free biomass

Mycelia from agar plates were suspended in 50 mL sterile water and agitated overnight. A 30 mL aliquot was inoculated into 100 mL of cereal liquid medium (20 g L^{-1} All bran) and incubated for 7 days at 120 rpm at room temperature. Biomass was harvested, washed, and divided: half was sterilized for dead biomass assays. Treatments consisted of 250 mL SMX solutions (20 mg L^{-1}), with and without prior photocatalysis, used as the sole substrate. Dead biomass served as control C0.

2.2.2 Immobilized biomass

Mycelia were immobilized in calcium alginate. Homogenized mycelia were mixed with sterile 3% sodium alginate and dripped into 30% CaCl_2 to form beads, which were stored at 4°C for 24 h [6]. Beads were incubated for 10 days

in medium AB, then washed with sterile water. Treatments used 30 mL of 20 mg L^{-1} SMX (with and without photocatalysis) in contact with 8 g wet-weight beads. Controls included plain alginate beads (C1) and beads containing dead biomass (C2).

Degradation in all treatments was monitored by UV-Vis spectrometry (Perkin Elmer Lambda).

3. RESULTS AND DISCUSSION

The molecular structure of $\text{g-C}_3\text{N}_4$ provides of functional groups like amine to form bonds with hydrogens or covalent connections with organic molecules [7]. The FTIR spectrum of $\text{g-C}_3\text{N}_4$ shown in Figure 1 confirmed its structural configuration through characteristic absorption bands corresponding to N-H (3165 cm^{-1}), C-N/C=N ($1630\text{--}1138 \text{ cm}^{-1}$), and triazine signals (806 cm^{-1}).

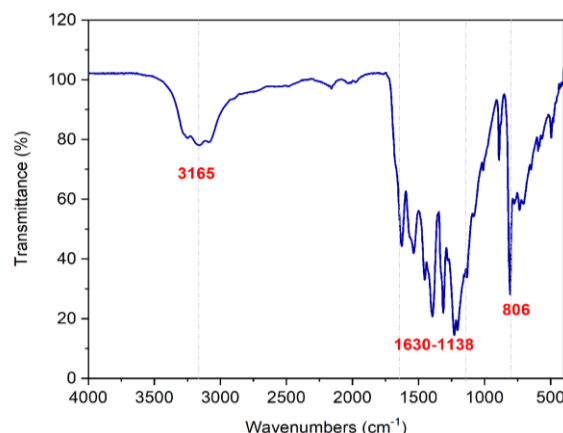


Figure 1. FTIR spectrum $\text{g-C}_3\text{N}_4$.

XRD analysis revealed diffraction peaks at 12.8° (100) and 27.2° (002), consisted with the characteristic in-plane structural packing and interlayer stacking of $\text{g-C}_3\text{N}_4$. The calculated crystallite size was 4.12 nm (Figure 2). Diffuse reflectance spectroscopy estimated the optical band gap at 2.66 eV, confirming its suitability for visible-light photocatalysis.

Photocatalytic experiments demonstrate approximately 40% SMX removal from an initial concentration of 20 mg L^{-1} after 180 min of irradiation, while direct photolysis was negligible (Figure 3).

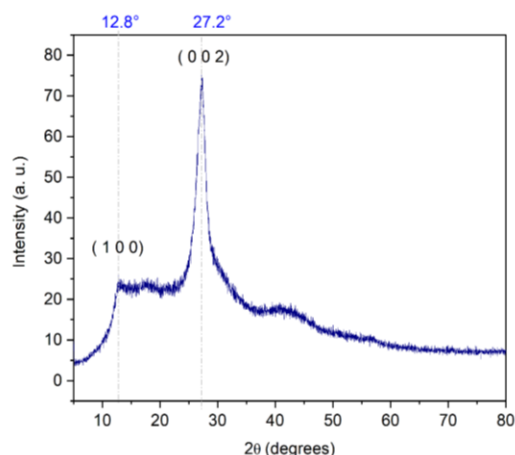


Figure 2. X-ray diffractogram of g-C₃N₄.

The photocatalytic performance of g-C₃N₄ is related to the generation of reactive oxygen species and an efficient charge transfer dynamics. In the case of sulphonamides and tetracyclines, they can hinder nitrogen conversion at higher concentrations (above 40 mg L⁻¹) [7]. In brackish water (high concentration of humic acids) photodegradation of SMX is associated to triplet sensitized degradation being the presence of dissolved organic carbon a dominant factor for decreasing degradation rates reaching one-week half-lives. In natural waters matrices, the irradiation of SMX at $\lambda > 340$ nm produce potentially toxic compounds [8].

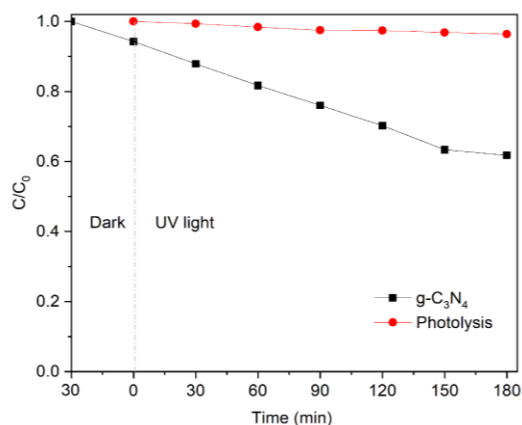


Figure 3. Photocatalytic treatment using g-C₃N₄ of 20 mg L⁻¹ SMX.

When SMX (20 mg L⁻¹) was first subjected to biological treatment with free mycelium for 10 days and subsequently exposed to photocatalysis, the UV-Vis spectra showed a

reduction in absorbance, though not to the same extent as photocatalysis alone (Figure 4). Previous studies have reported that catalytic ozonation with carbon nanotubes (CNT), TiO₂ and Fe/CNT, as well as Fenton and Fenton-like processes, electrochemical oxidation with boron-doped diamond anode, and solar Photo-Fenton, often generate intermediate compounds more toxic than the parent molecule. Commonly detected degradation products include 3-amino-5-methylisoxazole, other reported products include P-benzoquinone, oxalic acid, and oxamic acid. Complete mineralization has only been achieved using combined treatments such as photocatalytic ozonation with hydrogen peroxide and Fe/CNT catalysts [9].

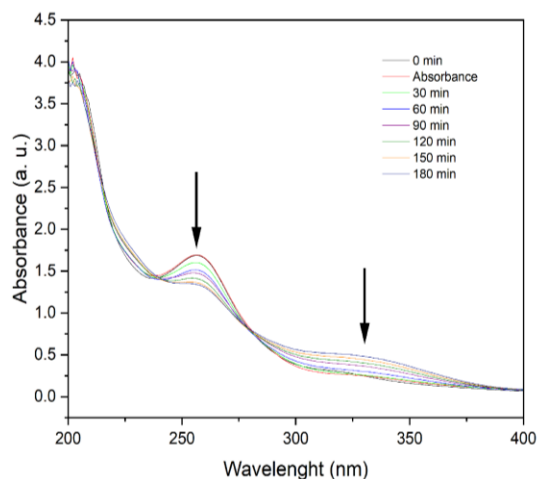


Figure 4. Biological SMX + Photocatalytic treatment using g-C₃N₄.

In the combined treatments with free mycelium of *P. chrysosporium*, spectral variations were observed over time (Figure 5a). In the sequence photocatalysis followed by biological treatment (T1), an increase in absorbance was detected by day 7, with a new peak emerging by day 18. This peak may correspond to metabolites derived from fungal biomass, as also observed in the control (C0) on day 7. In single biological treatment (Figure 5b), T2 the absorbance increases slightly on day 14 but to a lesser extent than in C0. The degradation of compounds is significantly affected by structural differences such as the presence or more electron withdrawing groups like SO₂, in which degradation is quicker compares to CH₂

groups (electron donating groups) [10]. The presence of changes in the relative absorbance and the formation of new peaks is reported in the removal of RR120 dye which is associates to the presence of new aromatic intermediates that absorb UV light [10]. In the case of Photocatalytic + Biological SMX (Figure 5) is observed the formation of a new peak around 250 nm which is not observed in the Biological SMX + Photocatalytic (Figure 4).

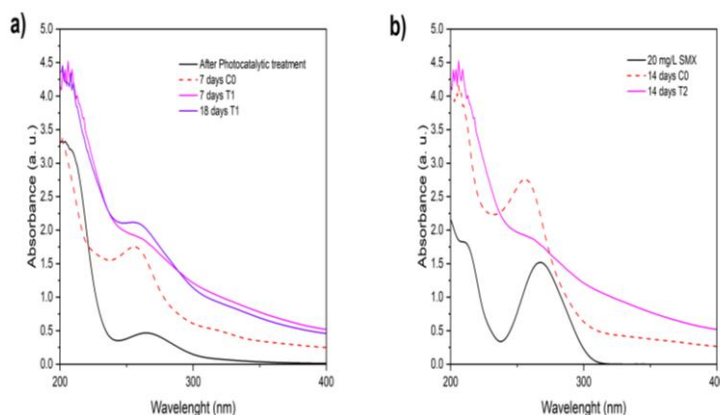


Figure 5. Free mycelium: a) Photocatalytic SMX + Biological and b) Biological SMX.

When photocatalytically treated SMX (20 mg L⁻¹, 180 min) was subsequently exposed to immobilized mycelium, the absorbance increased in treatment T4 by day 7, and a distinct peak was observed on day 14 (Figure 6 a). In contrast, controls C1 and C2 exhibited lower absorbances. For treatment T3 (biological treatment only) a reduction in absorbance was observed on day 7. Although an increase occurred on day 14, the absorbance remained lower than C1 and C2 (Figure 6b). *P. chrysosporium* immobilization on calcium alginate mixed with lignin is reported to improve the environment for growth facilitating the transport of pollutants into the bed with a higher absorption of molecules such as phenanthrene [11].

In this study no additional source of carbon was provided for the fungus, it is observed a different pattern for only biological treatments in comparison with the ones pretreated by photocatalysis. Immobilization reduced the peaks in C1 and C2 of Figure 6 in comparison with C0 of Figure 5 of free mycelium. Dead biomass allows the

absorption of contaminants, but it also liberates structural compounds from the hypha or residual nutrients that might remain after the washing.

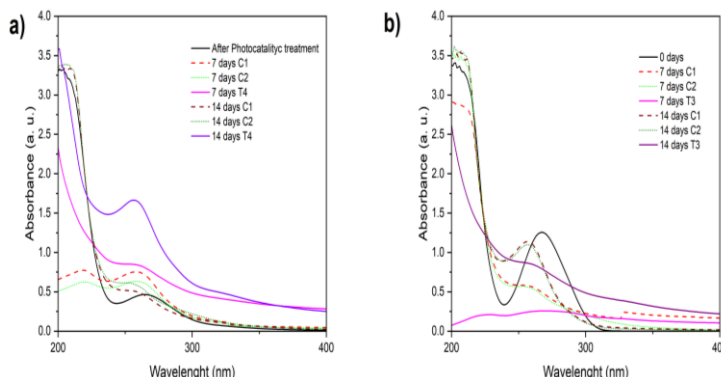


Figure 6. Immobilized mycelium: a) Photocatalytic SMX + Biological and b) Biological SMX.

The combined photocatalytic-biological treatments resulted in the formation of by-products. Previous work with *P. chrysosporium* BKM-F1767 demonstrate that the fungus alone reduced 5 mg L⁻¹ SMX under sterile conditions, achieving 79.7% removal in 4 days when supplied with a nutrient medium promoting enzymatic activity. Inhibition of SMX degradation was reported in the presence of 28 mg L⁻¹ Cd²⁺ [12]. *P. chrysosporium* achieved a degradation of 53% within 24 h of 10 mg L⁻¹ SMX because of laccase enzyme. The SMX stimulate laccase production reaching 6076 U L⁻¹ after 48 h with 50% degradation [13].

In the present study, the concentration tested was 20 mg L⁻¹ SMX in biological treatments and approximately 7 mg L⁻¹ SMX after pretreatment by photocatalysis showing no indicators of inhibition by the concentration and evidence of metabolic activity in the UV-Vis spectrums. Further research must be conducted to identify the presence of enzymes and to identify the by-products of SMX degradation. White rot fungi are known to produce biologically active compounds such as antioxidants that provide with competitive advantage for tolerate environmental stress and extreme conditions [14].

4. CONCLUSIONS

Biological treatments had an increment of absorbance which might be related to fungal metabolism. The effect was observed with dead and viable biomass. Photocatalysis generates transformation products that are partially metabolized or further transformed by the fungus into UV-active metabolites. Immobilization improves short-term removal stability compared with free biomass but does not prevent formation of secondary products. Combined photocatalytic and biological treatments transformed SMX but did not achieve complete mineralization and produced secondary products.

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Conflicts of interest

The authors declare no conflict of interest.

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