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Review

Physiologically Based Pharmacokinetic and Physiologically Based Biopharmaceutic models research in Latin America: A regional level bibliometric analysis, 2011-2023

Marx Ribeiro[1*], Juliana Cordeiro Cardoso[2], José Eduardo Severino Martins[3], Aline Ferreira Pinto[4], Eliana Maria Barbosa Souto[5], Patricia Severino[6]

[1]GRANTE, Mechanical Engineering Department, Federal University of Santa Catarina, Florianópolis, Brazil, [1]Clinic for Trauma and Reconstructive Surgery, University Hospital Halle, Halle(Saale), Germany, [2,6]Tiradentes University, Aracaju, Brazil, [2]Instituto de Tecnologia e Pesquisa, Aracaju, Brazil, [3,4]Laboratory of Research in Biotechnology and Hemoderivatives, Department of Pharmaceutical Sciences, Federal University of Pernambuco, Recife, Brazil, [5]UCD School of Chemical and Bioprocess Engineering, University College Dublin, Dublin, Ireland

The landscape of scientific research in Latin America (LA), particularly in the realms of the Physiologically Based Pharmacokinetic (PBPK) and Physiologically Based Biopharmaceutic models (PBPM), is a mosaic of varied contributions, collaborations, and specializations. This study examines research production in the region using data from the Scopus and PubMed databases collected between 2011 and 2023. Brazil stands out as a prominent country in terms of the quantity of publications. When considering thematic specialization, Colombia cones first as the country with the greatest Relative Specialization Index (RSI), followed by Brazil, Cuba, Uruguay, Mexico, and Argentina. Regarding internationalization, Brazil and Mexico are currently exerting significant influence, particularly through their increasing cooperation with the United States and Europe. Interestingly, there is a lack of cooperation inside Latin America at the regional level. Regarding the contribution of Latin-American institutions, the State University of Maringá leads in number of publications, followed by the University of São Paulo and the Federal University of São Paulo. In this work, we analyzed the strengths and weaknesses of LA's scientific contributions, offering a roadmap for future collaborative and specialized efforts in the field of PBPK and PBBM.

Keywords: PBPK. PBBM. Latin America Scientometric analysis. International collaboration.

INTRODUCTION

Science thrives by building on existing knowledge through cycles of observation and hypothesis testing. As happens with technology and economic growth, scientific progress relies on foundational capacities, such as previous knowledge, tools, human skills, and resources (Betz *et al*., 2023). By bringing these elements together, especially from varied backgrounds, science drives forward, opening doors to fresh insights and revisiting overlooked concepts. Regions blessed with a wealth of these resources often spearhead scientific advancements, indicating that local scientific contributions are a reflection of their inherent capabilities (Betz *et al*., 2023).

In the modern era, there is a common trend to evaluate scientific achievements, whether they are the result of individual scholars or of entire nations. A notable example involves May's evaluation of national research output with the Revealed Comparative Advantage (RCA) metric, which highlights the scientific documentation of each country (May, 1997). From a slightly different perspective, countries were positioned based on the global

***Correspondence:** M. Ribeiro Ernst-Grube-Street 40 · 06097 Halle (Saale) Germany Email: marx.ribeiro@medizin.uni-halle.de https://orcid.org/0000-0003-3341-3605, J. C. Cardoso: https://orcid.org/0000-0002-0357-4144, J. E. S. Martins: https://orcid.org/0000-0002-3855-5701, A. F. Pinto: https://orcid.org/0000-0003-2123-2284, E. M. B. Souto: https://orcid.org/0000-0002-9737-6017, P. Severino: https://orcid.org/0000-0001-6527-6612

recognition of their papers, with research funding as an additional determining factor (King, 2004). Given the fast advancements in understanding how substances interact within the human physiology, the disclosure of these mechanisms of action is becoming instrumental to develop potent therapeutic strategies and to anticipate potential adverse effects. Two methodologies have become particularly significant in this context: the Physiologically Based Pharmacokinetic (PBPK) and Physiologically Based Biopharmaceutic (PBBM) (Macente *et al*., 2023; Martins *et al.*, 2021; Severino Martins *et al*., 2023)"plainCitation":"(Macente et al. 2023; Martins et al. 2021; Severino Martins et al. 2023.

PBPK models offer a mathematical lens into the body's absorption, distribution, metabolism, and excretion processes of chemicals, considering the delicate balance between the physical and chemical properties of the drugs and the body's anatomical and physiological features of the human body (Kollipara *et al*., 2024; Macente *et al*., 2023; Martins *et al*., 2023; Martins *et al*., 2020; Patel *et al*., 2022)"plainCitation":"(Kollipara et al. 2024; Macente et al. 2023; Martins et al. 2023; Martins et al. 2020; Patel et al. 2022; Severino Martins et al. 2023. As a complement, PBBM models explore the biopharmaceutical interactions between drug formulation, physicochemical properties, and physiological factors. Together, these methodologies provide a holistic blueprint for predicting a drug's trajectory from their intake to the therapeutic action (Carapeto *et al*., 2023)a PBBM was developed in GastroPlus® and combined with a Taguchi L9 design, to evaluate the impact of different drug products (Reference, Generic #1 and Generic #2. PBPK and PBBM models are recognized by the US and EU regulatory authorities for the prediction of drug-drug interaction (DDI), dose optimization, support on drug and formulation development, etc. They are extremely useful also for risk assessment and allow the incorporation of a variety of populations for predictive purposes of these risks (Kollipara *et al*., 2024; Laisney *et al*., 2022; Rebeka *et al*., 2019; Saadeddin *et al*., 2024)physiologically based biopharmaceutics modeling (PBBM.

When doing research within the field of PBPK and PBBM research, it becomes important to assess not only the number of publications, but also the progression and emerging patterns of scientific input. Global collaboration stands at the forefront of this pursuit. Merging global resources and expertise accelerates the pace of breakthroughs, ensuring increased recognition and deeper understanding of research and development of drug dosage forms and medicines. This collective endeavor is promising not only for academic growth, but also to improve disease management underpinned by these models. To refine these models and improve the physiology and calculation of biochemical parameters, a multidisciplinary approach involving modelling scientists, clinicians and pharmacologists is key.

Bibliometric studies offer a roadmap of the publishing tendencies in dominant research fields, guiding researchers towards under-explored territories and revealing each nation's scientific footprint and the collaborations they nurture (Carapeto *et al*., 2023; Mejia *et al*., 2021)a PBBM was developed in GastroPlus® and combined with a Taguchi L9 design, to evaluate the impact of different drug products (Reference, Generic #1 and Generic #2. However, a remarkable gap exists in Latin America (LA), on key research contributors and nations. Given the importance of LA to the worldwide economy and science, a thorough exploration of scientific production trends, via bibliometric scrutiny and collaboration patterns, becomes essential.

This manuscript aims to position LA's research contributions within the global context. Using a comprehensive exhaustive scientometric analysis, our objective is to link research results with research-focused socio-economic parameters specific that are distinctive to LA. Centered on the PBPK and PBBM methodologies, our goals is to evaluate the regional contributions and their changes over time, understanding international collaborations, spotlighting LA's unique inputs, pinpointing research voids, and offering insights to elevate both research and healthcare in the region.

MATERIAL AND METHODS

Data for this study was sourced from the internationally renowned multidisciplinary databases Scopus and PubMed. The keywords employed for data extraction are detailed in Table I.

TABLE I - Search strategy used in bibliometric review of the Physiologically Based Pharmacokinetic (PBPK) and Physiologically Based Biopharmaceutic (PBBM) models

Database	Search strategy
PubMed	(PBPK OR "Physiologically Based Pharmacokinetic" OR PBBM OR "Physiologically Based Biopharmaceutic Model") AND ("Brazil" OR "Argentina" OR "Peru" OR "Chile" OR "Colombia" OR "Mexico" OR "Venezuela" OR "Ecuador" OR "Bolivia" OR "Paraguay" OR "Uruguay" OR "Guatemala" OR "Cuba" OR "Honduras" OR "Nicaragua" OR "Costa Rica" OR "Panama" OR "Puerto Rico" OR "El Salvador" OR "Dominican Republic")
Scopus	(TITLE-ABS-KEY(PBPK OR "Physiologically Based Pharmacokinetic" OR PBBM OR "Physiologically Based Biopharmaceutic Model")) AND (AFFILCOUNTRY(Brazil) OR AFFILCOUNTRY(Argentina) OR AFFILCOUNTRY(Chile) OR AFFILCOUNTRY(Colombia) OR AFFILCOUNTRY(Mexico) OR AFFILCOUNTRY(Peru) OR AFFILCOUNTRY(Venezuela) OR AFFILCOUNTRY(Uruguay) OR AFFILCOUNTRY(Paraguay) OR AFFILCOUNTRY(Costa Rica) OR AFFILCOUNTRY(Panama) OR AFFILCOUNTRY(Bolivia) OR AFFILCOUNTRY(Ecuador) OR AFFILCOUNTRY(Guatemala) OR AFFILCOUNTRY(Cuba) OR AFFILCOUNTRY(Honduras) OR AFFILCOUNTRY(Nicaragua) OR AFFILCOUNTRY(El Salvador) OR AFFILCOUNTRY(Dominican Republic) OR AFFILCOUNTRY(Puerto Rico))

These databases were chosen due to their superior geographic and thematic coverage, ensuring a more accurate representation of the global scientific contributions. For worldwide population data, we consulted the World Bank's portal. We included only papers that were indexed and had authors affiliated with LA institutions at the moment of publications.

The indicators used were:

- Total number of documents published between 2011 and 2023 (Ndoc)
- Number of citable documents: articles, reviews, and conference proceedings (Ndocc)
- Rate of growth calculated by the difference (%) between the number of works in relation with the previous period (RG)
- Relative Specialization Index (RSI)
- Specialization index (TSI).
- Number of times cited in any type of document (Cites).
- Number of self-citations by authors of the same region (Autocit).
- Average number of citations per document (Cpd)
- Percentage of documents cited (% Ndoc-cit)
- H-index, considering H as the number of documents of a region obtaining at least H citations
- Finally, we analyzed the correlation coefficient of the Spearman range applied to the indicators by countries.

Theory/calculation

Relative Specialization Index (RSI), or Relative Activity Index, indicates whether a country has a relative higher or lower share in world publication in a specific field than its overall share in world total publication. It is calculated based on the thematic Specialization index (TSI). This indicator is closely related to the so-called Activity Index (AI) long used in bibliometrics, which, in turn, is a version of the economists' Comparative Advantage Index. Equations (1) and (2) were used:

$$TSI = \frac{Ndoc\ PBPK\&PBBM\ (country) \div Ndoc(country)}{Ndoc\ PBPK\&PBBM\ (LA\ ) \div Ndoc(LA\ )} \quad (1)$$

$$RSI = \frac{TSI - 1}{TSI + 1} \quad (2)$$

where "Ndoc PBPK&PBBM (country)" stands for the number of documents dealing with PBPK and PBBM published by a specific country, "Ndoc (country)" for the total number of publications indexed by that country, "Ndoc PBPK&PBBM (LA)" for the number of documents dealing with PBPK and PBBM published by all LA, and "Ndoc (LA)")" for the total number of publications published in that region. RSI can take values in the range from −1 to 1, being 0 the LA average, RSI < 0 indicates below the average, RSI > 0 above the average activity.

All analyses and graphs were made using R studios (version 4.1-RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.), utilizing the packges "ggplot2", "igraph", "dplyr".

RESULTS

In a global context, our analysis reveals that out of the worldwide total of 4,146 scientific publications in the PUBMED and Scopus databases, 1.3% belong to LA under the PBPK and/or PBBM methodology (Figure 1a). The regional distribution is notably uneven, with Brazil leading the way by contributing with 61% of the LA publications, followed by Mexico and Uruguay (Figure 1b). Particularly, LA experienced a notable increase in scientific production, reflecting the global trends. There was a significant local peaks of 88% from 2018-2023.

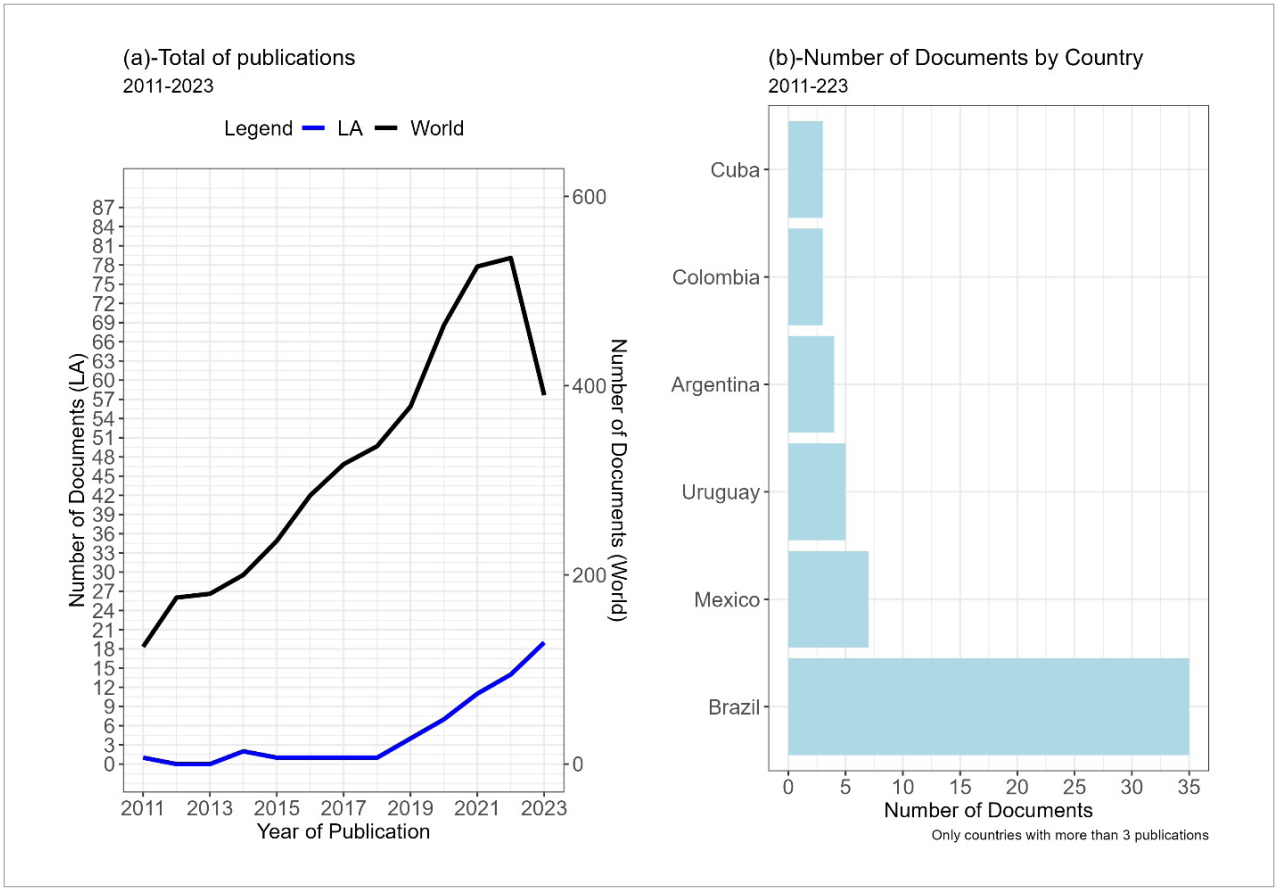

FIGURE 1 - Regional breakdown of scientific output in PBPK and PBBM.

Research has traditionally been evaluated based on the volume of outputs, both in absolute numbers and percentages. However, to identify specific thematic strengths, it is not always sufficient to rely solely on these metrics. Instead of just looking at domestic production isolated, it is beneficial to compare it to macro-regional benchmarks, such as those in the overall LA.

To achieve this, we used the Relative Specialization/ Activity Index. This index shows whether a country's share of publications in the PBPK and PBBM fields is higher or lower compared to its overall share in all of LA's publications. With this index, it is straightforward to determine if a country's contribution is above or below the regional average, revealing whether it is specialized in that field. Table II lists the top six countries in terms of scientific production, detailing their rank among the 33 LA countries that have published at least one paper in the PBPK/PBBM category.

In LA, Brazil leads in the number of publications (Ndoc). However, when examining thematic specialization, Colombia stands out with the highest Relative Specialization Index (RSI), indicating that it is the most specialized country. Following Colombia, we see Brazil, Cuba, Uruguay, Mexico and Argentina.

TABLE II - Countries with the higher output in PBPK and PBBM in Latin America

Country	Ndoc	Ranking Ndoc-LA	Ranking RSI-LA	H index
Argentina	4	4	6	71
Brazil	35	1	2	145
Colombia	3	5	1	29
Cuba	3	5	3	70
Uruguay	5	3	4	59
Mexico	7	2	5	37

Comparing the percentages from LA with those of specific areas, Brazil and Mexico are found to exhibit the highest rates of internationalization across all fields (Figure 2). Notably, the majority of LA's international collaborations are with the US and Europe, with minimal collaboration within the macro-region itself.

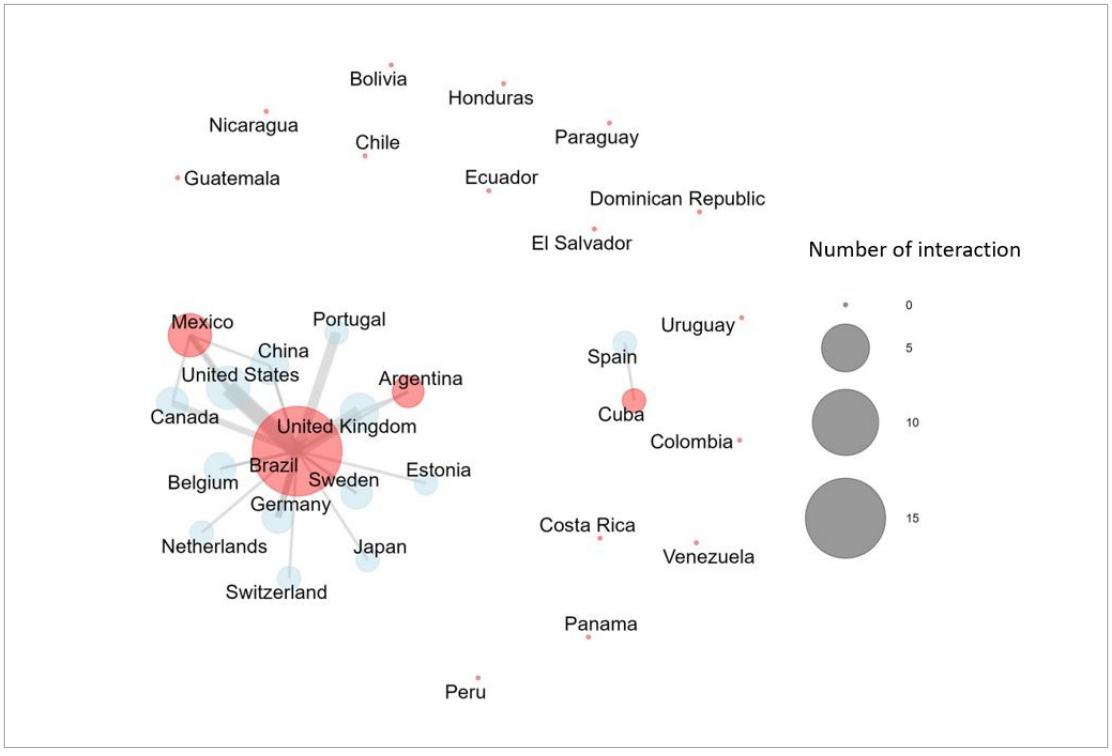

FIGURE 2 - Network visualization map for international collaboration of Latin America countries in the field PBPK and PBBM.

Also, authors names and their affiliations are identified and ranked in Figure 3. State University of Maringá is the university with the highest number of publications, followed by University of São Paulo and Federal University of São Paulo, whereas F. S. Martins leads the number of documents by author in the reporting period.

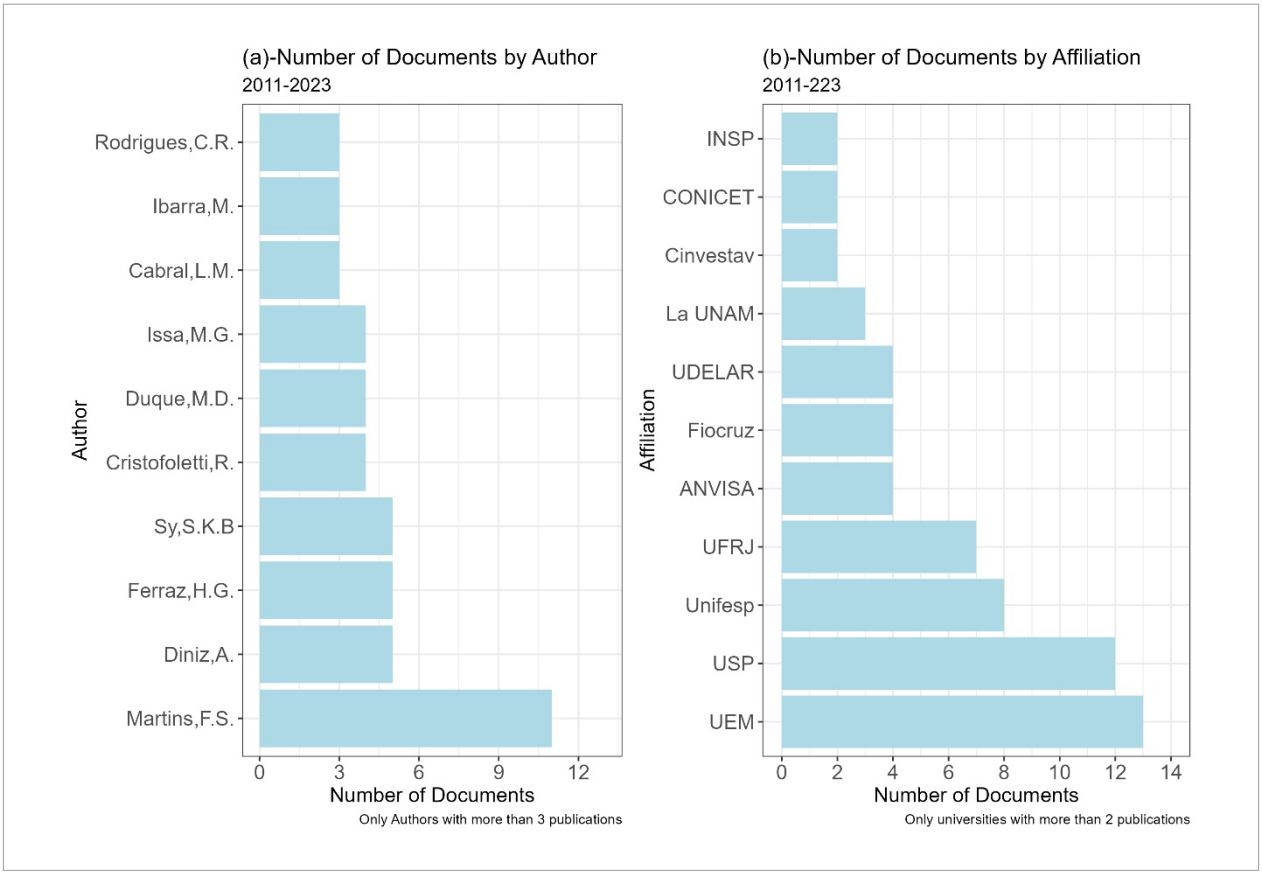

FIGURE 3 - Number of publications by author and by affiliation. INSP: Instituto Nacional de Saúde Pública; COINICET: Consejo Nacional de Investigaciones Científicas y Técnicas; Cinvestav: Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional: UNAM: Royal and Pontifical University of Mexico; UDELAR: Universidad de la República: Fiocruz: Fundação Oswaldo Cruz; ANVISA: Agência Nacional de Vigilância Sanitária: UFRJ: Universidade Federal do Rio de Janeiro; Unifesp:Universidade Federal de São Paulo: USP; Universidade de São Paulo; UEM: Universidade Estadual de Maringá.

To uncover consistent patterns in regional public document outputs, we utilized Spearman's rank correlation coefficients, assessing the standings of countries based on various indicators. Results are shown in Table III. Due to the high-level aggregation, results are less conclusive. While all indicators demonstrated some correlation, the strength varied. The link between the number of total documents and citable documents appears tenuous, likely attributed to the inherent characteristics of the indicator. Specifically, this indicator becomes less comprehensive in the concluding years of our analysis, as these documents are anticipated to garner citations beyond our study's timeframe. Additionally, the Relative Specialization Index (RSI) exhibits a faint negative correlation with output and citation indicators, indicating that there is no apparent correlation between volume and specialization, or between specialization and visibility.

TABLE III - Coefficient of Spearman range correlation among

Indicator	Ndoc	Ndocc	RSI	Cites	Autocit	Cpd	H index
Ndoc	1	0.95*	-0.29*	0.94*	0.96*	0.41*	0.97*
Ndocc	0.96*	1	-0.28*	0.98*	0.97*	0.51*	0.96*
RSI	-0.31*	-0.29*	1	-0.28*	-0.25*	0.15	-0.22*
Cites	0.96*	0.98*	-0.22	1	0.97*	0.59*	0.99*
Autocit	0.96*	0.97*	-0.24	0.98*	1	0.53*	0.98*
Cpd	0.43*	0.45*	0.16*	0.68*	0.51*	1	0.62*
H index	0.97*	0.97*	-0.19*	0.95*	0.98*	0.6	1

*Indicates significant bilateral correlation at a level of 0.01.

DISCUSSION

Our analysis indicates that LA countries contribute with 1.3% to the global PBPK and PBBM publications. This contribution, though seemingly modest, is marked by diverse contributions from various countries, with Brazil standing out as the primary contributor.

While Brazil leads the way in PBPK and PBBM research in LA, its position in terms of the Human Development Index (HDI) is not the highest in the region. This disparity suggests that other factors are strengthening Brazil's research prominence. Significant investments in research and development, a robust research infrastructure, and strategic academia-industry collaborations potentially play crucial roles in shaping Brazil's scientific landscape. Furthermore, Brazil's extensive geographical area and densely populated, combined with its robust economy, grant it the resources necessary to drive extensive research endeavors.

Brazil, as one of the largest economies in LA, likely employs its economic efforts to foster research, especially in the field of PBPK and PBBM. These methodologies, which are in high demand in pharmaceutical industry, expedite research and development processes, optimizing drug life cycles, and ensuring cost and time efficiencies. In this context, Brazil's pharmaceutical market worth significantly surpasses that of other LA countries, i.e., approximating 22.81 billion U.S. dollars in comparison to Mexico's 8.51 billion U.S. dollars. Collectively, LA countries contributed roughly with 3.7% to the global pharmaceutical market revenue in 2021. Despite Brazil's significant pharmaceutical production—valued at over 10.5 billion U.S. dollars in 2020—the industry remains import-driven. Brazil led LA in pharmaceutical imports in 2021, valued at around 11 billion U.S. dollars. However, a decline was observed in its pharmaceutical exports, dropping from 1.57 billion U.S. dollars in 2014 to 1.1 billion U.S. dollars in 2021. (*Pharma Market Value Latin America 2021*).

While economic indicators provide invaluable insights, a holistic understanding demands consideration of other factors. Governmental policies, a focus on science and technology education, and forward-looking visions, significantly influence research pathways. Brazil's emphasis on strengthening its scientific community—apparent through scholarships, global collaborations, and infrastructure enhancements—may well be the driving force that offsets its Human Development Index (HDI) rank.

Latin American countries that have higher Human Development Index (HDI) rankings might utilize their socio-economic advantages to further research in PBPK and PBBM research. By analyzing and adapting Brazil's successful model, these countries can increase their research contributions, fostering collaboration and innovation.

Education and training will play a crucial role in advancing PBPK and PBBM expertise in LA. Strengthening educational programs in these fields is essential to build a skilled workforce capable of conducting high-quality research and applying these models in clinical and regulatory settings. Initiatives could include developing specialized courses at universities, offering professional development workshops, and fostering partnerships between academia and industry for practical training. Encouraging interdisciplinary collaboration and providing opportunities for students to engage in international research projects can also broaden their perspectives. Investment in education and training will ensure a steady pipeline of skilled professionals, vital for sustaining and advancing the region's capabilities in PBPK and PBBM research.

CONCLUSION

Scientific progress, based on constant observation and testing of hypotheses, is a result of global collective efforts and the combination of different skills. This article emphasizes the importance of Latin America, in PBPK and PBBM research. Brazil, as a leader in scientific contribution in the region, shows a strong interaction between economic power, strategic investments, with a significant focus on research and development, especially in the pharmaceutical area.

However, it is also important to acknowledge that the economic size and the number of publications are not the only factors that impact scientific research. The quality of collaborations, thematic specialization, and an environment that fosters innovation, are also essential. Colombia's top position in Relative Specialization Index (RSI) and Brazil's extensive international collaborations, mainly with the US and Europe, highlight the diversity and depth of research contributions from the region.

In summary, as the world faces many scientific discoveries, Latin America, with its distinct mix of resources and expertise, can have a crucial role. The challenge is not only to increase the amount of research, but also to enhance its quality, relevance, and global impact. By using insights from bibliometric studies, identifying existing strengths, and addressing research gaps, Latin America can create a path of continuous scientific excellence and innovation.

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