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Latin American scientific production on nanotechnology-based products to fight COVID-19: a scoping review

Produção científica latino-americana sobre produtos à base de nanotecnologia para o enfrentamento da COVID-19: uma revisão de escopo

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ABSTRACT

Introduction: Scientific production has experienced an unprecedented increase with the COVID-19 pandemic in a short period of time. **Objective:** To identify and characterize the Latin American scientific production on nanotechnology-based products with potential applications in the areas of diagnosis, vaccine, pharmacological treatment, theranostics and non-pharmacological intervention to fight COVID-19. **Method:** A scoping review was conducted based on the framework of Arksey and O'Malley and sought to incorporate recommendations from the Joanna Briggs Institute Reviewer's Manual and Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). The bibliographic search took place in PubMed, Science Direct, LILACS and SciELO. Studies that reported nanotechnology-based products with potential applications in the areas of interest referenced previously were included. A simple quantitative analysis was conducted to provide numerical summaries of characteristics of interest from the studies added to the review. **Results:** 26 (3.4%) articles published in 14 international and regional journals were included. Authors from five countries (Brazil, Chile, Costa Rica, Ecuador, and Mexico) were responsible for the total number of articles that made up the review. The production of 6 (23.1%) articles included international collaboration, involving institutions from 10 countries. The median time from submission to publication of articles was 126 days (interquartile range: 58–200). Most of the Latin American scientific production consisted of narrative reviews (n = 19; 73.1%). The five areas defined as of interest for this study were addressed by one of the scientific articles, especially the products intended for pharmacological treatment of COVID-19 (n = 14; 53.8%). **Conclusions:** This is the first scoping review to provide a map of Latin American scientific production on nanotechnology-based products with potential applications in areas of interest to fight COVID-19. There are deficiencies related to the publication of basic research, representativeness of Latin American countries in the region, studies with greater strength of evidence and to international collaboration to produce scientific articles that merit to be reduced.

KEYWORDS: COVID-19; Coronavirus Infections; Nanomedicine; Nanotechnology; Scoping Review

RESUMO

Introdução: A produção científica tem experimentado um aumento sem precedentes com a pandemia de COVID-19 em um curto espaço de tempo. **Objetivo:** Identificar e caracterizar a produção científica latino-americana sobre produtos à base de nanotecnologia com potenciais aplicações nas áreas de diagnóstico, vacina, tratamento farmacológico, teranóstico e intervenção não farmacológica para o enfrentamento da COVID-19. **Método:** Uma revisão de escopo foi conduzida com base na estrutura de Arksey

e O'Malley e buscou incorporar recomendações do *Joanna Briggs Institute Reviewer's Manual* e do *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews* (PRISMA-ScR). A busca bibliográfica ocorreu na PubMed, *Science Direct*, LILACS e SciELO. Estudos que relataram produtos à base de nanotecnologia com potenciais aplicações nas áreas de interesse referenciadas anteriormente foram incluídos. Uma análise quantitativa simples foi conduzida para fornecer resumos numéricos das características de interesse dos estudos adicionados na revisão. **Resultados:** Foram incluídos 26 (3,4%) artigos publicados em 14 revistas internacionais e regionais. Autores de cinco países (Brasil, Chile, Costa Rica, Equador e México) foram responsáveis pelos artigos que compuseram a revisão. A colaboração internacional ocorreu para a produção de seis (23,1%) artigos, envolvendo instituições de dez países. O tempo mediano do envio à publicação dos artigos foi de 126 dias (intervalo interquartil: 58–200). A maior parte da produção científica latino-americana foi de revisões narrativas (n = 19; 73,1%). As cinco áreas definidas como de interesse deste estudo foram abordadas por algum dos artigos científicos, com destaque para os produtos destinados ao tratamento farmacológico da COVID-19 (n = 14; 53,8%). **Conclusões:** Esta é a primeira revisão de escopo a fornecer um mapa da produção científica latino-americana sobre produtos à base de nanotecnologia com potenciais aplicações em áreas de interesse para o enfrentamento da COVID-19. Existem deficiências relativas à publicação de pesquisa básica, representatividade de países da América Latina, estudos com maior força de evidência e colaboração internacional para a produção de artigos científicos que merecem ser reduzidas.

PALAVRAS-CHAVE: COVID-19; Infecções por Coronavirus; Nanomedicina; Nanotecnologia; Revisão de Escopo

INTRODUCTION

Scientific production has experienced an unprecedented increase in a short space of time due to the COVID-19 pandemic, since the first cases occurred in China in December 2019[1,2]. In the initial ten weeks after the pandemic was declared (week 12 to 21 of 2020), the number of scientific articles on COVID-19 grew from 28,596 to 77,417 in the same period of 2021, which is equivalent to an increase of 171.0%[1]. More than 4% of the articles listed in the *Dimensions* database in 2020 were related to COVID-19 and approximately 6% of those indexed in PubMed, which mainly covers the life sciences, were dedicated to the topic3. The United States (US) and China are the two main countries that have contributed the most publications on the disease in PubMed[4].

As the COVID-19 pandemic has evolved, numerous disruptive technologies, such as nanotechnology, have been widely required to tackle it. The use of nanomaterials, with the most diverse chemical compositions, structures, shapes and sizes, has been applied as an innovative tool not only as a new treatment strategy, but has also helped to improve a variety of prevention and diagnostic methods in the fight against COVID-19[5].

The application of nanotechnology for medical purposes has been called nanomedicine and is defined as the use of nanoscale materials (1 to 100 nm) for the diagnosis, monitoring, control, prevention and treatment of diseases6[,7]. There is a growing trend towards conducting and publishing research in nanomedicine. Between 2003 and 2019, the most productive countries were the USA and European countries, with China as an emerging region[8]. The most prominent topics in recent years have been nanodiagnostics and nanotheranostics and clinical applications in the subfields of oncology and infectology[8].

Scientific research on nanotechnology in Latin America has been concentrated mainly in three countries, Brazil, Mexico and Argentina, which contributed around 85% of all publications between 1990 and 2006[9]. The percentage of scientific articles published in the field of nanomedicine between 2003 and 2019 attributed to Latin America was 0.6% (n = 40) compared to 38.3% (n = 2,564) in North America and 35.1% (n = 2,350) in Europe[8].

In the midst of the growing literature on the SARS-CoV-2 coronavirus, the broad role that nanotechnology has been playing in the health area, combined with the trend of increasing publications and the need to systematize Latin American scientific production on nanotechnology aimed at tackling COVID-19, the scoping review is considered a useful tool for mapping and synthesizing the available evidence and identifying possible knowledge gaps10[,11].

The aim of this study was to identify and characterize Latin American scientific production on nanotechnology-based products with potential applications in the areas of diagnosis, vaccine, pharmacological treatment, theranostics, and non-pharmacological intervention to tackle COVID-19. As far as we know, there is no synthesis of the literature published on the subject that made use of the scoping review.

METHOD

A scoping review was conducted based on the methodological framework defined by Arksey and O'Malley[12] and sought to incorporate recommendations from the *Joanna Briggs Institute* Reviewer's Manual[10] and the *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews* (PRISMA-ScR)[11]. The review was carried out between June 20 and August 19, 2021, and the five phases described below made up this review.

Phase 1: identification of the research question

The PCC structure was used to formulate the research question: P (Population) - Any research or literature review article; C (Concept) - Nanotechnology-based products with potential applications in the areas of diagnosis, vaccine, pharmacological treatment,

theranostics and non-pharmacological intervention (sanitizing agents and personal protective equipment); C (Context) - COVID-19 pandemic, resulting in the following study question: "How is Latin American scientific production characterized on nanotechnology-based products with potential applications in the areas of diagnosis, vaccine, pharmacological treatment, theranostics and non-pharmacological intervention to tackle COVID-19?"

Phase 2: identification of scientific studies

The studies were identified using the following databases: a) PubMed, b) *Science Direct*, c) *Scientific Electronic Library Online* (SciELO) and d) *Latin American and Caribbean Health Sciences Literature* (LILACS). These databases are relevant in the area of life sciences and have a wide scope and academic credibility at international and Latin American level.

The search strategy for scientific articles was made up of combinations of keywords, in English, related to nanotechnology and COVID-19. Some of them in truncated form (*) and all of them extracted from the Health Sciences Descriptors (DeCS)/Medical *Subject Headings* (MeSH)[13]. The Concept and Context elements of the PCC structure were used to guide the choice of relevant keywords for the search for scientific articles. Chart 1 shows the search strategies for each database.

An additional limit was to require that the keywords of the review be present in the titles, abstracts or keywords of the scientific articles identified in PubMed and *Science Direct*.

After some initial tests to see if the largest number of articles could be found in LILACS, the decision was made to use the "*Words*" field in the search strategy. This means that the search took place in all parts of the publications, such as the title, abstract and keywords. In SciELO, the search took place using the standard "*All indexes*" field, which included searching the title and abstract of the studies (Chart 1).

The identification of articles and the initial extraction of the data of interest in PubMed and *Science Direct* occurred through the use of *Web-scraping* techniques developed in the Python programming language (*Python Software Foundation*, https://www.python.org/) in this study. *Web-scraping* allows for the automated identification and retrieval of data of interest about certain content available on the *Internet*, quickly and with a gain in scale[14]. Furthermore, its applicability in scientific repositories is already recognized in the literature[14].

The results obtained by the *scraper* developed for this study were validated by one of the study's authors. It consisted of validating completeness, in relation to the total number of articles found by the *scraper*, and consistency by sampling against the results presented by the PubMed and *Science Direct* search interfaces when subjected to the same search strategy. For each of the platforms, the first ten and last ten articles identified by the *scraper* were compared to those obtained manually, as well as ten other articles selected at random.

The procedure for identifying articles and initial extraction from the LILACS and SciELO databases was done manually.

The initial data of interest in the scoping review extracted from the articles identified in the four databases were: title of the study, authors, country and institution of the first author, name of the journal, month and year of publication, type of scientific article defined by the database or by the journal itself or (re) classified by the authors at a later stage, according to information in the text of the study, DOI publication identification code, abstract and keywords.

After eliminating repeated publications using the DOI, the data from the scientific articles identified was merged into a single database in Excel® spreadsheet format to be used in the subsequent phases of this review.

Phase 3: selection of relevant scientific studies

Studies were selected based on inclusion and exclusion criteria. The inclusion criteria for scientific articles were: (i) written in English, Portuguese, and Spanish; (ii) published between January

Chart 1. Search strategies for scientific articles by database.

Date and time of identification	Database	Search strategy
July 10, 2021 (10 h 40 min)	PubMed	(Nanomedicine OR Nanocomposit* OR Nanoparticl* OR Nanostructur* OR Nanotechnolog*) AND (COVID-19 OR coronavírus OR SARS-CoV-2)
	Science Direct	(Nanomedicine OR Nanocomposites OR Nanoparticles OR Nanostructures OR Nanotechnology) AND (COVID-19 OR coronavírus OR SARS-CoV-2)
July 11, 2021 (10 h 30 min)	LILACS	Nanocomposites [Words] AND COVID-19 [Words]; Nanocomposites [Words] AND SARS-CoV-2 [Words]; Nanocomposites [Words] AND coronavírus [Words]; Nanoparticles [Words] AND COVID-19 [Words]; Nanoparticles [Words] AND SARS-CoV-2 [Words]; Nanoparticles [Words] AND coronavírus [Words]; Nanostructures [Words] AND COVID-19 [Words]; Nanostructures [Words] AND SARS-CoV-2 [Words]; Nanostructures [Words] AND coronavírus [Words]; Nanotechnology [Words] AND COVID-19 [Words]; Nanotechnology [Words] AND SARS-CoV-2 [Words]; Nanotechnology [Words] AND coronavírus [Words] e Nanomedicine [Words] AND COVID-19 [Words]; Nanomedicine [Words] AND SARS-CoV-2 [Words]; Nanomedicine [Words] AND coronavírus [Words]
July 11, 2021 (10 h 48 min)	SciELO	(Nanomedicine OR Nanocomposites OR Nanoparticles OR Nanostructures OR Nanotechnology) AND (COVID-19 OR coronavírus OR SARS-CoV-2)

Source: Prepared by the authors, 2022.
SciELO: *Scientific Electronic Library Online*; LILACS: *Latin American and Caribbean Health Sciences Literature*.

1, 2020, and July 10/11, 2021; (iii) the first author was from a Latin American country; (iv) the main content was nanotechnology-based products with potential applications in the areas of diagnostics, vaccines, pharmacological treatment, theranostics, and non-pharmacological interventions to combat COVID-19. The exclusion criteria were: (i) publications of research protocols, commentaries, letters to the editor, *preprint* articles (not peer-reviewed), book chapters, and errata; and (ii) content of scientific articles that did not answer the research question of this study.

The authors (DMM and FTP) independently selected potentially eligible scientific articles on the basis of the title and abstract, reading the full text when necessary to confirm relevance to the research question.

By videoconference, the authors began this phase of the scoping review together from a sample of five studies, representing around 10% of the total number of articles identified and retrieved in the previous phase, as a way of ensuring that there was a common understanding of the inclusion (iv) and exclusion (ii) criteria. Whether or not the two criteria (iv and ii) were met was recorded in the database itself (Excel® spreadsheet) by the authors (DMM and FTP) for later comparisons, with a view to the final definition of the studies to be included in this scoping review.

Disagreements were discussed at the end of this phase and resolved by consensus. This also occurred in other aspects related to the other phases of this review. The selected studies made up the single database that was used in the fourth phase of this scoping review.

Phase 4: mapping study data

The single database containing only the eligible studies was added with the following variables: study objective, type of study, area covered by the scientific article (diagnosis, vaccine, pharmacological treatment, theranostics and non-pharmacological intervention), type of nanomaterial, national and international collaboration, dates of receipt and publication of the articles, in order to calculate the time spent during this period, and main conclusions.

An adaptation of the proposal defined by Röhrig et al.[15] was used to establish the types of study, which were classified as: i) basic research; ii) clinical research; iii) epidemiological research; iv) meta-analysis; v) systematic review; vi) narrative review; and vii) review in which the unit of analysis is not scientific articles.

National collaboration was considered for scientific articles produced with institutions other than those of the first author.

Further mapping of the data of interest was based on an iterative and recursive process of reading and re-reading the studies and extracting the data that would complement the new variables in the single database, using the full text when necessary.

Phase 5: compiling, summarizing and reporting the results

This last phase of the review was carried out as follows: a) the studies were grouped according to the variables contained in the single database that helped answer the research question; b) the results were synthesized using simple quantitative analysis, using descriptive statistics such as frequencies and measures of central tendency (median) and dispersion (interquartile range) to provide numerical summaries of the characteristics of interest of the studies included in this scoping review. The percentage level of agreement between authors (DMM and FTP) was calculated from the eligible scientific articles; and c) a descriptive account of the main characteristics of the studies that exclusively addressed only one area of interest.

Based on the recommendations of the *Joanna Briggs Institute* Reviewer's Manual[10] and PRISMA-ScR[11], no quality assessment of the studies was carried out. In addition, this study used secondary data from published scientific articles and therefore did not require approval by a Human Research Ethics Committee.

RESULTS

Data on the search and selection of scientific articles

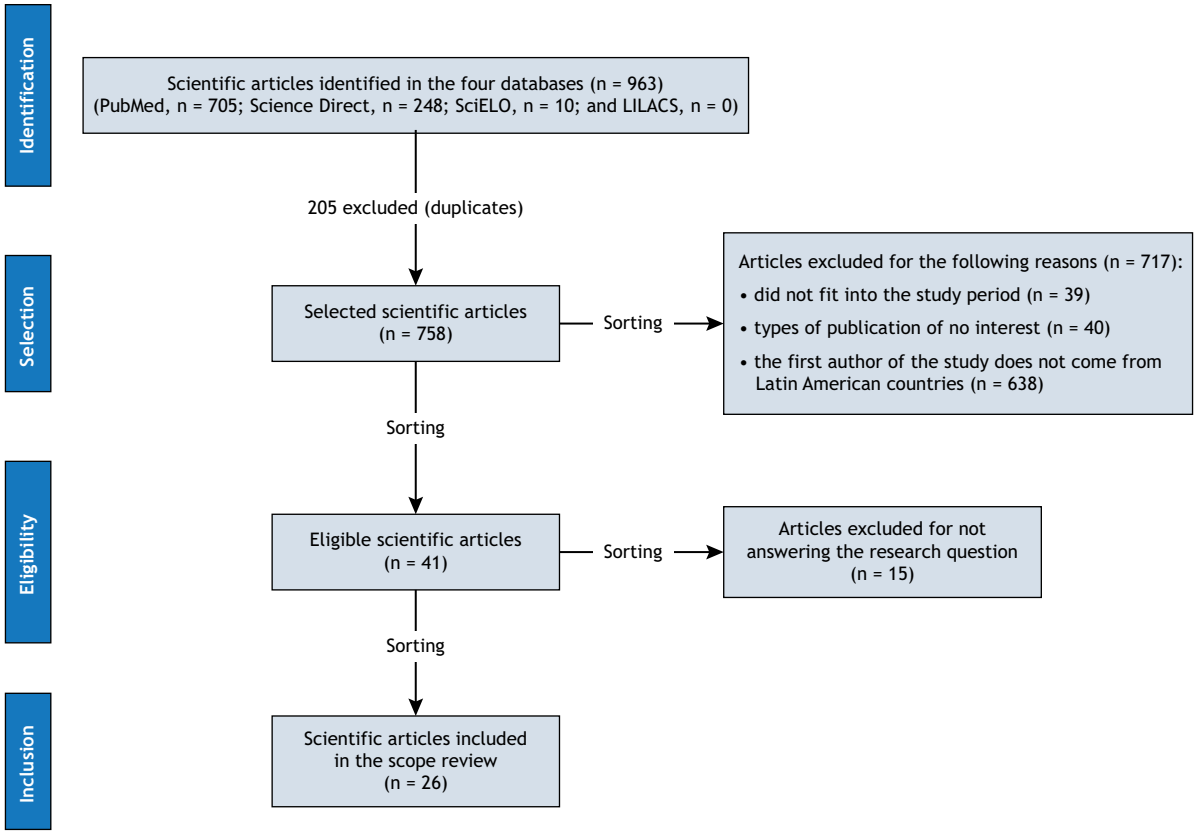
We identified 963 scientific articles in the four databases (PubMed, n = 705; *Science Direct*, *n* = 248; SciELO, n = 10; and LILACS, n = 0), of which 205 (21.3%) were excluded as duplicates.

In the selection phase, 758 articles were analyzed according to the inclusion and exclusion criteria. The following were excluded in this order: 39 (5.1%) scientific articles because they did not fall within the study period, 40 (5.3%) of them because they were types of publication of no interest, such as *preprint* articles (n = 32), book chapters (n = 5), commentaries (n = 2) and errata (n = 1) and 638 (84.2%) because the first author was not from Latin American countries. Based on the screening of title, abstract and full text (when required) by two reviewers, a further 15 (2.0%) articles were excluded because they did not meet the research question (Figure 1). Five articles among those eligible (n = 41) raised disagreements as to whether or not they should be included in the scoping review, resulting in a percentage level of agreement of 84.0% (n = 26/31).

Data on journals, origin of authors and international and national collaboration

This scoping review included 26 scientific articles, representing 3.4% of the number of publications added to the selection phase. The articles were published in 24 different journals, four of which come from Latin American countries: *Anais da Academia Brasileira de Ciências* (Brazil), *Revista de Ciencia y Tecnología* (Argentina), *Mundo Nano. Revista interdisciplinaria en nanociencias y nanotecnología* (Mexico), and *Genetics and Molecular Biology* (Brazil). Latin American journals published six scientific articles.

The names of seven journals that published articles by Latin American authors indicate a relationship with nanotechnology/nanomedicine, such as: *Nanomedicine: Nanotechnology,*



Source: Prepared by the authors, 2022.

Figure 1. Flowchart of the process of identification, selection, eligibility, and inclusion of scientific articles, based on PRISMA-ScR[11].

Biology and Medicine, *Journal of Nanobiotecnolonogy* and *ACS Nano*. With the exception of *Mundo Nano. Revista interdisciplinaria en nanociencias y nanotecnología*, which published three articles, the others had only one article during the study period.

The first authors of the scientific articles came from five Latin American countries (Brazil, Chile, Costa Rica, Ecuador, and Mexico). The Brazilian authors, from nine institutions, were responsible for 12 (46.1%) of the scientific articles published, followed by the Mexicans (n = 8; 30.7%) and Ecuadorians (n = 3; 11.5%), from six and two higher education institutions, respectively. All the authors came from 20 institutions, 18 (90.0%) of which were higher education establishments. The remaining two institutions, from Brazil and Costa Rica, are research centers in immunobiologicals and nanotechnology, respectively. Only one scientific article was published by 15 (75.0%) institutions. Another four institutions published two articles. The Federal University of ABC, a public higher education institution in Brazil, had the highest number of scientific articles published (n = 3).

International collaboration was involved in the production of six (23.1%) scientific articles, involving institutions from ten countries: Argentina, Brazil, Chile, Singapore, Spain, USA, India, Mexico, United Kingdom, and Uruguay. Two articles by Mexican authors involved international collaboration. The other articles, produced in partnership with international institutions, were written by authors from Brazil, Chile, Costa Rica, and Ecuador. The Chilean study had the largest number of foreign researchers (n = 3), who came from Argentina, Brazil, and Mexico. International partnerships were mainly for the production of narrative reviews (n = 5). Of the scientific articles in which there was no international collaboration (n = 20), six (30.0%) had the partnership of domestic institutions, four by Brazilian authors and two by Mexican authors.

Characterization of scientific articles

The articles for which receipt and publication dates were given (n = 24; 92.3%) took a median time of 126 days (interquartile range: 58-200 days) from submission to *online* publication. Two types of scientific article were identified: literature reviews (n = 22; 84.6%) and research articles (n = 4; 15.4%). The predominant languages were English (n = 24; 92.3%) and Spanish (n = 2; 7.7%). A total of 18 (69.2%) scientific articles presented a single objective for the study. Three articles had four objectives, another three had three objectives and one study had two. The objective was not explicitly identified in one of the scientific articles[16]. Review studies were those which presented more than one objective.

The distribution of articles based on the types of studies was, in this order: narrative review (n = 19; 73.1%), basic research

(n = 4; 15.4%), review in which the unit of analysis is not scientific articles (n = 2; 7.7%) and systematic review (n = 1; 3.8%). The units of analysis of the reviews in which the unit of analysis is not scientific articles were: patents for face masks[17] and nanotechnological products designed against COVID-19[18], which used specific databases. The systematic review was published by two Brazilian researchers[19].

Chart 2 shows the characterization of the studies classified as basic research. There was a predominance of publications by Mexican authors (n = 3), which addressed the area of non-pharmacological intervention against COVID-19 (n = 2) and which studied gold nanoparticles as a type of nanomaterial (n = 2).

Latin American scientific production on nanotechnology-based products with potential applications in the areas prioritized in this scoping review is shown in Chart 3. A total of 14 (54.0%) studies addressed a single area in which nanotechnology-based products were presented to tackle COVID-19. No study exclusively explored the area of theranostics, i.e., combining a diagnostic test with a specific therapy to form a single product.

The use of nanotechnology in pharmacological treatments against the disease was covered in 15 (57.7%) scientific articles. Hydroxychloroquine[30], curcumin[26], nitric oxide[27], and silver[29] were the chemical substances specifically addressed in the different articles in which the area covered was only "pharmacological treatment" (n = 5). The studies highlighted the therapeutic effects of these substances combined with nanomaterials to combat COVID-19. For example, one of the studies mentioned that nanosystems for releasing drugs into the respiratory system could be a viable alternative for administering hydroxychloroquine, which could potentiate its therapeutic effect with a consequent reduction in its toxicity, providing greater safety for application in the pharmacological treatment of COVID-19[30]. A summary of various drugs tested in the treatment of COVID-19 and the advantages of nanostructured antiviral drug delivery systems were explored in another scientific article[28].

The use of nanotechnology in diagnostics to detect COVID-19 was addressed by 11 (42.3%) studies. Biosensors, which are used to detect pathogens, were highlighted in one scientific article, out of a total of three, which looked exclusively at the area of diagnostics[24]. The authors explained how biosensors work in terms of bacterial and viral detection and the nanotechnological features that are contributing to faster and more efficient COVID-19 diagnosis at the user's point of care[24]. The other study surveyed the most commonly used methodologies for diagnosing COVID-19, which can basically be categorized into two types: detection of genetic material, using the real-time polymerase chain reaction technique, and detection of antibodies using immunoassay techniques[25]. The authors presented the bottlenecks preventing mass diagnostic tests in many countries and proposed strategies for future action, mainly associated with materials science and chemistry[25].

The last study, which focused solely on diagnostics, presented a simplified method for the large-scale production of magnetic nanoparticles for the extraction and purification of viral ribonucleic acid from nasopharyngeal cells for the detection of the SARS-CoV-2[20] virus. According to the authors, the research helps to reduce the cost of acquiring magnetic nanoparticles for various biomolecular applications, supporting developing countries' budget constraints and the availability of chemicals, especially during COVID-19[20].

As shown in Chart 3, three studies dealt only with the area of "Vaccine". One of these scientific articles provided a platform for the development of nanovaccines based on gold nanoparticles

Chart 2. Characterization of basic research studies (n = 4).

Title (month/year)	Country	Area covered	Type of nanomaterial	Experimental model	Reference
Optimized and scalable synthesis of magnetic nanoparticles for RNA extraction in response to developing countries' needs in the detection and control of SARS-CoV-2 (November/2020)	Ecuador	Diagnosis	Iron oxide nanoparticles (magnetite)	Not applicable	20
Biosynthesis of gold nanoparticles (AuNPs) and the reducing agents in the process (February/2021)	Mexico	Pharmacological treatment and non-pharmacological intervention (Sanitizing agent)	Gold nanoparticles	Not applicable	21
Synthesis and immunogenicity assessment of a gold nanoparticle conjugate for the delivery of a peptide from SARS-CoV-2 (March/2021)	Mexico	Vaccine	Gold nanoparticles	Animal	22
Promotion of surgical masks antimicrobial activity by disinfection and impregnation with disinfectant silver nanoparticles (April/2021)	Mexico	Non-pharmacological intervention (sanitizing agent)	Silver nanoparticles	Microbial cell culture	23

Source: Prepared by the authors, 2022.

Chart 3. Main areas addressed with nanotechnology-based products by scientific studies (n = 26).

Main areas covered (n)	Examples of product types
Diagnosis (n = 3)	Negatively charged polymer-coated magnetic nanoparticles for large-scale extraction and purification of viral RNA (detection of the SARS-CoV-2 virus)20; biosensors24; reverse transcriptase-polymerase chain reaction (RT-PCR) and immunoassays25
Pharmacological treatment (n = 5)	Curcumin26; nitric oxide27; nanostructured drug delivery systems28; silver nanoparticles29; and nanosystems for the delivery of hydroxychloroquine30
Vaccine (n = 3)	Vaccines16,22,31
Non-pharmacological intervention (n = 3)	Sanitizing agent[23]
	Personal protective equipment17,33
Diagnosis and vaccine (n =1)	Colorimetric assays, biosensors, photothermal plasmonic biosensors and vaccines[32]
Pharmacological treatment and vaccine (n = 1)	Nanocarriers to circumvent the conventional limitations of a drug candidate, chemically altered/(re) engineered drugs, nanomedicine for combined pharmacological treatments and vaccines[34]
Pharmacological treatment and non-pharmacological intervention (n = 2)	Gold nanoparticles and sanitizing agent[21]; silver, copper and copper oxide nanoparticles and sanitizing agent and personal protective equipment35
Theranostics and non-pharmacological intervention (n = 1)	Combination of treatment (iron oxide nanoparticles) with infrared light, sanitizing agent and personal protective equipment[36]
Diagnosis, pharmacological treatment, and vaccine (n = 1)	Biosensors, *loop-mediated* isothermal amplification, serological tests, nanosystems with antiviral activity and vaccines[37]
Diagnosis, pharmacological treatment, vaccine, and non-pharmacological intervention (n = 5)	Biosensors, ivermectin delivery by nanoparticles, pulmonary delivery of salinomycin by nanostructured lipid carriers, optimized nanoparticles with remdesivir, curcumin based on chitosan nanoparticles, vaccines, sanitizing agents and personal protective equipment19
	Biosensors, RT-PCR, enzyme-linked immunosorbent assay (ELISA) and colloidal gold immunochromatographic assay, antimalarials such as hydroxychloroquine, antiviral agents such as remdesivir, and antineoplastic or immunomodulatory agents such as baraticinib and tocilizumab, vaccines, sanitizing agents and personal protective equipment38
	Biosensors, therapeutic substances based on nanoparticles that act by: (i) blocking receptor binding and entry into the cell; (ii) inhibiting viral infection; and (iii) inactivating the virus, vaccines and sanitizing agents[39].
	Biosensors, RT-PCR, *loop-mediated* isothermal amplification, immune therapies based on nanomaterials, such as exosomes derived from mesenchymal stem cells and chimeric-Fc nanobodies (a variable region of the nanobody is fused to the Fc of human immunoglobulin), viral inactivating nanomaterials, vaccines, sanitizing agents and personal protective equipment40
	Biosensors, nanocarriers and delivery systems for substances with the potential to control viral infection, vaccines, sanitizing agents and personal protective equipment41
Diagnosis, pharmacological treatment, vaccine, theranostics, and non-pharmacological intervention (n = 1)	Biosensors, *loop-mediated* isothermal amplification, nitric oxide, cellular nanosponges, vaccines, theranostic nanoparticles with a focus on intranasal administration, sanitizing agents, personal protective equipment18

Source: Prepared by the authors, 2022.

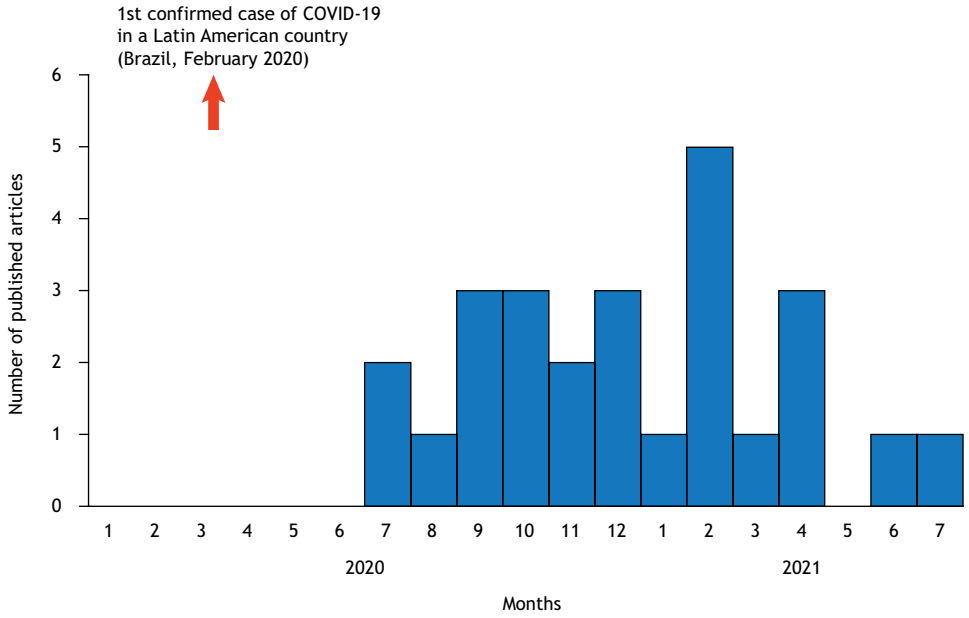
targeting specific epitopes of SARS-CoV-2[22]. According to the authors, the study paves the way for the formulation of epitope-based vaccines against SARS-CoV-2, which will be of great relevance in the development of next-generation vaccines[22].

The other study focused on the development of vaccines against SARS-CoV-2, describing initiatives worldwide and specifically in Brazil. Some examples of the categories of vaccine development described worldwide were: i) inactivated vaccines (e.g., CoronaVac, developed and produced by the Chinese company Sinovac); ii) non-replicating adenovirus vector vaccines (e.g., ChAdOx1, developed by the University of Oxford in partnership with the pharmaceutical company AstraZeneca); and iii) RNA-based vaccines (e.g., BNT162, developed by BioNTech in partnership with Pfizer)[16].

The last article described a procedure for producing a messenger ribonucleic acid (mRNA) vaccine against the SARS-CoV-2 virus, including the potential advantages of using the enzyme that carries out the mRNA transcription process, called RNA polymerase II. In addition, the authors reviewed the main applications of mRNA-based nanomedicines and their potential therapeutic uses[31].

The studies that exclusively addressed the area of non-pharmacological intervention against COVID-19, in a total of three, are characterized below. The first of these developed a nanodesinfectant based on silver nanoparticles that provided a valuable strategy for the decontamination, reuse and even effective antimicrobial promotion of surgical masks for frontline healthcare clinical staff. This product has been shown to be broadly effective against a large number of SARS-CoV-2[23] microbial surrogates.

The second article discussed the use of nanostructures in virus prevention, mainly through the development of self-disinfecting materials, which can be used in the manufacture of gloves, masks and various other devices[33]. Nanostructured metal oxides,



Source: Prepared by the authors, 2022.

Figure 2. Monthly distribution of articles published between January 1, 2020, and July 10/11, 2021 (n = 26).

such as silver nanoparticles, can reduce the viability of the virus on surfaces when associated with polymers and textiles, especially under conditions of exposure to light[33].

The last article assessed current patents related to the protective mask. The review was carried out in the patent database from May 2019 to May 2020. The results showed that most masks used cotton fabrics, nylon, silver fibers, among others, as fabrics to develop the masks. There are also many types of masks used for protection, such as N95 masks, medical masks and homemade masks. The authors also analyzed masks composed of nanotechnology that increase the filtration and retention capacity of the virus, given that the filtration efficiency of masks depends on the characteristics of the filter and the size of the pores. The review also looked at ways of sterilizing and reusing personal protective equipment during the COVID-19[17] pandemic.

Figure 2 shows the distribution of the 26 scientific articles over the period studied, with February 2021 recording the peak number of publications (n = 5; 19.2%). The first studies were published in July 2020 (n = 2; 7.7%). Both were narrative reviews published in English. The temporal flow of publications was interrupted in May 2021, and publications returned in subsequent months.

DISCUSSION

This scoping review identified and characterized Latin American scientific production on nanotechnology-based products with potential applications in strategic areas for tackling COVID-19. All the areas defined as being of interest in this scoping review, diagnosis, pharmacological treatment, vaccine, theranostics and non-pharmacological intervention, were addressed by some of the scientific studies. This reflects, in a very short period of time, the diversity of scientific production in the region in an innovative field of research such as nanotechnology, dominated by the USA, European countries, and China[8], coupled with a situation of serious global health crisis.

Scientific production was concentrated in international journals and in five countries, representing 25% of the countries that make up Latin America. Some of the journals appear among the top 22 in a list of 50 journals with significant academic impact in the category of nanoscience and nanotechnology, such as: *ACS Nano, Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, Journal of Nanobiotechnology, Nanomedicine: Nanotechnology, Biology, and Medicine and International Journal of Nanomedicine*[42]. The publication of articles in international journals, some of which have a high academic impact, plays a significant role in disseminating research findings, as well as suggesting a positive trend in the quality of studies in the region[43].

Brazil and Mexico, two of the three countries where the development of nanotechnology is most advanced in Latin America[44], have registered the highest number of scientific articles published. Between 2000 and 2007, Brazil produced 5,254 publications on nanotechnology, Mexico 2,261 and Argentina 1,376 scientific articles[44]. In addition, Brazil and Mexico have continued to expand the absolute number of publications, while Argentina, Chile and Uruguay have seen a relative halt in the growth of publications in recent years[9]. These results denote a similar pattern found in this scoping review with regard to the scientific production of Brazilian and Mexican authors on nanotechnology-based products with potential applications in the areas of diagnosis, vaccine, pharmacological treatment, theranostics, and non-pharmacological intervention to combat COVID-19.

In this scoping review, the median time taken from submission to *online* publication of scientific articles was much longer when compared to the study that characterized the growth of the initial medical literature on COVID-19 between January 1 and March 24, 2020, using evidence maps and bibliometric analysis (median: eight days; interquartile range: 4-16)[45]. It is salutary that the results of scientific articles on any type of COVID-19-related subject, for the duration of the global health crisis, are available much more quickly, without compromising scientific rigor in the peer review process.

The main producers of scientific articles in Latin America were universities. The participation of government laboratories was low, with only two scientific articles published. This scenario is partly consistent with the reality of the region as described in the scientific literature. Around 255 different institutions carry out nanotechnology research in Brazil, with universities being the most active publishers[9]. Publications from government laboratories and industry are few in Brazil, Chile and Uruguay, while in Argentina four government laboratories are among the top ten institutions with more than 40% of national research[9]. In this scoping review, no publications by Argentine authors were identified.

The pattern of international collaboration in Latin American scientific production on nanotechnology-based products with potential applications in the areas of diagnostics, vaccines, pharmacological treatment, theranostics and non-pharmacological interventions to combat COVID-19 has been low. A study that carried out a bibliometric analysis of the region's scientific production on COVID-19 found a high proportion of publications with international collaboration (52.8%)[43]. The proportion of publications with national collaboration (33.8%) found in this bibliometric analysis was very similar to the result obtained in this review (30.0%). Perhaps the narrower research focus adopted in this scoping review is one of the explanations for the different patterns between the studies with regard to international collaboration.

Literature review articles, especially narrative reviews, predominated in scientific production in Latin America, denoting the need to diversify the types of studies with greater strength of scientific evidence that address nanotechnology-based products in the fight against COVID-19 in the strategic areas studied. A similar result occurred with the bibliometric study, based on a non-systematic search of the literature in predefined databases, which confirmed an exponential growth of articles on nanomedicine in humans, although the vast majority were review articles[46].

Several studies have reported the promising role of nanotechnology in reducing the spread of COVID-19 through the application of nanomaterials/nanoparticles in the areas of diagnosis, pharmacological treatment, vaccine, theranostics and non-pharmacological intervention against the SARS-CoV-2 virus[47,48]. The publications included in this scoping review contribute in this direction by highlighting the therapeutic effects of substances such as hydroxychloroquine, curcumin, nitric oxide and silver, combined with nanomaterials/nanoparticles in the pharmacological treatment of COVID-19. Another example addressed by the Latin American studies was the possibility of developing nanovaccines based on gold nanoparticles, targeting specific SARS-CoV-2 epitopes.

Some authors have mentioned that nanotechnology can have a positive impact on the COVID-19 pandemic more quickly when implemented in two areas: (1) viral disinfectants through the development of nano-effective antimicrobial and antiviral formulations that are not only suitable for disinfecting air and surfaces, but also effective in reinforcing personal protective equipment; and (2) viral detection, through the development of highly sensitive and accurate nanosensors that allow for the early diagnosis of COVID-19[49]. Nanotechnology-based sanitizing agents and biosensors were explored by scientific articles included in this scoping review, suggesting that Latin American production is in line with international trends in nanotechnology research to combat COVID-19.

Despite the interruption in the flow of publications and an uneven distribution in the number of articles published over the period studied, the number of scientific articles included in this scoping review can be considered reasonable enough to characterize Latin American scientific production on nanotechnology-based products with potential applications in areas of interest for tackling COVID-19. This study could also be useful in directing calls for proposals from funding agencies to finance scientific research in nanotechnology aimed at the prevention, treatment and control of COVID-19 in Latin America.

The findings of this review should be considered in relation to its limitations, as it did not have a published study protocol, as suggested by the literature[10]. The electronic databases used were limited to those in which the study authors had experience. This means that some relevant studies may not have been included in the review. A formal assessment of the methodological quality of the studies was not carried out. However, it should be pointed out that the aim of scoping reviews is to provide a map of the evidence that has been produced, rather than just looking for the best available evidence to answer the research question[50].

Despite the limitations, this scoping review has some positive aspects that should be highlighted: (i) a systematic search was carried out based on internationally recognized references, such as the *Joanna Briggs Institute Reviewer's Manual*[10,50] and PRISMA-ScR[11]; (ii) text mining techniques were used to identify scientific articles in two databases (PubMed and *Science Direct*) which generated a very important gain in scale to complete this review in a reasonably short time; and (iii) databases of international and regional relevance and scope, academic credibility and rigor in journal indexing were used.

CONCLUSIONS

This is the first scoping review to provide a map of Latin American scientific production on nanotechnology-based products with potential applications in areas of interest for tackling COVID-19.

Nanotechnology-based products are being widely investigated for their potential use in strategic areas to combat COVID-19, including by Latin American authors, as demonstrated in this scoping review.

The development of science in this field of knowledge becomes even more relevant due to the emergence of new strains and viral mutations of SARS-CoV-2[51]. Based on this challenge, it is essential to continue Latin American scientific production in nanotechnology aimed at tackling COVID-19, prioritizing gaps and minimizing the deficiencies identified in this scoping review such as: i) the need to reduce the time taken to publish *online the* studies developed by Latin American authors; ii) diversification of the types of studies, with the strengthening of basic and clinical research in nanomedicine, and with greater strength of scientific evidence, such as systematic reviews; iii) an increase in publications with international and national collaboration, with a view to pooling knowledge, efforts and resources to provide more timely responses to diseases in the areas studied in this review; and iv) an increase in the participation of countries in the region in scientific production on nanomaterials/nanoparticles applied to diagnosis, pharmacological treatment, vaccines, theranostics, personal protective equipment and sanitizing agents in the fight against the SARS-CoV-2 virus and its mutations.

It is hoped that this scoping review will motivate further studies, preferably by strengthening collaboration between regional and foreign institutions, with the aim of creating a more significant Latin American scientific production scenario in terms of the number of articles published, with a greater representation of Latin American countries, more diversified in terms of the types of studies and with greater strength of evidence.

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Authors' Contribution

Mota DM - Conception, planning (study design), analysis, data interpretation, and writing of the work. Ferreira PJG - Acquisition, data analysis, and writing of the work. Primo FT - Planning (study design), analysis, data interpretation, and writing of the work. All the authors approved the final version of the work.

Conflict of Interest

The authors inform that there is no potential conflict of interest with peers and institutions, political or financial, in this study.