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Organic Chemistry and Biochemistry

The state of the art of marine natural products in Colombia

El estado del arte de los productos naturales marinos en Colombia

O estado da arte dos produtos naturais marinhos na Colômbia

Abstract

Marine Natural Products (MNPs) isolated from samples collected in Colombia have been an object of study since the early 1980's; however, this information is neither integrated nor compiled. This systematic review describes the articles published in scientific journals up to December 2019. 173 papers met the inclusion criteria of focusing on MNPs obtained from specimens collected from Colombian seas; all original papers written in English, Portuguese or Spanish. The selected papers were mostly authored by researchers from Colombian groups, with low interaction amongst themselves. 99.4% of the papers studied samples collected from the Caribbean Sea; 183 species were studied, mainly sponges and octocorals. In this study, 1,690 compounds (238 new ones) were reviewed, mainly diterpenes and sterol derivatives. Of the selected papers, 76.8% measured various biological activities, including antibiotic (34%) and anticancer (30%). These papers were published in 51 journals (74.6% were international). In conclusion, scientific work on natural marine products of Colombian origin has incremented over time. The most relevant opportunities to address and fill existing gaps comprise: exploring Pacific Ocean organisms and several of the misrepresented taxa; promoting strong interactions amongst the MNPs research groups, and accordingly with other areas of knowledge; and having the productive sector participate in MNPs research.

Keywords: Biodiversity; marine natural products; Colombia.

Resumen

Los productos naturales marinos (PNM) aislados de muestras recolectadas en Colombia han sido estudiados desde principios de los años 1980, mas esta información no está integrada, ni recopilada. Esta revisión sistemática describe los artículos publicados hasta diciembre de 2019. 173 artículos cumplieron los criterios de inclusión de enfoque en PNM obtenidos de especímenes recolectados en mares colombianos; trabajos originales escritos en inglés, portugués o español. La mayoría de los artículos fueron escritos por investigadores de grupos colombianos, con poca interacción entre ellos. El 99,4% de los artículos estudiaban muestras recolectadas del mar Caribe. Se estudiaron 183 especies, especialmente esponjas y octocorales. Se identificaron 1690 compuestos (238 nuevos), principalmente diterpenos y derivados de esteroles. En el 76,8% de los artículos se midió alguna actividad biológica, principalmente antibiótica (34%) y anticancerígena (30%). Los artículos se publicaron en 51 revistas (74,6% internacionales). En conclusión, la investigación sobre los PNM de origen colombiano ha crecido con el tiempo. Algunas oportunidades para abordar las lagunas encontradas comprenden: explorar los organismos del océano Pacífico y los taxa poco estudiados; promover interacciones entre los grupos de investigación de los PNM y de otras áreas del conocimiento; e involucrar al sector productivo en la investigación de los PMN.

Palabras clave: biodiversidad; productos naturales marinos; Colombia.

Resumo

Os Produtos Naturais Marinhos (PNMs) isolados de amostras coletadas na Colômbia têm sido objeto de estudo desde a década de 1980; porém, esta informação não está integrada nem compilada. Esta revisão sistemática descreve os artigos publicados em revistas científicas até dezembro de 2019. 173 artigos atenderam aos critérios de inclusão de foco em PNMs obtidos de espécimes coletados em mares colombianos; artigos originais escritos em inglês, português ou espanhol. A maioria dos autores dos artigos eram pesquisadores de grupos colombianos, com baixa interação entre eles. 99,4% dos artigos estudavam amostras coletadas no Mar do Caribe. Foram estudadas 183 espécies, especialmente esponjas e octocorais. Nesta revisão, identificaram-se 1690 compostos (238 novos), principalmente diterpenos e derivados de esterol. 76,8% dos artigos mediram algumas atividades biológicas, incluindo antibiótica (34%) e anticancerígena (30%). Os artigos analisados foram publicados em 51 periódicos (74,6% internacionais). Em conclusão, o trabalho científico sobre PNM de origem colombiana cresceu ao longo do tempo. As oportunidades mais relevantes para preencher as lacunas existentes incluem: explorar organismos do Oceano Pacífico e os taxa pouco estudados; promover interação entre os grupos de pesquisa de PNMs e com grupos de outras áreas do conhecimento; e envolver o setor produtivo na pesquisa de PNMs.

Palavras-chave: Biodiversidade; produtos naturais marinhos; Colômbia.

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Introduction

Oceans occupy vast areas on the planet Earth, providing important ecosystem services and supporting a huge biodiversity [1]. Among the 37 phyla described by science, 15 are found only in the marine environment, while only one of them is found exclusively in terrestrial environments [2].

On one hand, many marine invertebrates are sessile and soft-bodied; therefore, they must base their communication and defense with other organisms on chemical compounds [3]. On the other hand, some Marine Natural Products (MNPs) have presented potent biological activity and promising efficacy in the treatment of various human diseases [4]. Regarding their structure, it has been possible to establish that MNPs are more diverse than their terrestrial equivalents; for instance, 71% of the MNPs reported in the *Dictionary of Natural Products* are exclusive to marine organisms [5]. At present, thirteen marine derived compounds have been approved as commercial drugs, while dozens of drug candidates are presently undergoing clinical evaluation [6].

The regions/countries with the greatest amount of research on MNPs include China, USA, Japan and Europe [7], with nearly 35 thousand compounds identified so far. On the other hand, when searching for articles on "Marine Natural Products" in the Scopus database and filtering the results by affiliation territory, 624 of the 10,321 results were found to be associated with Latin American countries (search carried out on May 5, 2020).

Regarding Colombia, several MNPs have been isolated with interesting biological activities; however, at the present time, this information has not been appropriately systematised or compiled. This systematic review aimed to carry out a *scoping study* to describe the scientific work on MNPs isolated from samples collected from Colombian seas with a view to establishing the state of the art thereof and identify possible gaps in this research area.

Materials y methods

Search and selection

To identify papers on MNPs of Colombian origin, a systematic search of the scientific literature published in indexed journals was carried out. The specialised databases Pubmed, Scopus, Scifinder, Scielo, MarinLit, Google Scholar and Web of Science were consulted, using the search equations shown on Table 1. The information retrieved was organised and complemented by a manual search, in official applications of the Ministry of Science, Technology and Innovation of Colombia (Minciencias), in the Latin American and Caribbean Curriculum Vitae (CvLAC) [8] and in the records of each Colombian research group (GrupLAC) [9] whose authors and/or groups had the largest number of articles retrieved by systematic search. Additionally, a search by author was performed in the MarinLit and Scifinder databases regarding the authors most frequently cited as the corresponding authors.

The inclusion criteria were original scientific papers on the chemistry of organisms collected from Colombian marine territories, published up until December 2019 in English, Spanish or Portuguese. Bibliographic reviews, monographs, book sections, articles related to other areas of knowledge were not included, neither were publications regarding non-marine organisms nor concerning organisms collected from territories other than the Colombian seas.

The selection of articles comprised two phases. The titles and abstracts were reviewed first; and the papers whose inclusion was open to doubt were retained for the second phase, which consisted of considering the full text. Two reviewers independently (CAB and CAP) were in charge of selecting the papers; in case of disagreement, they discussed and, if yet no consensus was reached, a third reviewer (LC) made the inclusion/exclusion decision.

Data extraction

Year of publication and authors' details were obtained from the registry generated by Zotero® for each paper. Data on the authors' affiliation and gender were extracted from the papers' information section. To analyse this information, first a standardisation of citation variants and authors' names and affiliations was established. With respect to affiliations, the most complete information (group, department or institute, and institution) was also standardised. The information regarding financing sources was obtained from the articles' acknowledgements sections. To determine the level of dedication to MNPs research of each Colombian research group, their number of published papers was counted using the records of Colciencias' GrupLAC.

Data related to the species, phyla, sample collection site and number of compounds were obtained by reading the papers. Reached isolation level, types of bioassays, and types of chemical compounds were classified by two reviewers independently (CAB and CAP), and disagreements were resolved by a third reviewer (LC).

To determine the visibility of the papers included in this analysis, three verifications were carried out. First, a search by title was performed in each database to check indexing. Second, the number of citations of the articles in each database was verified, except for MarinLit, because it is a specialised MNPs database. As for Google Scholar®, the search described whether the publication was indexed as an article or only as a citation.

Table 1. Databases and keywords used to complete the search for articles.

Database	Key words
Pubmed	"Marine natural products" [All Fields] AND ("Colombia" [MeSH Terms] OR "Colombia" [All Fields]) OR Colombian [All Fields])
Scopus	ALL ("Marine natural products" AND (Colombia OR Colombian) AND DOCTYPE (ar OR re)
Scifinder	"Marine natural products" and "Colombia".
Scielo	"Marine natural products" AND (Colombia OR Colombian)
MarinLit	Colombia
Google Scholar	"Marine natural products" AND (Colombia OR Colombian)
Web of Science	"Marine natural products" AND (Colombia OR Colombian)

Table 2. Indicators analysed for the scoping study.

Type of indicators	Variable	Calculated indicator
Productivity indicators	Year of publication	Number of papers by five-year period, according to participation of Colombian research groups
	Affiliation	- Number of institutions by country of origin (Colombia or other) - Number of institutions by type (universities, research institutes or companies) and by nature (public or private) - Number of papers by institution or research group - Average dedication of Colombian research groups to work on MNPs according to papers reported by GrupLAC, Minciencias - Interaction among the 21 research groups with the highest number of papers
	Author	- Number of papers by author - Number of papers by corresponding author - Year the author begins to appear as a corresponding author - Number of papers with participation of female authors
	Funding source	- Number of papers by funding source - Number of funding institutions by type (government body, universities, research centers, foundations) - Number of funding institutions by nature (private or public) - Number of funding institutions by country of origin
Content indicators	Collected species	Number of papers by species studied
	Phylum of collected samples	Number of papers by phylum studied
	Sample collection site	Number of papers by geographical area of collection
	Described compounds	Total number of compounds according to the following categories: new compounds, already reported compounds; and compounds obtained by semi-synthetic approaches
	Structural classification	- Number of papers by compound category according to chemical structure - Number of papers by five-year period according to compound category and to participation of Colombian research groups
Methodology indicators	Level of separation of described compounds	Number of papers by level of separation: raw extracts, putative identification in mixture (LC-MS and GC-MS); and pure compounds
	Bioassays	Number of papers by type of bioassays carried out according to the classification proposed by Blunt et al. (2006)
Journal indicators	Country of origin of the journal	Number of papers published in Colombian or foreign journals
	Number of published papers	- Top 10 journals with the highest number of papers - Number of papers published with participation of Colombian groups in these top 10 journals
	Classification in ranking journals	- Number of journals ranked in Scimago (quartile) - Number of journals ranked in JCR (IF) - Number of journals ranked in Google Scholar (h-5, median h-5)
	Journal quartile in Scimago (SJR) since 1999. The best classification and year of publication were considered	- Number of papers by quartile in each five-year period, according to participation of Colombian research groups - Number of papers by quartile for the 21 research groups/institutions with the highest number of papers
	Impact factor according to Journal Citation Reports since 1997. The papers' publication year were considered	- Average IF of the journals, according to participation of Colombian research groups - IF range of the journals according to participation of Colombian research groups - Impact Factor of the top 10 journals with the highest number of papers - Top 10 journals with the highest impact factor - Number of papers published with the participation of Colombian research groups in these top 10 journals
	h-5 value for the journal according to Google Scholar	- Top 10 of the journals with the highest h-5 - Number of papers published with participation of Colombian research groups in these top 10 journals
	Median-h-5 for the journal according to Google Scholar	- Top 10 of the journals with the highest median h-5 - Number of papers published with participation of Colombian research groups in these top 10 journals
Article visibility indicators	Indexation in the databases	- Number of identified papers indexed in Google Scholar - Number of identified papers indexed in Scopus - Number of identified papers indexed in Scifinder - Number of identified papers indexed in Marinlit - Number of identified papers indexed in Web of Science - Number of identified papers indexed in Pubmed - Number of identified papers indexed in Scielo

Type of indicators	Variable	Calculated indicator
Article visibility indicators	Trend of indexation in databases over the time	- Number of identified papers indexed in Google Scholar in each five-year period according to participation of Colombian research groups - Number of identified papers indexed in Scopus in each five-year period according to participation of Colombian research groups - Number of identified papers indexed in Scifinder in each five-year period, according to participation of Colombian research groups - Number of identified papers indexed in Marinlit in each five-year period according to participation of Colombian research groups
	Citation in the research series review: "Marine Natural Products" in the journal Natural Product Reports	Number of papers cited in the review titled "Marine Natural Products", by five-year period, according to participation of Colombian research groups
	Article citations	- Top 10 papers with the highest number of citations in Scopus - Top 10 papers with the highest number of citations in PubMed - Top 10 papers with the highest number of citations in Scifinder - Top 10 papers with the highest number of citations in Google Scholar - Top 10 papers with the highest number of citations in Web of Science
	Research group citations	- Top 5 research groups with the highest number of citations in Scopus - Top 5 research groups with the highest number of citations in PubMed - Top 5 research groups with the highest number of citations in Scifinder - Top 5 research groups with the highest number of citations in Google Scholar - Top 5 research groups with the highest number of citations in Web of Science

Data analysis

The selected articles were analysed using the indicators described on Table 2. As the search identified a considerable number of articles published by researchers from the University of Puerto Rico without the cooperation of Colombian institutions, this factor was taken into account in the analysis of several indicators.

Results and discussion

The systematic search retrieved 1,553 articles, of which 173 met the selection criteria (Figure 1). Then, the articles were carefully read, and data concerning research productivity, content, and methodology indicators (Table 2) were extracted. The data regarding journal and paper citation indicators were consulted in the databases mentioned in the method section. The variables and indicators calculated for each type of indicator are analysed below.

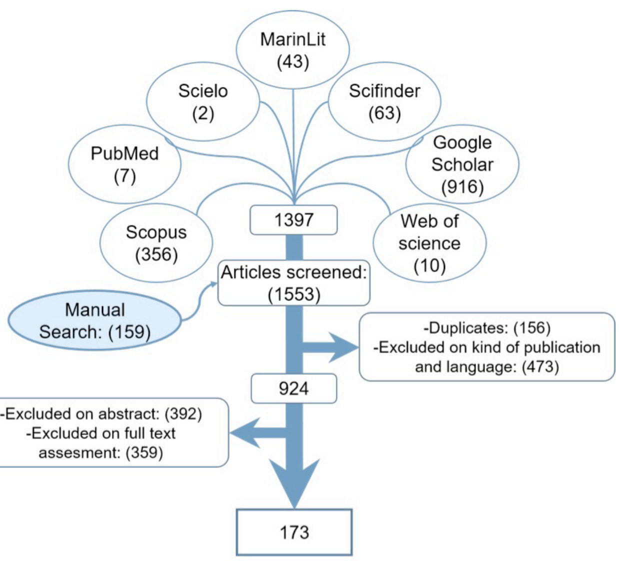

Figure 1. Flowchart of the articles included in the review.

Productivity indicators

The number of papers on MNPs developed in Colombian has incremented over time, going from 41 papers in two decades (1981-2000) to 63 in the 2011-2019 period. This trend is similar to that of the global article publishing on MNPs reported by Scopus (Figure 2). The increased number of papers published subsequent to the 1990's can be explained by several aspects, particularly the creation in 1986 of the PhD Chemistry Programme at the Universidad Nacional de Colombia (UNAL) [10]; the implementation since 1987 of policies to promote scientific research in Colombia, i.e. the National Policy on Science and Technology under Law 29 of 1990 [11]; the credit in 1990 from the Inter-American Development Bank (IDB II) to financially support scientific work [12], and the fact that for the very first time the Colombian Administrative Department of Science, Technology and Innovation (Colciencias, today Minciencias) offered research grants for projects on marine sciences [13].

The last analysed period (2016-2019) showed a decreased number of papers, which can be explained not only by the fact that it was a shorter period (4 years while the other periods comprised five years), but also due to changes in the funding policies for science in Colombia. On one hand, since 2012, there has been a decrease in basic science financing by Colciencias because the General System of Royalties became the main source of financing, and it is focused on applied research [10]. On the other hand, reassessing the calls announced by Colciencias, a change in the project financing policy proved evident, which led to the elimination of specific calls for the Marine Sciences area. The last call for the Marine Sciences area was "Convocatoria para Proyectos de Ciencia, Tecnología e Innovación en Ciencias del Mar para la Región Caribe - 2016" [14]. In view of that, MNPs researchers had to seek funding opportunities in other areas, for example by means of call 852 "Conectando Conocimiento - 2019", whose topic number 4 included "Bioprospecting of active ingredients and metabolites of interest to the health, food, agriculture, and industry, making efficient and sustainable use of biodiversity (continental and/or marine)" [15]. All those changes in funding policies since 2016 have decreased the visibility of MNPs, and the resources assigned have been affected by competition with projects respecting other knowledge areas.

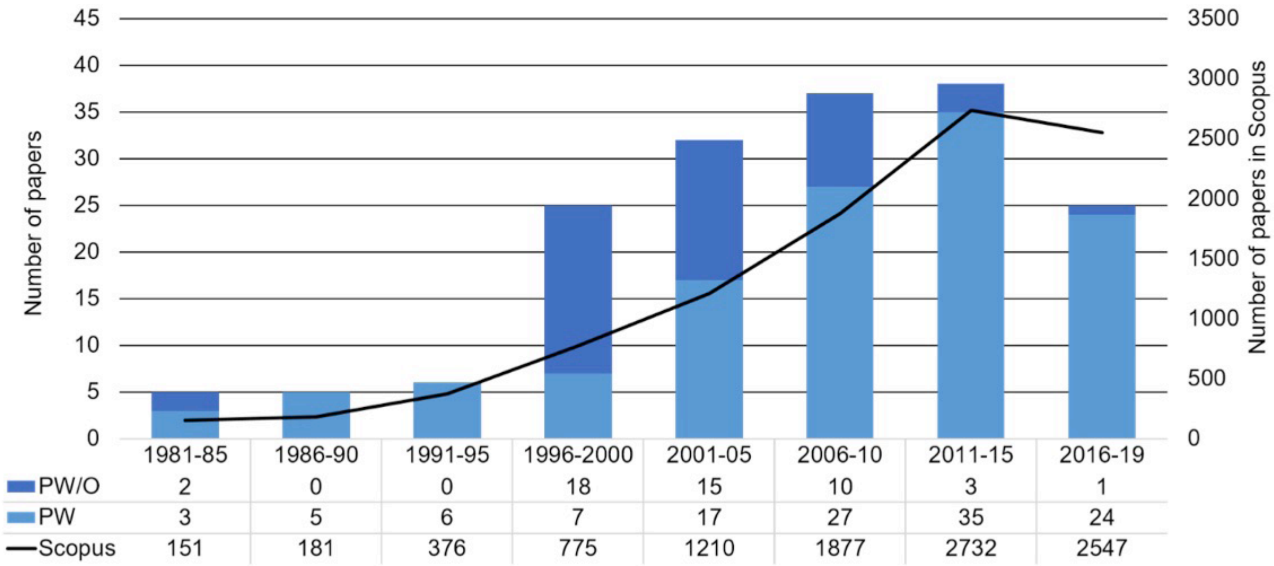

Figure 2. Trend of article publishing on MNPs isolated from organisms collected from Colombian seas. Number of papers published according to participation of Colombian institutions vs. those reported by Scopus worldwide in the 1981-2019 period; (PW/O) paper without participation of Colombian groups; (PW) paper with participation of Colombian groups; (Scopus) Scopus search for "Marine Natural Products". The number of articles published in five-year periods is represented by the graph bars (the far-right bar corresponds to the period from 2016 to 2019). The global article publishing data were obtained from Scopus (right scale) with the key words "Marine Natural Products", organising it by year of publication. The papers that included Colombian samples are shown on the left scale.

In the 173 articles that met the selection criteria, 97 different affiliations were identified, including research groups, faculty departments, research institutes, etc., linked to 65 institutions: 38 foreign and 27 Colombian. The Colombian institutions comprised 20 universities (14 public and 6 private); two research institutes (one private and one public) and five companies (three private, one public, and one mixed). These data show that the development of research on MNPs in Colombia is concentrated in the universities, and with low participation of productive industries. This implies that many results obtained in this area are produced and "stored" only for academic purposes and do not deliver social benefits.

The 27 Colombian institutions participated in 125 articles (72.3%), thus showing that most of said academic publications originated in Colombia. However, the trend over time shows that in 1996 (Figure 2) there was a greater number of publications by researchers linked to foreign institutions, which then decreased to almost disappear in the last two periods analysed (2011-2019). This trend can be explained by changes in Latin American and Colombian government policies regarding biopiracy, biodiversity and genetic protection (Law 99 of 1993, Congress of Colombia, 1993; Decision 391 of 1996, Comunidad Andina de Naciones; [16]. It is worth mentioning that as of 2006 there has been a change in attitude on the part of the Colombian Ministry of Environment and Sustainable Development (MinAmbiente). In strict compliance with current regulations, it has included a permission request for both collection and research of natural products (derived products) upon consultation with the communities living in the collection area.

The research group "Estudio y aprovechamiento de productos naturales marinos y frutas de Colombia" from the Universidad Nacional de Colombia (UNAL) is the one with the highest number of published papers (n=67; 38.7%), followed by the research group from the University of Puerto Rico (UPR) (n=46; 26.6%), with publications not linked to Colombian institutions. The successive groups, in number of publications, are: "Productos Naturales Marinos" of the Universidad de Antioquia (UdeA) (n=30; 17.3%), "Instituto de Estudios en Ciencias del Mar -Cecimar-" of UNAL (n=24; 13.9%); "Bioprospección y Biotecnología" from the Department of Biological and Environmental Sciences of the Universidad Jorge Tadeo Lozano (UTadeo) (n=13; 7.5%); and "Biotecnología Animal" of UNAL (n=13; 7.5%). It is surprising that of all the groups or institutions that participated in those publications, only Cecimar and Invemar are located in a coastal city (Santa Marta), which indicates the need to invest in human and research resources in this geographical area of Colombia with a view to decreasing centralism and developing local research capacities.

Research groups in Colombia are not usually dedicated to a single topic; instead, they conduct research in different areas, and this is the reason why it was important to identify their fields of activity regarding MNPs studies. To calculate that, the number of their publications on MNPs was divided by their total publications, and expressed as a percentage. Dedication percentages varied from 57.14% to 0.64%. The research groups most dedicated to MNPs research are: "Comunicación y comunidades Bacterianas" of UNAL (57.14%), "Estudio y Aprovechamiento de Productos Naturales Marinos y Frutas de Colombia" of UNAL (47.86%), "Bioprospección y Biotecnología" of UTadeo (46.43%) and "Productos Naturales Marinos" of UdeA (46.15%) (Table 3).

The interaction among the 21 research groups with the largest number of articles published on MNPs is presented in Figure 3 using the Roman numerals from Table 3. Colombian groups are represented by (○), while foreign groups are represented by (□); the size of the symbol is proportional to the number of papers published on MNPs, the lines represent collaborative work, and their width is also proportional to the number of papers published in collaboration.

Figure 3 shows two main clusters. The first one comprises mainly the Colombian groups and their collaboration network, while the second cluster includes mainly foreign groups. Colombian groups (○) showed interaction amongst themselves; only the group from the Universidad de Cartagena – UCartagena (XVIII) has not yet begun to establish research links with other institutions. Similarly, Unicórdoba (VII) produces most of its work without the cooperation of other research groups. With respect to interaction amongst Colombian groups, Figure 3 shows that the most productive groups (I and III) have very little interaction with one another. Likewise, the seven research groups from UNAL have worked together, except for the Biotecnología Animal group (VI) from the Medellín campus, which manifested a strong relationship with group III from UdeA, also located in Medellín. These data evidence the establishment of interdisciplinary networks (chemistry, pharmacy and biology) at the regional level rather than solely at the institutional level.

Table 3. List of the 21 research groups with the largest number of publications and their code number.

Code	Research group name and affiliation	No. of papers	Contribution (in %) of total published papers
I	"Estudio y Aprovechamiento de Productos Naturales Marinos y Frutas de Colombia", (Minciencias Code*: COL0004569) Department of Chemistry, Universidad Nacional de Colombia, Bogotá Campus, Colombia	67	38.7
II	Department of Chemistry, University of Puerto Rico, Rio Piedras Campus, Puerto Rico	46	26.6
III	"Productos Naturales Marinos", (Minciencias Code: COL0015043), Faculty of Pharmaceutical and Food Sciences, Universidad de Antioquia, Medellín Campus, Colombia	30	17.3
IV	Instituto de Estudios en Ciencias del Mar (Cecimar), Department of Biology, Universidad Nacional de Colombia, Caribbean Campus, Colombia	24	13.9
V	"Bioprospección y Biotecnología", (Minciencias Code: COL0070232) Department of Biological and Environmental Sciences, Universidad Jorge Tadeo Lozano, Bogotá Campus, Colombia	13	7.5
VI	"Biotecnología Animal", (Minciencias Code: COL0001093) Science Faculty, Universidad Nacional de Colombia, Medellín Campus, Colombia	13	7.5
VII	"Química de los Productos Naturales", (Minciencias Code: COL0015319), Department of Chemistry, Universidad de Córdoba, Montería Campus, Colombia	11	6.4
VIII	Department of Chemistry, Tokyo Institute of Technology, Japan	10	5.8
IX	"Invemar - Bioprospección Marina" (Minciencias Code: COL0033069), Institute of Marine and Coastal Research "José Benito Vives De Andréis" (Invemar), Santa Marta, Colombia	10	5.8
X	Department of Pharmacy, Faculty of Sciences, Universidad Nacional de Colombia, Bogotá Campus, Colombia	9	5.2
XI	"Comunicación y Comunidades Bacterianas", Department of Biology, Universidad Nacional de Colombia, Bogotá Campus, Colombia	8	4.6
XII	Center of Molecular and Behavioral Neuroscience, Central University of the Caribbean, Bayamón, Puerto Rico	6	3.5
XIII	Nice Institute of Chemistry, University of Nice Sophia Antipolis, France	6	3.5
XIV	"Grupo de Investigación en Bioprospección (GIBP)", (Minciencias Code: COL0143114), Faculty of Engineering, Universidad de La Sabana, Puente del Común Campus, Colombia	5	2.9
XV	Department of Fundamental Chemistry, Faculty of Sciences, Universidad de Coruña, Spain	5	2.9
XVI	Institute for Advanced Scientific Research and High Technology Services, Center for Biomedical Studies, Clayton, Panama	5	2.9
XVII	Department of Systematic Biology and Laboratories of Analytical Biology, Smithsonian Institution, Washington, USA	4	2.3
XVIII	"Grupo de Productos Naturales de la Universidad de Cartagena", (Minciencias Code: COL0010913) Faculty of Pharmaceutical Sciences, Universidad de Cartagena, Cartagena, Colombia	4	2.3
XIX	Department of Biology, Universidad Nacional de Colombia, Bogotá Campus, Colombia	3	1.7
XX	Department of Chemistry, University of Missouri, Columbia, USA	3	1.7
XXI	Chicago College of Osteopathic Medicine, Department of Pharmacology, Midwestern University, Downers Grove Campus, Illinois, USA	3	1.7

* Minciencias Code is the Colombian Group Registration Code (CCRG) assigned to each research group registered with the Ministry of Science, Technology and Innovation.

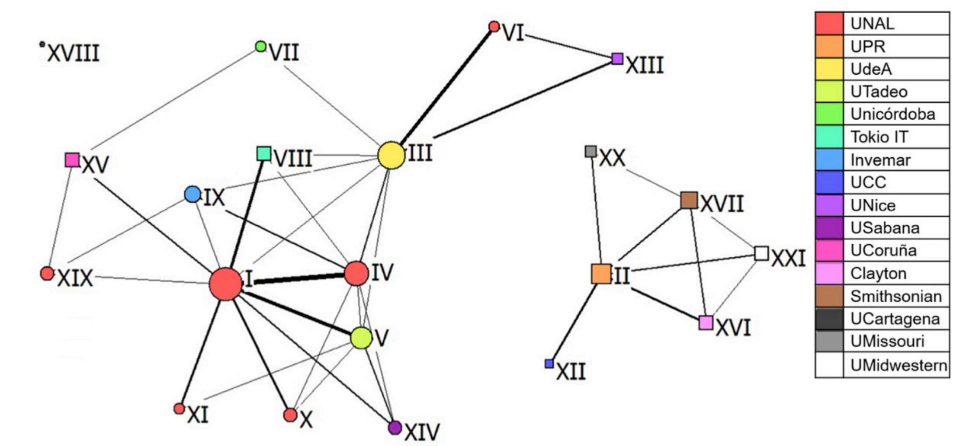

Figure 3. Network of interaction among the 21 research groups with the highest number of publications; origin and classification according to institution affiliation; (○) Colombian Groups; (□) foreign groups. The groups with the largest size are those that have the highest number of papers. The lines indicate the links between them, and the thickness of the line represents the strength of their interaction. The different colors indicate the groups' affiliations with institutions, namely: (UNAL) Universidad Nacional de Colombia; (UPR) University of Puerto Rico, Puerto Rico; (UdeA) Universidad de Antioquia, Colombia; (Unicórdoba) Universidad de Córdoba, Colombia; (Tokio IT) Tokyo Institute of Technology, Japan; (Invemar) Instituto de Investigaciones Marinas y Costeras, Colombia; (UCC) Universidad Central del Caribe, Puerto Rico; (UNice) University of Nice, France; (USabana) Universidad de La Sabana, Colombia; (UCoruña) Universidade da Coruña, Spain; (Clayton) Centro de Estudios Biomédicos, Panama; (Smithsonian) Smithsonian Institute, USA; (UCartagena) Universidad de Cartagena, Colombia; (UMissouri) University of Missouri, USA; (UMidwestern) Midwestern University, USA.

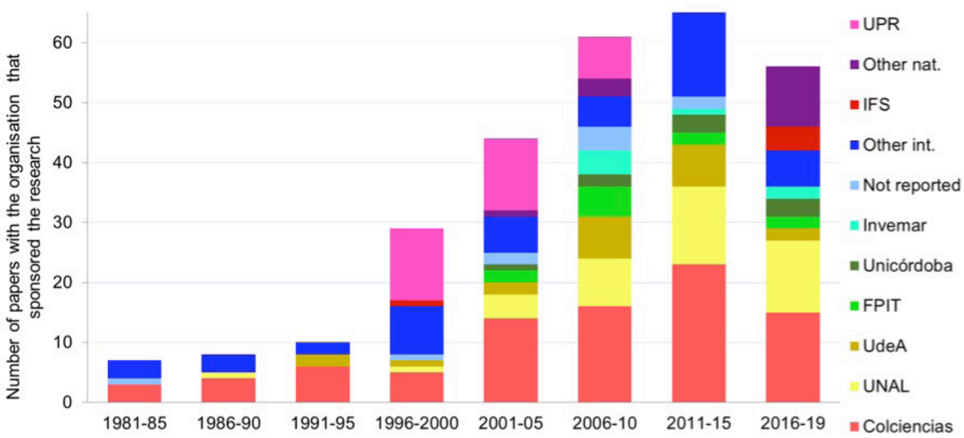

Figure 4. Sources of financing reported in articles on MNPs published by Colombian groups; (UPR) University of Puerto Rico, Puerto Rico; (Other nat.) Other national institutions; (IFS) International Foundation for Sciences, Sweden; (Other Int.) Other international institutions; (Invemar) Instituto de Investigaciones Marinas y Costeras, Colombia; (Unicórdoba) Universidad de Córdoba, Colombia; (FPIT) Fundación para la Promoción de la Investigación y la Tecnología del Banco de la República, Colombia; (UdeA) Universidad de Antioquia, Colombia; (UNAL) Universidad Nacional de Colombia.

As for the eight foreign institutions (□), only three of them showed any collaboration with Colombian groups. The group from the Tokyo Institute of Technology (Tokio IT) (VIII) maintains a relationship with groups I, III and IV, while the group from the Universidad de Coruña – UCoruña (XV) works with groups I, XIX and VII; the French group XIII (Université Nice – UNice) works only with groups III and VI.

A total of 290 authors were identified, thus evincing a large number of researchers working with MNPs, with the following authors having the highest number of papers: Carmenza Duque (n=49; 28.3%) and Leonardo Castellanos (n=33; 19.1%) from UNAL; Abimael Rodríguez (n=46; 26.6%) from UPR, and Alejandro Martínez (n=34; 19.7%) from UdeA. Amongst them, there were 44 researchers in the role of corresponding authors, the most prolific ones being Abimael Rodríguez (n=44; 25.4%) and Carmenza Duque (n=30; 17.3%). These two authors are pioneers and leaders of the two most prolific research groups.

Professor Carmenza Duque was the graduate thesis advisor of other Colombian researchers, namely Leonardo Castellanos (n=10; 5.8%) and Freddy Ramos (n=9; 5.2%), who appear as corresponding authors since 2005 and 2011, respectively; both are the current leaders of Group I (UNAL). Alejandro Martínez (n=8; 4.6%) was also advised by Dr. Duque, and appears as corresponding author since 1991, from the UdeA group (III), who then advised Diana Márquez (n=6; 3.5%), who appears as corresponding author since 2005. Other researchers counseled by Carmenza Duque are Gilmar Santafé (n=8; 4.6%), who appears as corresponding author since 2005 and leads the Unicórdoba group (VII); and Edison Tello (n=4; 2.3%) who leads the USabana group (XIV). These results show that, in Colombia, researcher Carmenza Duque has played a very important role in the development of research regarding MNPs and has contributed to the extension of this topic to other regions of the country.

Finally, women's participation in MNPs research was considered regarding the 124 articles published with the participation of Colombian groups (see Fig. 2), which evinced that 51% of the total authors (n = 235) are women. However, when filtering among the top 20 authors with the most publications, 67% of them are men and only 33% are women. On the other hand, 40% (n = 10) of the leaders of the top 10 Colombian research groups (see Table 3) are women. No gender parity was observed, neither in terms of authorship nor in terms of leadership of the research groups in question. This highlights Professor Carmenza Duque's seminal contribution, who reinforced the important role of women as active subjects in the development of science in Colombia. In 2015, the participation of

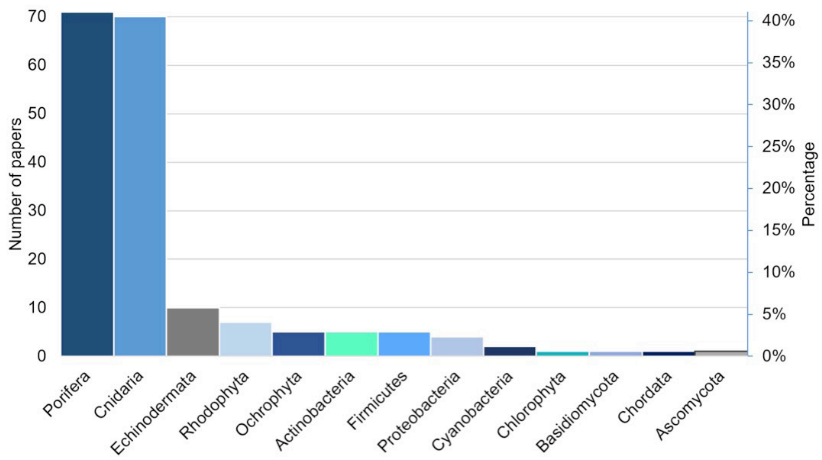

Figure 5. Percentage of publications by phylum studied.

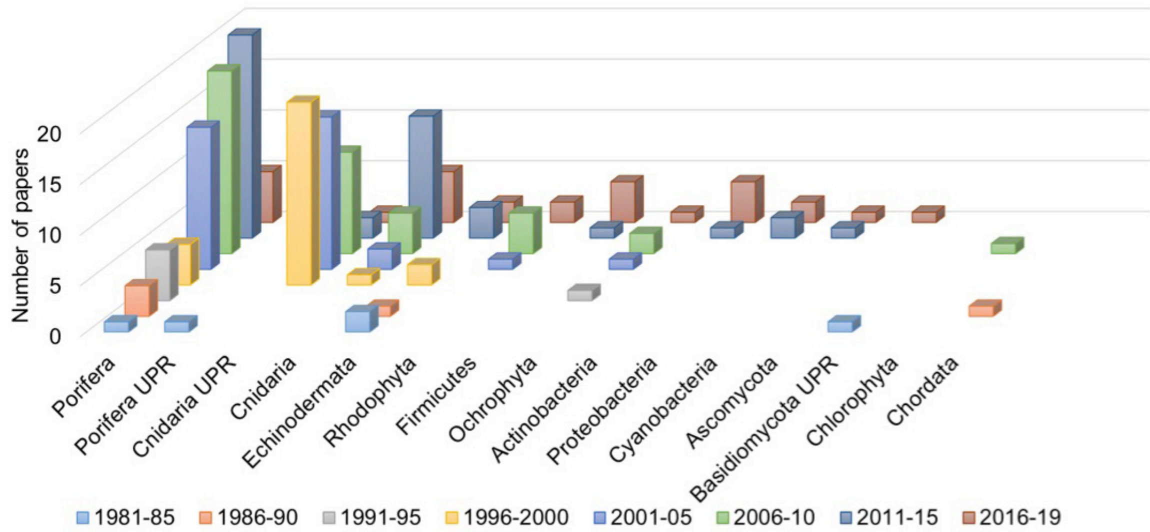

Figure 6. Phyla of most collected Colombian samples, by five-year periods; The studies carried out by University of Puerto Rico were marked with the acronym UPR as a way to differentiate them from the studies developed by Colombian groups.

women in science in Colombia represented only 39% of the total number of researchers [17] and, in 2013, 29% of the leaders of natural science research groups in Colombia were women [18] – in the area of MNPs, the percentage is higher, but it does not reach parity.

Regarding funding sources, 50 different institutions were identified, of which 16 were from Colombia – including 4 government organisations, nine universities (one of them private), two research centres (one of them private), and one private foundation. In the 125 articles in which Colombian institutions participated, the most cited funding sources were Colciencias (now called Minciencias) (n=86; 68.8%); UNAL (n=39; 31.2%); UdeA (n=21; 16.8%) and *Fundación para la Promoción de la Investigación y la Tecnología del Banco de la República* (FPIT) (n=11; 8.8%). As can be seen in Figure 4, over time Colciencias has been one of the main funding sources for these studies, although in percentage terms its impact has been decreasing. This is due to the increased investments by other institutions, especially universities with their own resources, and the increased participation of other national and international sources, mainly by virtue of cooperation partnerships with researchers from Brazil and Argentina. This situation can also be explained by the reduction in funding from Colciencias toward basic science research, as previously mentioned [10]. In 10 of the selected papers, there was no reporting of funding sources.

Content indicators

In the 173 selected papers, approximately 500 samples belonging to 222 species were studied – 187 samples identified at the species level and 35 identified solely at the genus level. The species reported in most publications belong to the phyla: Porifera (n=71; 41%) and Cnidaria (n=70; 40.5%), representing 81.5% (n=141) of the publications analysed (Figure 5). In particular, *Antillogorgia elisabethae* (syn *Pseudoptergorgia elisabethae*) (n=31) and *Pseudoptergorgia bipinnata* (n=10) of the phylum Cnidaria; and *Iricina capana* (n=10), *I. felix* (n=10), and *Topsentia ophiraphidites* (n=10) sponges (of the phylum Porifera) were the species studied in the majority of the papers. It is worth noting that studies on the phylum Porifera have increased over time, while the phylum Cnidaria had a marked increase only after the mid-1990s by reason of the articles (n = 21) produced by the UPR group (Figure 6), almost all of them with regard to the octocoral *Pseudopterogorgia elisabethae* collected in Colombia. In addition, the studies regarding species of the phylum Cnidaria by Colombian researchers have increased significantly in the last five years, indicating that these organisms have been included in the work of national researchers (Figure 6, Cnidaria vs Cnidaria UPR). The phylum Echinodermata is the third

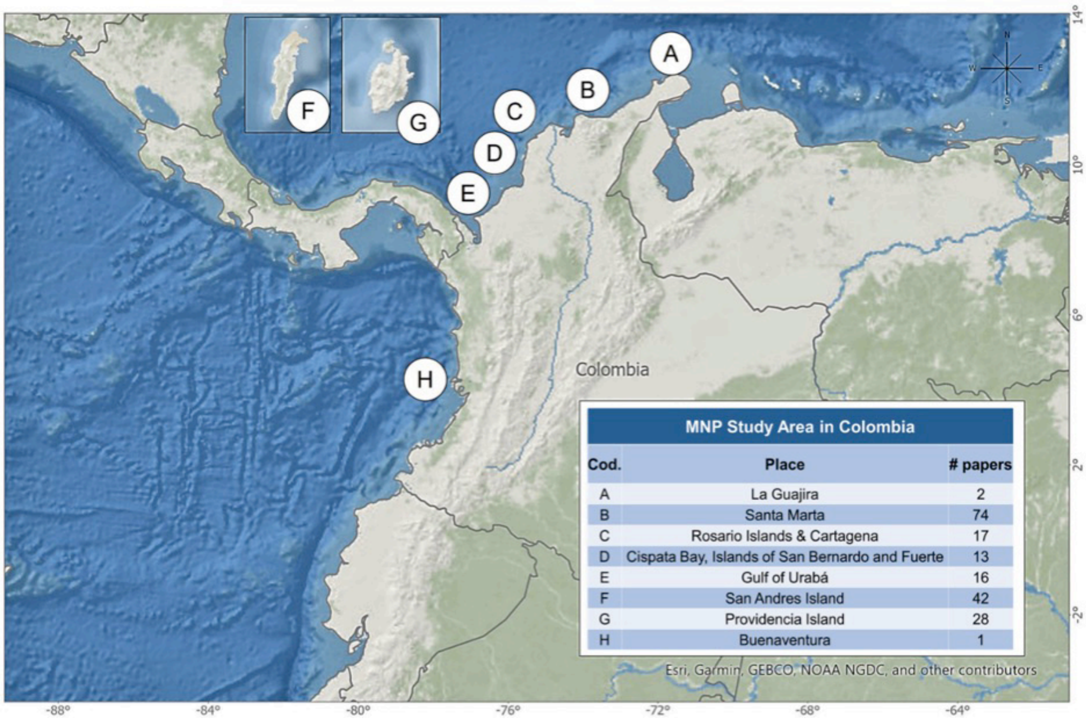

Figure 7. Main sampling areas of marine organisms for MNPs studies in Colombia.

most studied and represents 5.8% (n=10) of total publications. These investigations have not been consistent over time and have had ups and downs, and evidenced a new increase between 2011 and 2019 (Figure 6).

It is important to compare the records showing the presence of various organisms in Colombian Oceans (Colombian Marine Environmental Information System, SIAM) with their corresponding chemical studies to verify whether the abundance of any kind of organism is reflected in the related chemical studies. Notwithstanding, there are numerous records for several species, meaning that biologists have been collecting them, with a bare minimum number of chemical studies on them, indicating that researchers have not been taking advantage of the potential synergy between chemists and biologists. An example illustrating this situation is the phylum Chlorophyta, regarding which only one article has been published, while in the SIAM there are 1,123 related records with 76 identified species. Moreover, the phyla Rhodophyta (7 articles) and Ochrophyta (5 articles) have 1,491 and 1,287 records, with 121 and 35 recognised species, respectively. The Echinodermata phylum, despite being the third most studied group, was addressed in only 10 articles; however, 5,130 records of 257 species can be found in the SIAM. Finally, there is no chemical study regarding the phylum Mollusca, and there are 11,746 records of 1,147 identified species of these organisms in the SIAM system [19]. The foregoing shows that there are numerous chemically unexplored phyla, from which the production of a large number of compounds with high added value could be expected.

The aforementioned results show that the trend regarding phyla and species in Colombia is consistent with the global trend, with Porifera and Cnidaria being the most studied phyla, based on the fact that a large number of bioactive compounds have been obtained from them [20]. The concentration of chemical studies on these two phyla can also be explained by the fact that the MNPs groups carrying out such research in Colombia include experts in Porifera (Ph.D. Sven Zea, UNAL) and Cnidarian (Ph.D Mónica Puyana, UTadeo) taxonomy. Furthermore, even though the research institutions in question also have experts in other taxonomies of phyla, there is no interaction between them and the natural product chemists, hence these organisms are not being studied from a chemical point of view. This is the case, for example, of algae and mollusks. The foregoing shows that associations should be reinforced or initiated between research groups with a long history and newly formed ones to join efforts in MNPs research.

Nowadays, globally, the most studied source of MNPs is microorganisms, particularly phyla Ascomycota (fungi), Actinobacteria (gram positive bacteria) and Cyanobacteria (photosynthetic bacteria) [21]. This is a consequence of the fascinating number of compounds that can be isolated from them, and because they are a sustainable source thereof, overcoming the supply problem that affects natural products. In Colombia, studies on marine microorganisms are incipient (Figure 6), with a few examples found in the last period studied, and others isolated in early 1980's. This lack of chemical information is consistent with the limited records in the Marine Environmental Information System [22] on microorganisms – a consequence of lack of interest and the small number of trained researchers in the area. To overcome this problem, Colombia should focus on training researchers and building links between microbiologists and chemists. In the abovementioned data system, there are hardly any marine biological records on the phyla Ascomycota (11 records without description of the species), Proteobacteria (107 records with the description of 16 species), Actinobacteria (seven records with the description of only one species) and Cyanobacteria (210 records with the description of 10 species) [19]. There are other strain collections at different Colombian institutions but the access to such information is not easy.

Some institutions such as the CorpoGen Corporation and the Humbolt Institute currently have collections of microorganisms isolated from marine environments. In this sense, efforts are being made to consolidate initiatives such as the database of the Colombian Biodiversity Information System (SiB), which is a national open data network on biodiversity in which the aforementioned institutions and many others take part; however, the information on this network is not yet fully available.

Some efforts have been made toward the study of marine microorganisms by microbiology research groups, for instance, the groups conducted by "Microbiodiversidad y Bioprospección/UNAL Medellín" and "Bioprospección Marina/Invemar" on exploration and characterisation of microorganisms for a sustainable microbial biotechnology use. Their publications include more than 35 articles but without any chemical studies [9], thus reflecting the lack of collaborative research with natural product chemists.

Regarding sample collection sites, 195 were reported and were grouped into 8 large geographic areas: 7 located in the Caribbean Sea (San Andrés Island; Providencia Island; Santa Marta Bay; Rosario and Cartagena Islands; Cispata Bay, San Bernardo Islands and Isla Fuerte; Gulf of Urabá and La Guajira); and one in the Pacific Ocean (Buenaventura Bay) (Figure 7). The most explored sites correspond to the Caribbean Sea, particularly Santa Marta (74 articles; 42.8%), San Andrés (42 articles; 24.3%) and Providencia (28 articles; 16.2%). The concentration of research activities in the Caribbean Sea can be explained by the enormous biological diversity of such areas (Márquez, 1996), and because UNAL, UdeA and Unicórdoba have facilities for the development of these activities in this region.

Even though Colombia has more than 1,300 km of the Pacific Ocean coastline, just one paper was published with samples collected at the Colombian Ocean Pacific shore, reflecting a deep unbalance between the Caribbean and Pacific regions for the development of the country. This lack of research on MNPs cannot be associated with a lack of biological knowledge resources regarding the Pacific Ocean, given that several universities and public research institutions have been conducting research in this area. One example is the fact that the Universidad del Valle (Cali, Colombia), with great influence on the Colombian Pacific coastline, has a doctoral programme in Marine Sciences [23]. It also has research groups on estuary ecology, plant and organism biology, oceanographic sciences, coral reef ecology and animal ecology [24]. This means that many organisms in this area have already been biologically characterised, as evidenced by the 143 articles published by the research group called “Ecología de Arrecifes Coralinos” [9]; however, they carry out no chemical studies. Moreover, in the four Colombian states (departamentos) that encompass the Pacific Coast, there are research groups on natural products [25], mainly on phytochemistry, which means they have the knowledge and facilities to work with marine natural product chemistry. One reason that could explain this situation is the lack of interaction between the groups identified as leaders in MNPs research in Colombia and the research groups in the Pacific.

Therefore, some questions remain: Why have studies on MNPs chemistry not been carried out in this region? Would there be any new and interesting compounds identified in the Colombian Pacific? The safest answer is yes, especially considering the interesting compounds isolated from organisms on the Panamanian Pacific coast, mainly from the phyla Cyanobacteria and Cnidaria [26]; [27]. In any case, the South American Pacific coast, particularly comprising Colombia, Ecuador, and Peru, has been little explored as shown by [28]. This is one of the issues to be overcome to ensure the development of MNPs in Latin America.

In the 173 analysed publications, covering the period from 1981 to 2019, a total of 1,690 compounds were reported, many of them described in more than one paper. These compounds can be classified as previously reported compounds (n=1358; 80.4%); new compounds at the time of their publications (n=238; 14.0%); and compounds obtained by semi-synthesis (n=94; 5.6%)). The compounds were classified into 11 groups according to their structural characteristics (Table 4). Diterpenes were the most cited compounds, present in 77 articles (44.5%), of which 54 were published by research groups from the University of Puerto Rico without cooperation with Colombian research groups. Taking such data into account, the analysis by group of compounds was performed based on time, without considering those published by the UPR, to characterise the compounds identified by Colombian groups (Figure 8).

Sterols and sesquiterpenes, and their derivatives, have been studied since the beginning of research on MNPs in Colombia. This same trend is observed for lipids and diterpenes, although their study began later. The number of articles reporting diterpenes has increased significantly over time, despite the decrease (from 23 to 7) in the number of articles published by UPR researchers in the 1996-2019 period. Likewise, since the last decade, the study of alkaloids, peptides, triterpenes and polyketides, sterols and sesquiterpenes, has begun to increase, thus showing a strengthening of the research capacity of Colombian groups.

Table 4. Number of publications by groups of chemical compounds according to their structural characteristics.

Compound groups	Compounds included	No. of articles (%)*
Diterpenes	Diterpenes, bis-diterpenoids, nor-diterpenes, and glycosylated diterpenes	77 (44.5%)
Sterol compounds	Sterols, sulfated steroids, epidioxysterols and steroidal saponins	30 (17.3%)
Lipids	Fatty acid methyl esters obtained by hydrolysis of glycerides, phospholipids, ceramides, and related compounds; Prostaglandins	17 (9.8%)
Others	Aromatic compounds, acylhomoserine lactones (AHL), phenylpropanoids, products of combined metabolic pathways, carbohydrates and complex mixture of volatile compounds	12 (6.9%)
Sesquiterpenes compounds	Sesquiterpenes and non-cyclic nitrogenous sesquiterpenes	7 (4.0%)
Sesterpenes compounds	Sesterpenes and their esterified derivatives	5 (2.9%)
Bromotyrosines derivatives	Bromotyrosine derivatives	5 (2.9%)
Peptides	Oligopeptides	5 (2.9%)
Triterpenes compounds	Triterpenes and triterpenoidal saponins	4 (2.3%)
Alkaloids	Alkaloids and cyclic amino acid derivatives	4 (2.3%)
Polyketide	Discodermolide	4 (2.3%)
Raw Extracts	Compounds were not identified in mixture or were isolated as pure compounds	39 (22.5%)
Total		209

* The denominator used to calculate the percentage was the total number of articles (173); Because more than one type of compound can be reported in the same article, the total sum may be greater than 173 and 100%.

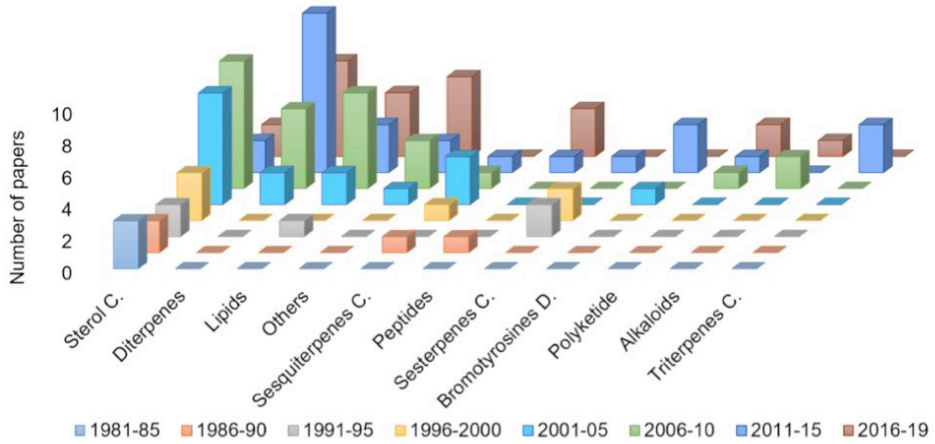

Figure 8. Trend of article publishing by type of Natural Products identified, by five-year periods (not including the UPR); C - compounds, D - Semisynthetic derivatives.

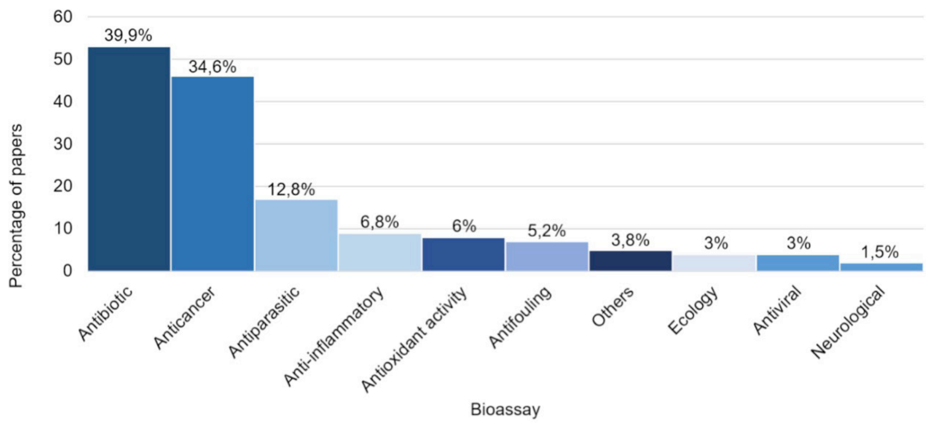

Figure 9. Distribution of publications by type of bioassays performed; Antibiotic: includes inhibition of quorum sensing, inhibition of biofilms, antimicrobial, antibacterial, antifungal and anti-tubercular activity; Anticancer: includes anticancer, antitumor, antimitotic, cytotoxic, antiproliferative and genotoxic activity; Antiparasitic: includes anti-malaria, anti-leshmanial, antiparasitic, anti-protease and anti-plasmodial activity; Anti-inflammatory: includes anti-inflammatory, degranulation, enzymatic elastase and MPO activity; Antioxidant: includes DPPH and ABTS activity; Antifouling: includes antiepibiotic activity; Ecology: includes allelopathic activity, toxicity, exudation, predation inhibition in aquarium, Others: includes inhibition of β glucosidase enzyme, ichthyotoxicity, insecticide and immunomodulatory activity; Antiviral: includes anti-herpes activity; Neurological: includes antinociceptive and muscle relaxation activity.

Methodology indicators

The workflow regarding natural products has different steps to isolate and identify secondary metabolites. In this methodology section, three levels were used for classification: raw extracts, putative identification in mixture (LC-MS and GC-MS), and isolated compounds. In the category, "Raw Extracts", 39 articles (22.5%) were found, whose bioassays had been conducted on crude extracts without any separation process. In the "Putative identification in mixture" category, 34 articles (19.7%) were found, in which compounds had been analysed and identified by LC-MS or LC-UV methodologies – these publications involved compounds such as lipids and sterols. Finally, in the "Isolated compounds" category, 100 articles (57.8%) were found, in which purification had been performed by chromatographic methods, and compound identification by spectroscopic methods (NMR, MS, IR, etc.) – in these publications, 238 new compounds were identified, and another 94 semi-synthetic products were obtained using the natural products as the starting material.

The next aspect considered was whether or not the papers included an evaluation of biological activity. This analysis noted that most of the studies (n=133; 76.8%) included bioassays, while 40 of the 173 articles (23.12%) did not carry out this type of analysis. According to the 10 categories described by [29], the most studied activities with regard to Colombian MNPs were: antibiotic (n=53; 39.9%), anti-cancer (n=46; 34.6%) and antiparasitic (n=17; 12.8%) (Figure 9). Compared with the global trend [2], it can be seen that, in Colombia, antibiotic bioactivity is the most studied activity, while worldwide it is ranked second in terms of importance, representing 13%. Anticancer activity, on the other hand, is the most important activity on a worldwide scale (56%), and in Colombia it represents 29.7% of the studies [2]. It is worth noting that in Colombia there have been no studies on cardioprotectors and neuroprotectors, which together represent 2% of the worldwide publications on this topic. Conversely, in Colombia, studies on antifoulants and antiparasitics are important, however these do not represent a significant percentage of studies worldwide.

Journal indicators

Journal citation indicators are used to evaluate the quality of scientific journals; however, their actual use and value is controversial [30]. In this study, they were used as an approximation to estimate the quality of the journals in which the MNPs articles with Colombian samples were published.

Table 5. Journals with the highest number of publications containing species collected from the Colombian territory and their citation indicators IF, h-5 and Median-5 (M-h5).

Journal	# of papers	CA*	IF	h5**	M-h5**
Journal of Natural Products	19	7	3,285	43	51
*Vitae******	13	13	0,259	6	10
Journal of Organic Chemistry	10	0	4,219	72	89
Tetrahedron Letters	9	2	2,683	48	72
Organic Letters	8	1	5,42	91	111
Tetrahedron	7	3	3,025	47	58
*Boletín del Instituto de Investigaciones Marinas y Costeras****	7	7	0	0	0
Marine Drugs	6	6	3,854	62	86
*Revista Colombiana de Química****	6	6	0	5	12
Biochemical Systematics and Ecology	5	5	1,170	18	22
Total	**90**	**56**			

*CA: Articles from Colombian research groups. **Values according to Google Scholar, accessed on June 10th 2020. ***Colombian journals. The data reported for each journal corresponds to the year of publication of the article with the best classification for this indicator.

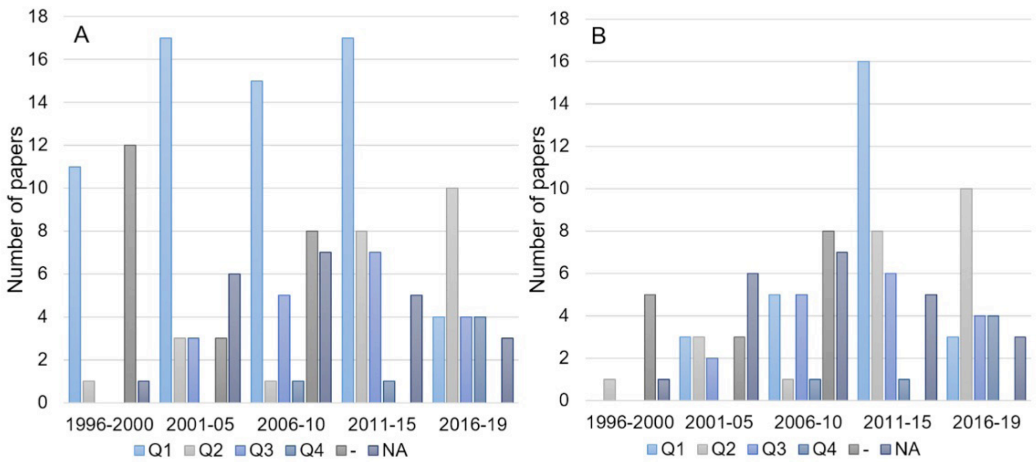

Figure 10. Total number of articles published, by five-year periods, ranked in quartiles according to Scimago: (A) Total of papers (B); Only Colombian groups' papers. Scimago ranks journals annually in quartiles, from Q1 to Q4, according to different quality criteria. This platform began its ranking in the year 1999, but here it was graphed from 1996 onwards to continue the traceability of the five-year periods. There are journals that do not provide publication data of all the years; when this was the case, the publication was coded with the symbol: "-". Several journals are not ranked by Scimago, and in this case the articles were coded as: "NA". If more than one category was applicable, the best one was selected.

Of the 173 articles analysed, most were published in foreign journals (n=129; 74.6%) and 25.4% (n=44) in Colombian journals. For articles with the participation of Colombian groups, the analysis showed that 64.8% (n=81) out of 125 articles had been published in foreign journals, indicating that Colombian scientists prefer to publish their results in these journals. Of the top 10 journals (Table 5), comprising those with the highest number of publications on organisms collected from Colombian seas, 7 were foreign and 3 were Colombian journals; the foreign ones have better classification values (IF, h-5 and M-h5) compared to the Colombian ones. The journals with the highest number of published articles on Colombian MNPs are: Journal of Natural Products; Vitae (Colombian journal); and Journal of Organic Chemistry; where both of these foreign journals have higher impact factors (IF), with most of their publications being by researchers from the University of Puerto Rico. The second Colombian journal with most publications (n=7), the "Boletín del Instituto de Investigaciones Marinas y Costeras", has not been classified by any of the 3 indicators used.

Regarding the visibility of the journals, the analysis considered whether they are indexed on Scimago, JCR and Google Scholar. It was observed that 64.7% (n=112), 60.1% (n=104) and 87.3% (n=151) of these journals are included on these platforms, respectively, showing the acceptable/low visibility of the journals selected by MNPs researchers. Regarding the quality of the journals, the Scimago ranking was used (Figure 10). The number of publications in Q1 journals is more expressive from 1996 to 2015, and Q2 journals appear more often in the last period analysed (2016-2019); on the other hand, the number of publications in low-ranked journals has increased through time (Figure 10A). When the analysis excluded articles without the participation of Colombian researchers, a change in the trend is observed. In this sense, the number of articles published in Q1 journals is not predominant but has increased over time, going from 3 articles in the 2001-2005 period to 16 articles in the 2011-2015 period; however, there was a decrease to 3 in the 2016-2019 period (Figure 10B). This could be explained by the change in the project financing policy, as previously discussed.

The research groups with the highest number of publications in Q1 journals are the UPR group (II) (37 papers) and the "Grupo de estudio y aprovechamiento de productos naturales marinos y frutas de Colombia" (I) of the UNAL (22 papers). In general, the papers with the participation of Colombian researchers are published in journals of less international visibility compared to papers published by foreign researchers working with Colombian samples. The results of this indicator show that, although the publication of articles in high-impact journals has increased, there are still challenges to overcome in order to achieve visibility for part of the scientific work in this area of study.

Table 6 displays the top 10 journals with the highest JCR-IF, also including the values of h-5 and median h-5. All the journals are foreign, none of them are Latin American (Table 6). These data also evidence that only 20 of the 57 articles published in these top-ranked journals have the participation of Colombian groups, indicating that articles published in high-impact journals are written chiefly by foreigner researchers. The average IF of the journals was 2.349 (range: 0.244 - 5.420), and when the UPR group was not considered, the average drops to 2.028 (0.244 - 4.659). This confirms that the UPR group published in journals with higher IF compared to the journals in which the Colombian groups published their papers. The publication of Colombian research groups in high-IF journals is an issue to address toward improving the visibility of their research.

Table 6. Top 10 most important journals, based on Impact Factor, in which Colombian MNPs samples were published.

Journal	TA*	CA**	IF***	H-5^{+}	M-h5ǂ
Organic Letters	8	1	5.420	91	111
Journal of Organic Chemistry	10	0	4.219	75	89
Marine Drugs	6	6	3.854	62	86
Marine Biotechnology	2	1	3.430	27	32
Pure and Applied Chemistry	1	0	3.386	25	42
Journal of Natural Products	19	7	3.285	43	51
Journal of Functional Foods	1	1	3,197	57	70
Journal of Supercritical Fluids	1	1	3,122	46	58
European Journal of Organic Chemistry	2	0	3.096	37	53
Tetrahedron	7	3	3.025	47	58
Total Items	**57**	**20**			

*TA: total articles published; **CA: Articles from Colombian research groups; ***IF: (Sci Journal); +,ǂH-5 and median-h5 (M-h5) in which articles with Colombian MNPs samples were published.

Article visibility indicators

To determine the visibility of the analysed articles, each article was searched in the following universal databases: Scopus, Scifinder, Web of Science, PubMed, and Google Scholar; in the Iberoamerican database Scielo; and in the specialised database MarinLit, to verify whether it was present or not in these databases, regardless of the previous search results with keywords (Table 1). Accordingly, of the 173 articles included in the analysis, 172 (99.4%) were indexed in Google Scholar, among them 4 were only present in the form of citations; 134 (77.5%) in Scopus; 127 (73.4%) in Scifinder; 103 (59.5%) in MarinLit; 94 (54.3%) in Web of Science; 67 (38.7%) in PubMed and 36 (20.2%) in Scielo. These data indicate that most of the articles are visible through Google Scholar, which is the largest database; while in more specific databases such as PubMed or Scielo the visibility is less expressive, since the former is specialised in health issues and the latter only includes Iberoamerican journals. Interestingly, because Marinlit is a database specialised in MNPs, a greater visibility of the publications would be expected; however, it has a percentage of no more than 59.5%, thus indicating a lack of relevance of the published papers.

The indexing trend of the 173 papers over time in the 4 databases with the largest number of referenced articles (Google Scholar, Scopus, Scifinder, and MarinLit) was also analysed. Between 1981 and 1995, the number of indexed articles with the participation of Colombian authors sustained a small and constant increase (Figure 11, those with the letter C). Since 1996, the number of indexed articles has grown significantly, with a steady slight increase in Google Scholar. The other databases, including MarinLit, have remained constant but with a slight downward trend. The results for the papers developed only by foreign groups (Figure 11, those with the letter F) show higher indexing over time in all 4 databases, including the one specialised in MNPs, i.e., MarinLit. Nonetheless, foreign scientific publications have decreased over time, whereas the indexing of articles produced by Colombian researchers has not been affected.

Another indicator of visibility for articles on MNPs is their citation in the research series reviews titled “Marine Natural Products” in the journal “Natural Products Reports” (NPR) of the Royal Society of Chemistry (Carroll, Copp, Davis, Keyzers, & Prinsep, 2020). These reviews are focused on articles that describe novel MNPs with relevant biological activities. Of the 173 articles, 75 (43.3%) were cited in the reviews. The number of articles referenced by this review shows a peak in 1996-2000 (n=20; 26.6% of the articles were referenced) and after that it decreased to 25% (Figure 12A). A similar behaviour is observed regarding the articles published only by Colombian groups (Figure 12B), with a maximum percentage of citations in the 1990s. Although the number of articles by Colombian researchers has been increasing gradually (Figure 12B), their visibility has not improved due to the fact that the percentage of articles cited in the NPR has decreased.

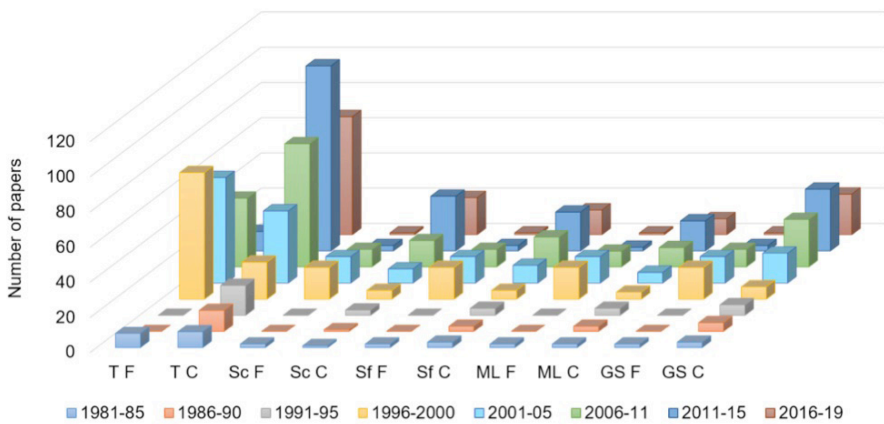

Figure 11. Timeline of the indexing of publications in the most important search engines, for Colombian (C) and foreign (F) research groups. Articles indexed by Sc F: Scopus for foreign groups; Sc C: Scopus for Colombian groups; Sf F: Scifinder for foreign groups; Sf C: Scifinder for Colombian groups; ML F: MarinLit for foreign groups; ML C: MarinLit for Colombian groups; GS F: Google Scholar for foreign groups; GS C: Google Scholar for Colombian groups. T F: Total articles for foreign groups; T C: Total articles for Colombian groups.

Table 7. Top 10 articles most cited in each database (Scopus, PubMed, Scifinder, Google Scholar, and Web of Science), year of publication and their reference.

Paper	Year	Number of citations in Scopus	Number of citations in PubMed	Number of citations in Scinder	Number of citations in Google Scholar	Number of citations in Web of Science
Rodríguez, A. D., & Ramírez, C. (2001). Serrulatane diterpenes with antimycobacterial activity isolated from the West Indian Sea whip Pseudopterogorgia elisabethae. Journal of Natural Products, 64(1), 100–102. https://doi.org/10.1021/np000196g	2001	77	6	76	83	72
Marrero, J., Rodríguez, A. D., Baran, P., Raptis, R. G., Sánchez, J. A., Ortega-Barria, E., & Capson, T. L. (2004). Bielschowskysin, a Gorgonian-derived biologically active diterpene with an unprecedented carbon skeleton. Organic Letters, 6(10), 1661–1664. https://doi.org/10.1021/ol049495d	2004	75	11	72	106	70
Rodriguez, A. D., Gonzalez, E., & Huang, S. D. (1998). Unusual terpenes with novel carbon skeletons from the West Indian Sea whip Pseudopterogorgia elisabethae (Octocorallia). Journal of Organic Chemistry, 63(20), 7083–7091. https://doi.org/10.1021/jo981385v	1998	73	4	70	68	-
Rodriguez, A. D., Ramírez, C., Rodiiguez, I. I., & Barnes, C. L. (2000). Novel terpenoids from the West Indian sea whip Pseudopterogorgia elisabethae (Bayer). Elisapterosins A and B: Rearranged diterpenes possessing an unprecedented cagelike framework. Journal of Organic Chemistry, 65(5), 1390–1398. https://doi.org/10.1021/jo9914869	2000	68	10	6	71	-
Rinehart, K. L., Kishore, V., Bible, K. C., Sakai, R., Sullins, D. W., & Li, K. I. M. (1988). Didemnins and tunichlorin: Novel natural products from the marine tunicate trididemnum solidum. Journal of Natural Products, 51(1), 1–21. https://doi.org/10.1021/np50055a001	1988	67	6	40	128	-
Tymiak, A. A., Rinehart, K. L., & Bakus, G. J. (1985). Constituents of morphologically similar sponges. Tetrahedron, 41(6), 1039–1047. https://doi.org/10.1016/s0040-4020(01)96471-3	1985	52	-	35	64	-
Rodríguez, A. D., & Ramírez, C. (2000). A marine diterpene with a novel tetracyclic framework from the West Indian gorgonian octocoral Pseudopterogorgia elisabethae. Organic Letters, 2(4), 507–510. https://doi.org/10.1021/ol991362i	2000	50	5	48	48	-
Rodríguez, I. I., Shi, Y. P., García, O. J., Rodríguez, A. D., Mayer, A. M. S., Sánchez, J. A., … González, J. (2004). New pseudopterosin and seco-pseudopterosin diterpene glycosides from two Colombian isolates of Pseudopterogorgia elisabethae and their diverse biological activities. Journal of Natural Products, 67(10), 1672–1680. https://doi.org/10.1021/np049802o	2004	49	9	49	69	42
Rodríguez, A. D., Shi, J. G., & Huang, S. D. (1998). Pinnatins A-E: Marine diterpenes of the rare gersolane class derived from a photochemically induced rearrangement of a conjugated 2,5-bridged furanocembrane precursor. Journal of Organic Chemistry, 63(13), 4425–4432. https://doi.org/10.1021/jo980256b	1998	43	-	43	44	-

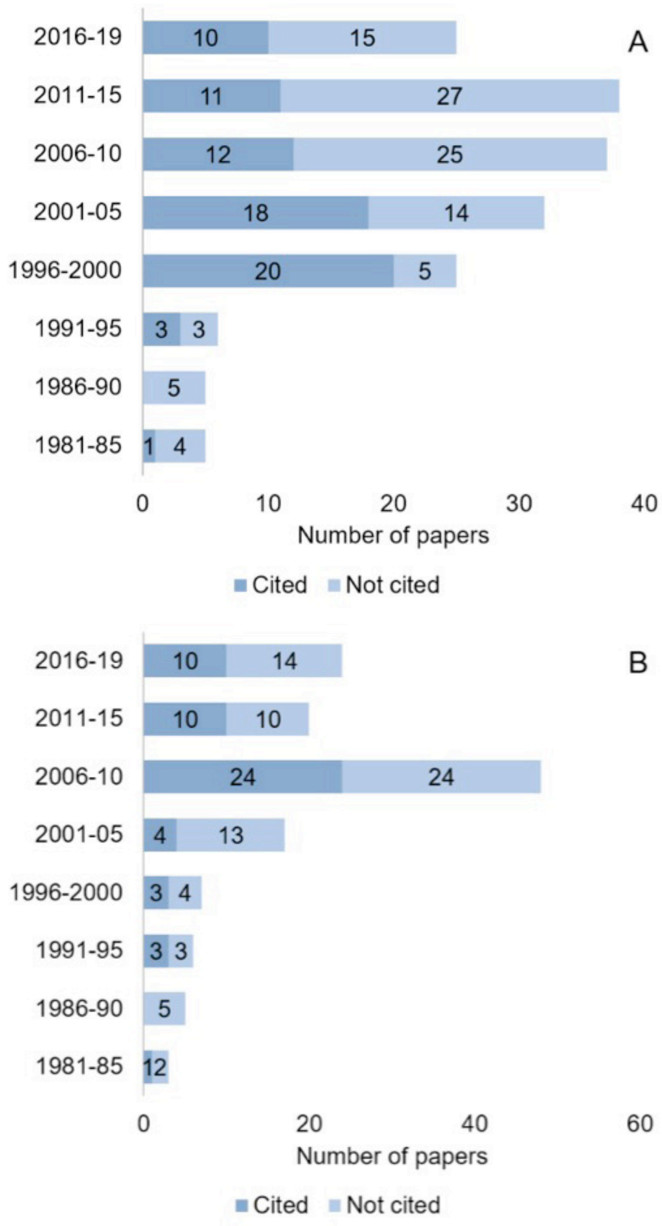

Figure 12. Articles cited in the Marine Natural Products research series review, by five-year periods. (A) Total papers. (B) Colombian groups' papers.

Table 7 shows the top 10 articles most cited in each of the databases (Scopus, PubMed, Scifinder, Google Scholar, and Web of Science), as well as the year of publication, the number of citations for each one, and their reference. Based on these results, it is interesting to note that the most cited articles correspond to products of the research group from the University of Puerto Rico, evincing the great impact that such publications have. The absence of papers by Colombian researchers indicates the lesser impact of Colombian publications. The most cited articles focused on the species *Pseudoptergorgia elisabethae* and *Pseudoptergorgia kallos*.

To better illustrate the impact of said publications, the number of citations for the entire scientific work on MNPs collected in Colombia per research group is summarised on Table 8. Surprisingly, among the top eight most cited research groups, only two are Colombian institutions and the remainder are foreign. The most cited group is the UPR (II), followed by the UNAL group "Estudio y Aprovechamiento de Productos Naturales Marinos y Frutas de Colombia" (I). The difference in number of citations is considerable and, in all cases, the UPR group is three times more than the Colombian group. This analysis also evinced that although some institutions, according to the analysis of the number of articles, are not visible, the number of citations evidenced that they have an important role in MNPs research.

Specific examples are "Instituto de Investigaciones Científicas Avanzadas y Servicios de Alta Tecnología, Centro de Estudios Biomédicos, Clayton" (XVI); "Department of Systematic Biology and Laboratories of Analytical Biology, Smithsonian Institution" (XVII); "Department of Chemistry, Chemistry Building, University of Missouri-Columbia" (XX); and "Center of Molecular and Behavioral Neuroscience, Universidad Central de Caribe" (XII).

Conclusions

Scientific publications on MNPs of Colombian origin have increased over time, as has the participation of Colombian research groups. In the last period studied, the number of publications presented a slight decline, possibly related to the loss of specific funding for marine science in the country. The interaction between the research groups identified is low, an aspect that should be improved. It is also necessary to strengthen the research on Pacific Ocean organisms, in addition to the exploration of several organisms, such as microorganisms. The lack of strong interactions among MNPs-specific research groups, and with other groups of other areas of knowledge is a gap to be addressed to allow for more robust studies that will provide greater visibility for the knowledge generated in Colombia. Finally, it is imperative to involve the productive sector in MNPs research so as to give an adequate value to Colombian marine resources.

Table 8. Research groups most cited in each of the databases (Top 5, for each database).

Research groups	Citations				
	Sc*	**PM****	**Sf*****	**GS+**	**WOS‡**
Department of Chemistry, University of Puerto Rico (II)	1482	175	1495	1924	732
Estudio y Aprovechamiento de Productos Naturales Marinos y Frutas de Colombia (I)	510	93	519	1018	481
Institute for Advanced Scientific Research and High Technology Services, Center for Biomedical Studies (XVI)	198	34	213	307	193
Department of Systematic Biology and Laboratories of Analytical Biology, Smithsonian Institution (XVII)	195	36	216	298	187
Department of Chemistry, Tokyo Institute of Technology (VIII)	174	13	183	251	94
Center of Molecular and Behavioral Neuroscience, Central University of the Caribbean (XII)	174	13	163	215	0
Department of Chemistry, University of Missouri (XX)	156	26	169	190	72
Departamento de Biología y Centro de Estudios en Instituto de Estudios en Ciencias del Mar – CECIMAR (IV)	145	21	132	345	136

*Scopus; **PubMed; ***Scifinder; +Google Scholar; ‡Web of Science.

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