Journal of Applied Biology & Biotechnology Vol. 12(2), pp. 48-61, Mar-Apr, 2024
Available online at http://www.jabonline.in
DOI: 10.7324/JABB.2024.159864

A bibliometric landscape of polyhydroxyalkanoates production from low-cost substrates by *Cupriavidus necator* and its perspectives for the Latin American bioeconomy

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ARTICLE INFO

Article history:
Received on: August 05, 2023
Accepted on: January 08, 2024
Available online: February 20, 2024

Key words:
Polyhydroxyalkanoates,
Cupriavidus necator,
Low-cost substrates,
Bioeconomy.

ABSTRACT

The replacement of petroleum-based plastics with biodegradable materials emerges as a potential solution to the environmental issues caused by the constant consumption of non-degradable plastic materials. Polyhydroxyalkanoates (PHA) are natural biopolymers produced by several bacteria species as an evolutive mechanism to store carbon and energy. Among these PHA-producing bacteria, the Gram-negative bacterium *Cupriavidus necator* has been studied as the model organism for PHA production due to its high accumulation capacity (up to 90% of dry cell weight). Nevertheless, the large-scale production of those biopolymers is still limited by the production costs, especially regarding the carbon source, which may represent up to 50% of the total cost of the PHA production process. For this study, a bibliometric analysis was conducted to investigate the trends in PHA production studies by *C. necator* with an emphasis on the use of low-cost substrates, in addition to the perspectives for this emerging industry in Latin America as a continent with access to significant biomass resources, agroindustry products, and byproducts. The Scopus and the Web of Science databases were used for data collection, and a total of 532 and 2995 articles were identified for the period between 1992 and 2022, and between 2000 and 2022, respectively.

ARTICLE HIGHLIGHTS

- Bibliometric analysis of PHA production from low-cost substrates by *C. necator* was carried out.
- Potential and available biomasses in LATAM are reported for PHA production.
- The most commonly low-cost carbon sources used to production of PHA by *C. necator* are waste oils and fats, sugar-rich residues, and derivatives.

1. INTRODUCTION

Bioeconomy has provided new technologies and business solutions to industries compared to the traditional and linear fossil-based production model [1]. Modern consumption habits have inevitably led to the growing generation of plastic waste and the production necessary to meet such demand. Conventional plastics derived from petrochemical monomers stand out for their mechanical properties, biological and chemical resistance, but these advantages for the industry unfortunately have been translated into a big environmental problem. In 2021, the annual production of petrochemical-based polymeric materials was 390.7 million tons per year [2]. Due to the large oil refinery capacity worldwide, monomers required to produce synthetic plastic materials are considered low-priced commodities with high-volume and high-demand transactions. Likewise, their physical properties, such as high mechanical strength, thermal stability, and resistance to physicochemical and biological degradation mechanisms, have turned plastics into a major pollutant with serious consequences for the environment and health [3,4]. An extensive number of studies in the past 20 years have shown the effects of plastics pollution in marine environments and freshwater ecosystems such as rivers, lakes, estuaries, and inland water [4,5]. The current generation of plastic waste exceeds in approximately 1% the production since some production from previous years incorporates the generation. At less 12% of plastic waste is mismanaged, leading to ocean inputs of 8 million tons per year, as reviewed by Albuquerque and Malafaia [6].

Bio-based biopolymers, especially biodegradable ones emerge as alternatives in many fields where plastics are currently used as an essential material [7]. However, the global production and market share of these biopolymers are still incipient, with a volume of 2.217 million tons per year in 2022, of which only 51.5% corresponds to biodegradable bioplastics [8]. By 2027, the total capacity forecast will

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be 6.3 million tons, distributed as 56.5% and 43.5% for biodegradable and bio-based/non-biodegradable bioplastics, respectively.

In the field of bioplastics, biologically compatible polymers are of great interest [6,9,10]. The so-called biodegradable plastics can be assimilated by microorganisms in short periods (18 months - 2 years), under appropriate environmental conditions such as temperature, pH, humidity, and nutrient supply [11]. According to review by Albuquerque and Malafaia [6], there are several types of commercially available biodegradable plastics, such as polyhydroxyalkanoates (PHA) and polylactates (PLA), as well as various blends of biopolymers. Among the bioplastics, PHA stands as one of the most promissory materials for reaching industrial production and massive commercialization in the mid-term due to its characteristics and high performance [12].

PHA are biopolymers produced intracellularly by various organisms such as archaea, bacteria, yeast, algae, plants, and their recombinant forms. These biopolymers are bioaccumulated under limited conditions of nitrogen and in excess of carbon source diverting the metabolism towards carbon accumulation as energy reservoirs [13]. *Cupriavidus necator* is a Gram-negative bacterium among the most studied and employed for PHA synthesis due to the ease of cultivation and its ability to accumulate higher amounts of PHA from renewable carbon sources such as glucose, fructose, and glycerol [14,15]. This bacterium has been given various names over time, including *Hydrogenomonas eutropha, Alcaligenes eutrophus, Ralstonia eutropha,* and *Wautersia eutropha* [16]. At present, more than 90 genera of microbial species with the capacity to accumulate PHA are reported in the literature, as reviewed by Albuquerque and Malafaia [6].

Currently, the PHA industrial production is not profitable compared to that of synthetic polymers, as reviewed by Kumar *et al*. [17]. Several factors hamper the production cost of PHA, such as the nature and precedence of the carbon source, the cultivation cost, the productivity of the process, the efficiency of the metabolic machinery in the biosynthesis and the further downstream processing [18,19]. The use of inexpensive and easily assimilable substrates, as well as microorganisms with high PHA synthesis capacity, may contribute to improving the gross margin of PHA production [17]. In this sense, (agro)industrial by-products/waste compounds such as glycerol, waste vegetable oils, animal fats, wastewater streams with high organic content, and sugar-rich materials such as molasses, lignocellulose, whey, and starch, as well as mixtures of these feedstocks, are envisioned as suitable low-cost substrates for PHA production [20-22]. Alves *et al*., recently reviewed PHA-producing companies and their global production according to the substrates employed [23]. Several investigations have focused on the search for alternative substrates [10,24,25], identification of synthesis pathways [26], reconstruction of genome-scale models [27,28], and PHA recovery methods [29-31] that enable efficient and economically feasible PHA production.

Given the high relevancy and worldwide interest in developing the large-scale production of PHA, there is a high volume of scientific publications related to PHA, which difficult to get an appropriate glance at the main/recent findings on the topic. Bibliometric analysis is a useful tool for understanding the evolution, growth, and prospects of a research area. In addition, bibliometric analysis allows identifying the connection between subjects and even interdisciplinary collaborations over time, contributing the researchers to get insights into topics of global interest. Furthermore, bibliometric analysis can be used to find innovative information that explains/supports recent trends in new processes or applications. In the case of PHA production, some systematic reviews are available on specific topics such as genetic engineering tools for PHA production using inexpensive carbon sources for potential large-scale applications [32], continuous cultivation processes for PHA production [33], carbon waste streams from (agro) industrial for a cost-effective and sustainable PHA production [34], regulation of PHA synthesis [35], volatile fatty acids as carbons sources for PHA production [36], lignocellulosic feedstocks for PHA production [37], rapid quantification of intracellular PHA [38], among others. However, bibliometric research analysis of studies on PHA production is still lacking.

In this study, a bibliometric analysis was carried out to investigate the trends of the PHA production by *C. necator* aimed to provide a clear perspective on the current research landscape, highlighting renewable and low-cost carbon sources. In addition, the results were used to explore the PHA bioeconomy ecosystem in Latin America.

2. MATERIALS AND METHODS

2.1. Database Selection

Data search and collection were performed in the Scopus and WOS databases since both are among the largest databases of peer-reviewed literature worldwide in the field of science, technology, etc. These databases allow for the use of Boolean operators, leading to the design of a comprehensive search query. In addition, Scopus and the WOS allow exporting bibliometric data into Excel® and text format, respectively, which are suitable for further analysis and systematic scientific mapping.

2.2. Search Strategy and Bibliometric Indicators

The search query was designed in two search topics joined by the Boolean operator "AND". The first topic was "PHA." While the second topic was *H. eutropha, A. eutrophus, C. necator, W. eutropha,* and *R. eutropha*, but all the terms were joined by the Boolean operator "OR," to include all the names of *C. necator* over time.

The search strategy included terms in the article title, abstract, and keywords as described elsewhere [39,40]. The document type was constrained only to articles (i.e., other document types such as letters, editorials, proceedings, and books were excluded), and VOSviewer 1.6.18 was used for visualization and data analysis [41]. All searches were done on March 14, 2023.

For the analysis of the carbon source used to produce PHA, the first one thousand author keywords with the greatest total link strength were analyzed, and the nodes related to *C. necator* and carbon sources were selected for the bibliometric network mapping.

Search

(TITLE-ABS-KEY (PHA) AND TITLE-ABS-KEY ("*H. eutropha*") OR TITLE-ABS-KEY ("*A. eutrophus*") OR TITLE-ABS-KEY ("*C. necator*") OR TITLE-ABS-KEY ("*W. eutropha*") OR TITLE-ABS-KEY ("*R. eutropha*")) AND (LIMIT-TO (DOCTYPE, "ar")).

Database: Scopus. Timespan: 1992 - 2022. 532 records were retrieved.

Database: Web of Science (WOS). Timespan: 2000 - 2022. 2995 records were retrieved.

In all studies, a screening of retrieved articles was performed to exclude duplicates. Bibliometric networks were designed to contain between 40 and 60 nodes for better results visualization. The volume and growth

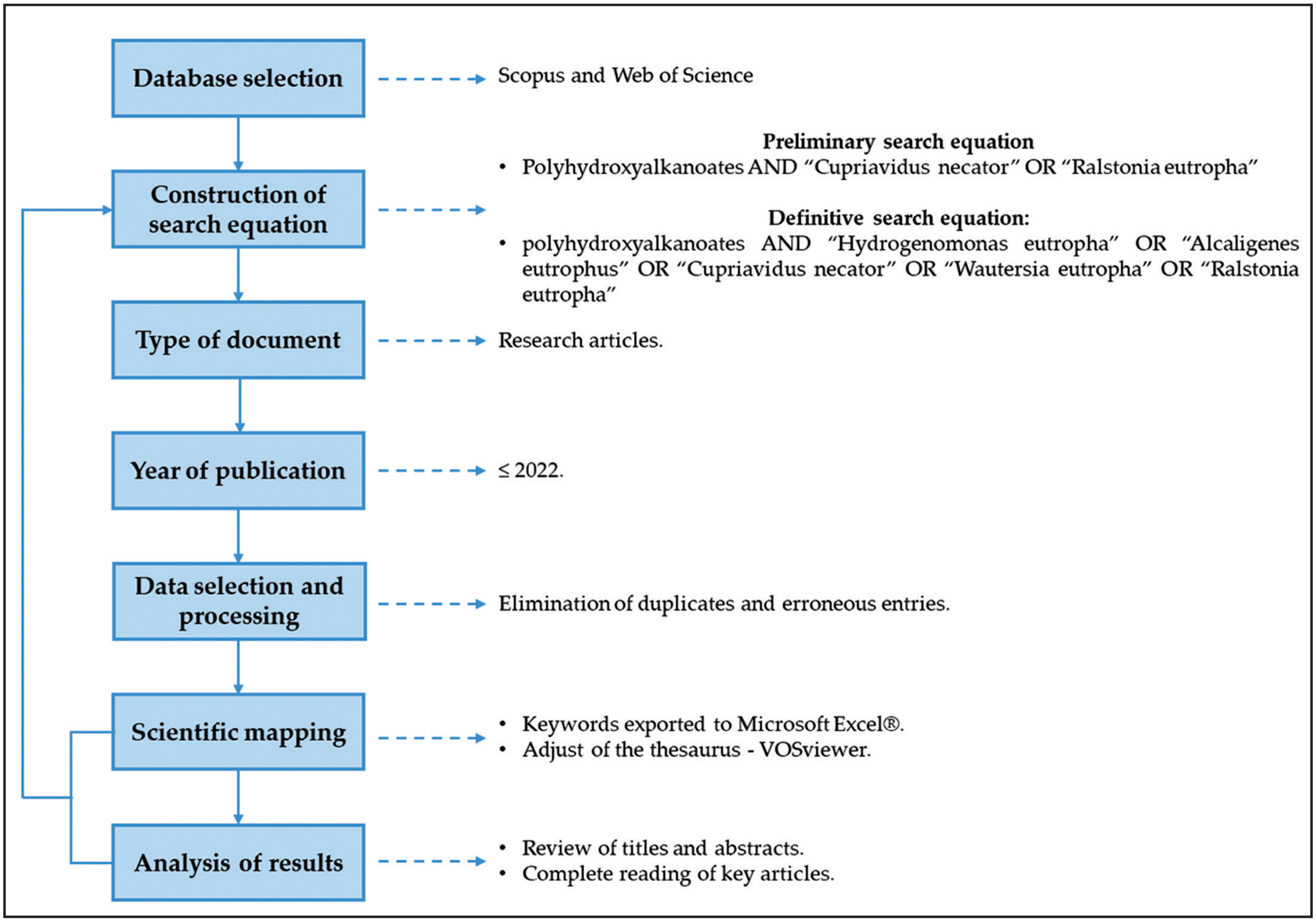

Figure 1: Methodology flowchart for bibliometric analysis.

of publications, subject areas, top 10 leading countries, institutions and cited papers, co-occurrence keyword network visualization, and co-occurrence keyword overlay visualization analysis were the bibliometric indicators evaluated in this study. Figure 1 represents the methodology described and used in this study.

3. RESULTS AND DISCUSSION

3.1. Evolution of Research Literature Related to PHA Production by *C. necator*

Fulfilling the search criteria for the selected databases, a total of 532 articles were identified in Scopus between 1992 and 2022, while 2995 articles were identified in WOS between 2000 and 2022. Figure 2 shows the evolution of the number of publications per year, showing an increase in the number of publications from 2010 onwards in both databases. The interest in bioplastics emerged from the global concern about the environmental issues of plastic waste and the need for reducing petroleum dependence [10]. The increase in publications on the topic from 2010 onwards correlates with the appearance of the first policies on bioeconomy and the increase in the funding for bioeconomy-related topics [42]. In addition, the results indicated that the studies on this topic have been conducted mainly in the last two decades (from 2000 onwards), since the first reports on PHA production optimization and genetic engineering of *C. necator* date back to the early 2000 decade. The results and discussion may be presented separately, or in one combined section, and may optionally be divided into headed subsections.

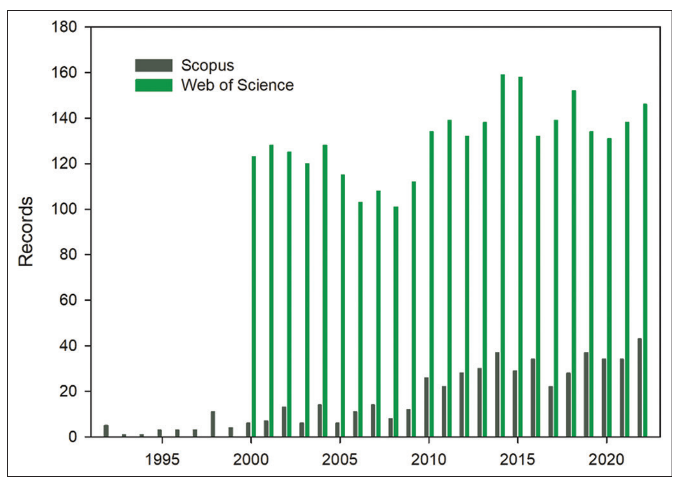

Figure 2: Evolution of research articles related to polyhydroxyalkanoates production by *Cupriavidus necator* during 1992–2022 and 2000–2022 by using the Scopus and the Web of Science databases, respectively.

3.2. Most Productive Countries and Research Institutions Worldwide in the Scientific Literature on PHA Production by *C. necator*

The Scopus and WOS databases show that the studies on PHA production by *C. necator* have been carried out in Asia (260 and 1181 papers), Europe (75 and 726 papers), North America (71 and

Table 1: Top 10 most productive research countries worldwide on the topic of PHA.

Database	Country/Region	Number of publications
Scopus	Japan	83
	United States	71
	South Korea	58
	Malaysia	48
	China	47
	Germany	46
	Brazil	30
	United Kingdom	29
	Russian Federation	26
WOS	Germany	563
	United States	452
	Japan	401
	China	282
	South Korea	203
	England	163
	India	159
	Malaysia	136
	France	113
	Brazil	98

PHA: Polyhydroxyalkanoates, WOS: Web of Science

Table 2: Top 10 most productive research institutions worldwide on the topic of PHA production.

Database	Research Institution	Number of publications
Scopus	Tokyo Institute of Technology	45
	Universiti Sains Malaysia	38
	Siberian Branch, Russian Academy of Sciences	23
	Biophysics Institute of the Siberian Branch of the RAS	23
	Massachusetts Institute of Technology	18
	Tsinghua University	18
	Westfälische Wilhelms-Universität Münster	16
	Riken	16
	Korea Advanced Institute of Science and Technology	15
WOS	Tokyo Institute of Technology	138
	University Of Munster	124
	Universiti Sains Malaysia	103
	Humboldt University of Berlin	99
	Riken	95
	Technical University of Berlin	95
	Helmholtz Association	76
	Centre National de la Recherche Scientifique CNRS	73
	Chinese Academy of Sciences	68
	Udice French Research Universities	61

PHA: Polyhydroxyalkanoates, WOS: Web of Science

452 papers), and South America (30 and 98 papers), respectively. In addition, Japan and Germany are the leader with 83 and 563 papers (according to Scopus and WOS) equivalent to 15.6% and 18.7% of the world's scientific production for the period evaluated [Table 1], followed by the United States (13% and 15%), respectively. Of the total number of countries reported in the mentioned databases, most publications are by authors with affiliations from European and Asian countries [Table 2]. The above is also consistent with the most cited papers in this field as shown in Table 3.

In the top 10 countries, Brazil is the only South American country publishing in this area of knowledge with 30 and 98 papers in Scopus and WOS, respectively [Table 1]. For the period studied, other Latin American countries such as Argentina and Colombia are only in the 27th and 28th position with 5 papers each in Scopus, and 30th and 40th position with 31 and 9 papers, respectively, in WOS. This indicates that more work needs to be done in this research field, but above all that Latin American countries establish policies aimed at promoting and strengthening research.

Likewise, when reviewing the scientific production of PHA by *C. necator* from research institutions, it is evident that European and Asian institutions are the majority in the top 10. The exception is the Massachusetts Institute of Technology (USA), which occupied the fifth position [Table 2]. This shows also that they are the countries with the highest investment in this scientific research field in the world.

3.3. Main Research Approaches on PHA Production by *C. necator*

Figure 3 shows the top 10 areas of knowledge related to published studies on PHA synthesis using *C. necator*, in both databases. In this regard, and based on WOS, the main areas were (i) biotechnology applied microbiology, (ii) microbiology, and (iii) biochemistry molecular biology, and concentrated 43.2%, 24.6%, and 16.5% of the records, respectively. In the case of Scopus, the main areas were (i) biochemistry, genetics, and molecular biology (ii) immunology and microbiology, and (iii) chemical engineering, and contributed 61.2, 43.8, and 40.7% of the indexed documents, respectively.

The two areas of knowledge with the most publications and cited studies in the databases consulted show that PHA production by *C. necator* is being worked on and developed in the basic sciences with approaches related with submerged cultures by using low-carbon sources and at the same time studies in the line of metabolic and genetic engineering [Tables 3 and 4].

All the papers listed in Table 3 are research articles that have been the basis for supporting recent research in the field of PHA by *C. necator*. The most cited paper in Scopus was authored by Cavalheiro *et al*. [43] and published in 2009. This work describes PHB production by *C. necator* DSM 545 strain using a byproduct from the biodiesel industry (glycerol) as a carbon source. The authors explored two strategies that seek to enhance PHA production: (i) High-density cultivation to increase the volumetric productivity of PHA and (ii) the use of low-cost carbon sources. In WOS, the second paper most cited was authored by Pohlmann and collaborates [44], and published in 2006. The authors reported the complete genome sequence of the two chromosomes of *C. necator* H16. This paper provides an analysis that has undoubtedly been the basis for researchers to continue to explore the biotechnological potential of this microorganism and at the same time to understand its metabolic diversity.

Table 3: Top 10 highest cited papers on the topic of PHA production according to Scopus.

Title	Year	Journal	Citations number	References
Poly (3-hydroxybutyrate) production by *Cupriavidus necator* using waste glycerol	2009	Process Biochemistry	326	[43]
Environmental analysis of plastic production processes: Comparing petroleum-based polypropylene and polyethylene with biologically-based poly-β-hydroxybutyric acid using life cycle analysis	2007	Journal of Biotechnology	310	[45]
Environmental life cycle comparison of PHA produced from renewable carbon resources by bacterial fermentation	2003	Polymer Degradation and Stability	293	[46]
High yield production of PHA from soybean oil by *Ralstonia eutropha* and its recombinant strain	2004	Polymer Degradation and Stability	260	[47]
Production of PHA from waste materials and by-products by submerged and solid-state fermentation	2009	Bioresource Technology	230	[48]
Metabolic engineering of *Escherichia coli* for the production of polylactic acid and its copolymers	2010	Biotechnology and Bioengineering	224	[49]
Multiple β-ketothiolases mediate poly(β-hydroxyalkanoate) copolymer synthesis in *Ralstonia eutropha*	1998	Journal of Bacteriology	189	[50]
Efficient production of PHA from plant oils by *Alcaligenes eutrophus* and its recombinant strain	1998	Applied Microbiology and Biotechnology	184	[51]
PHA synthase activity controls the molecular weight and polydispersity of polyhydroxybutyrate *in vivo*	1997	Nature Biotechnology	178	[52]
Microbial utilization and biopolyester synthesis of bagasse hydrolysates	2008	Bioresource Technology	168	[53]

PHA: Polyhydroxyalkanoates

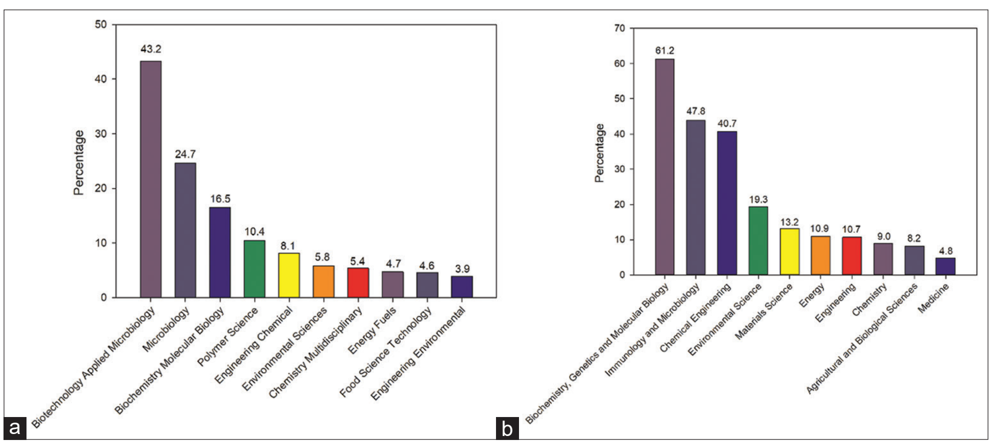

Figure 3: Contributions in polyhydroxyalkanoates production by *Cupriavidus necator* per area of knowledge (a) between 2000 and 2022 in Web of Science (b) between 1992 and 2022 in Scopus.

3.4. Bibliometric Networks of Production of PHA by *C. necator*

Figures 4 and 5 shows the bibliometric networks of research topics related to PHA production by *C. necator* by using Scopus and WOS, respectively. The network visualization of Scopus contains 32 nodes grouped into 9 clusters [Figure 4a] while the WOS has 38 nodes grouped into 7 clusters [Figure 5a]. Figures 4b and 5b show which topics have focused the research over time, respectively. The clusters of Figure 4a (color-coded) can be classified as follow: cluster 1 (red color): fermentation, optimization, biodiesel; cluster 2 (green color): molecular weight, palm oil, *C. necator*, recovery, recombinant *Escherichia coli*; cluster 3 (blue color): bioconversion, biosynthesis, PHA, characterization; cluster 4 (yellow color): *Escherichia coli*, metabolic engineering, synthetic biology, *Pseudomonas putida*, PHB; cluster 5 (purple color): bioplastic, biorefinery, levulinic acid; cluster 6 (magenta blue color): copolymer, pha synthase, substrate specificity; cluster 7 (orange color): PHBV, volatile fatty acids; cluster 8 (brown color): biodegradable plastics and cluster 9 (pink color): β-oxidation.

The information retrieved from WOS displays the clusters as follows: cluster 1 (red color): PHBV, biodegradable plastics, activated sludge, volatile fatty acids, fed-batch fermentation; cluster 2 (green color): bacteria, biodegradation, bioremediation, hydrogen, hydrogenase; cluster 3 (blue color): *Bacillus megaterium*, glycerol, fermentation, optimization, characterization; cluster 4 (yellow color): molecular weight, palm oil, substrate specificity; cluster 5 (purple color): biodegradable polymer, PHBHHX, *P. putida*; cluster 6 (magenta blue color): bioplastic, biorefinery, recovery; and cluster 7 (orange color): *Escherichia coli*, metabolic engineering, synthetic biology [Figure 5a].

Table 4: Top 10 highest cited papers on the topic of PHA production according to WOS.

Title	Year	Journal	Citations number	References
Water splitting-biosynthetic system with CO_2 reduction efficiencies exceeding photosynthesis	2016	Science	571	[54]
Genome sequence of the bioplastic-producing "Knallgas" bacterium *Ralstonia eutropha H16*	2006	Nature Biotechnology	424	[44]
Bacterial respiration: a flexible process for a changing environment	2000	Microbiology-SGM	424	[55]
Metabolic engineering of *Saccharomyces cerevisiae* for the production of n-butanol	2008	Microbial Cell Factories	365	[56]
Molecular analysis of the copper-transporting efflux system CusCFBA of *Escherichia coli*	2003	Journal of Bacteriology	365	[57]
Taxonomy of the genus Cupriavidus: a tale of lost and found	2004	International journal of systematic and evolutionary microbiology	368	[58]
Producing microbial PHA biopolyesters in a sustainable manner	2017	New Biotechnology	308	[59]
Poly (3-hydroxybutyrate) production by *Cupriavidus necator* using waste glycerol	2009	Process Biochemistry	286	[43]
Production of isoprenoid pharmaceuticals by engineered microbes	2006	Nature Chemical Biology	277	[60]
The crystal structure of an oxygen-tolerant hydrogenase uncovers a novel iron-sulphur centre	2011	Nature	276	[61]

PHA: Polyhydroxyalkanoates, WOS: Web of Science

In summary, and considering the information retrieved from both databases, we consider highlighting the inexpensive carbon sources for PHA production, and their relationship with the Latin American Bioeconomy.

3.5. Carbon Sources for PHA Production

The main barrier to the large-scale production of PHA is the high cost of the carbon source used, representing up to 50% of the total cost of the bioplastic. Therefore, recent research has included the search for low-cost raw materials as a priority, including raw materials from (agro)industrial by-products, as well as renewable sources, which guarantee stable and cost-effective production over time [62].

Figure 6 shows the bibliometric networks of carbon sources used in the production of PHA by *C. necator* for the periods 1992-2022 and 2000-2022 by using Scopus [Figure 6a] and WOS [Figure 6b] databases, respectively. A review of the networks over time shows that the first carbon sources used to produce PHA by *C. necator* were invert sugars, organic acids, activated sludge, among others. These studies date back to the year 2000. For the years 2010–2015, the production of PHA is centered on waste oil, oleic acid, waste glycerol, and from 2020, the trend is to use carbon sources such as vinasse, sugarcane molasses, fruit residues, CO_2, starchy and vegetable oils.

One of the great current efforts in the field of research on PHA production is the tireless search for rational alternatives to reduce the production costs of these biopolymers. Carbon sources from agro-industrial, domestic, and industrial wastes are currently the subject of study in most of the research related to PHA, as reviewed by Guleria *et al*. [62]. In this section, the carbon sources most used in the production of PHA by *C. necator* are discussed, considering the results of the bibliometric analysis [Figure 6].

3.5.1. Fat and oils residues

As the research shows, there is currently a great interest in the use of waste fats and oils as raw materials to obtain new value-added products. The generation of waste from the meat industry worldwide represents 20% of the total waste generated by the food industry. As a result, animal fat is being valorized to produce various products, including PHA, as a result of the waste management policies of many countries and the interest of the scientific community in optimizing resources and reducing environmental impact [63].

Fats obtained from different by-products of the meat industry were used to obtain the copolymer poly(hydroxybutyrate-co-hydroxyhexanoate) [P(HB-co-HHx)], using *R. eutropha* Re2058/pCB113. Initially, the by-products of this industry were subjected to either mechanical or enzymatic pre-treatment. Then, the fat was obtained by means of a thermo-pressure hydrolysis process at a temperature of 130–180°C and pressure of 3–20 bars, followed by a separation phase. To obtain the polymer, they used pork fat, fish fat, pork fat/protein emulsion, pork mineral-fat-mixture, pork fat-greaves, and canola oil as carbon sources. The authors report an accumulation of 90% of the polymer with a HHx content of 12%–26 mol% [64]. Gutschmann *et al*. [65], using the same strain, employed animal fat to produce P(HB-co-HHx). For the use of fat as a carbon source they carried out thermal liquefaction, using a 150 L pilot scale double jacketed feeding system, employing continuous feeding. The laboratory scale cultures yielded results of 80% PHA accumulation and 17 mol% HHX content. Riedel *et al*. [66] evaluated of production of PHA using low-quality and poorly consumable animal fats after an emulsification strategy. The authors conducted cultivations of the wild-type *R. eutropha* strain H16 for PHB production and also cultivations of the recombinant strain Re2058/pCB113 for the production of P(HB-co-HHx) copolymer. An accumulation of 79–82% PHB was achieved with wild-type strain while recombinant strain reached 49–72% (w/w) of PHA per CDW with an HHx content of 16–27 mol%.

Our search also showed that waste oils are low-cost sources of carbon to produce PHA. Indeed, many research reporting the use of olive oil waste effluent used cooking oil, palm oil, coffee waste oil, jatropha oil, and other oils [62,67-70]. Coffee waste is also an inexpensive substrate containing fatty acids. Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) was produced in engineered strain *C. necator Re2133* overexpressing

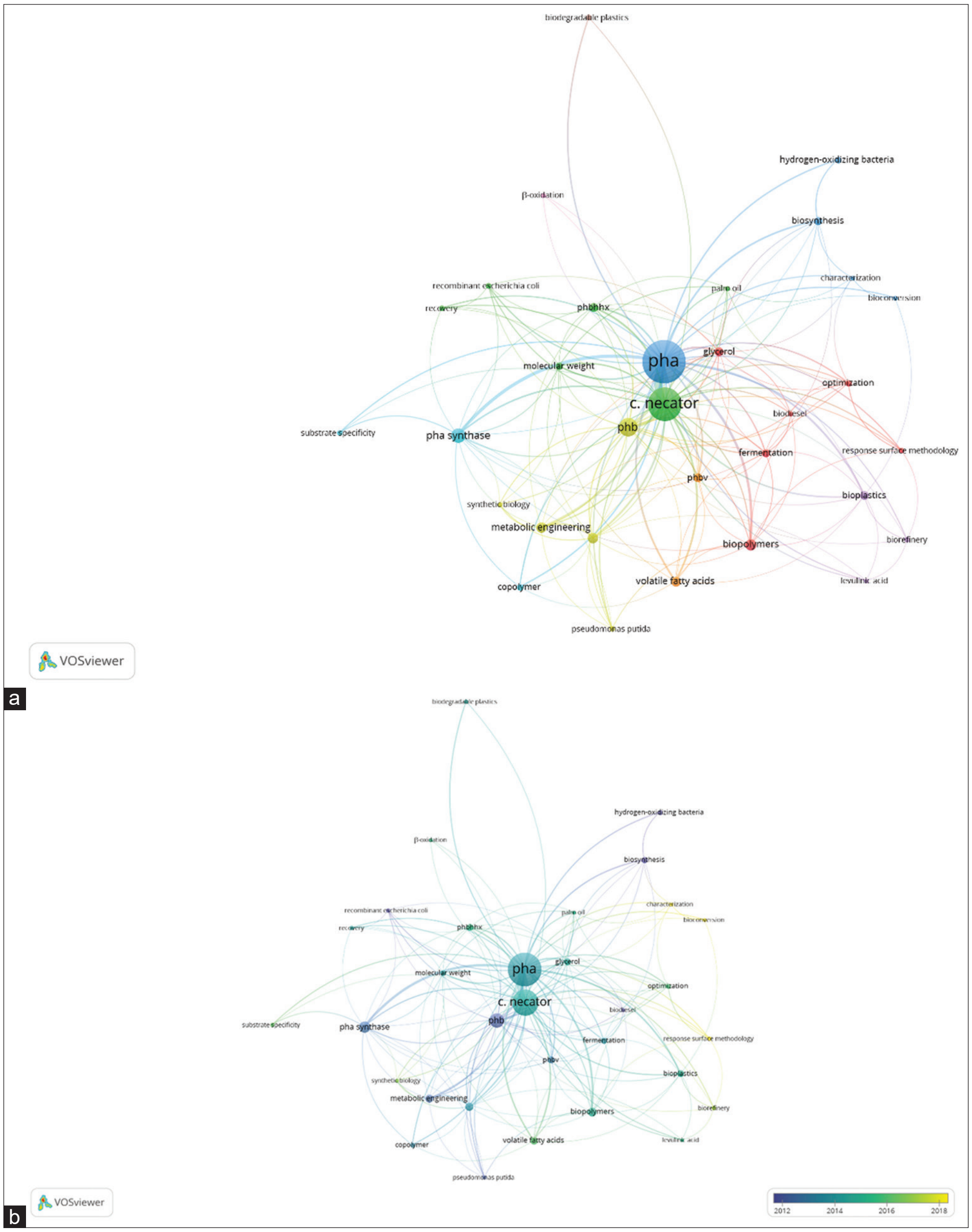

Figure 4: Bibliometric network of studies related to polyhydroxyalkanoates production by *Cupriavidus necator* between 1992 and 2022 in Scopus (a) Network visualization of the research-topic map (b) Overlay visualization of the research-topic map. The minimum number of occurrences of a keyword is 5.

(R)-specific enoyl coenzyme-A hydratase (*phaJ*) and PHA synthetase (*phaC2*) with deletion of acetoacetyl Co-A reductases (*phaB1, phaB2, and phaB3*) from coffee waste oil. PHA copolymer yield was 69% and was obtained with a coffee oil concentration of 1.5% and C/N ratio of 20. In addition, the PHA accumulation PHA consisted of HB (78 mol%) and HHx (22 mol%) [67].

Glycerol is another residual carbon source from oil processing, which is used in the synthesis of PHA. Indeed, PHA of different compositions was synthesized by using glycerol as a carbon substrate. In that work, PHB was effectively synthesized by *C. eutrophus B-10646* (a patented engineered strain of *C. necator*) in fed-batch cultivations with purity degrees ranging 82–99%, yielding a maximum of 78% polymer accumulation [71]. Furthermore, tung oil, a natural oil obtained from the seeds of the tung tree, which is used industrially to treat wood because of its high strength, was used as a carbon source using the *R. eutropha* Re2133/pCB81 strain to produce the terpolymer P(3HB-co-3HV-co-3HHx) [72]. Furthermore, the authors also reported that the oil coating on the surface of the PHA films had antioxidant activity. This bioactive PHA may be expanded to medical field applications.

3.5.2. Sugar-rich residues and derivatives

The world sugar industry produces roughly 70 million tons of molasses per year. Despite it being considered a byproduct of sugar production, its world trade is consistently decreasing due to the valorization activities on site. Bioplastics production is also an interesting alternative for sugar waste valorization. Currently, research on engineered PHA producers from sugar byproducts is still low. *C. necator* has a deficient utilization of simple sugars as a carbon source for PHA production. Therefore, some engineered strains have been constructed to allow the assimilation of simple sugars as a substrate in the production of

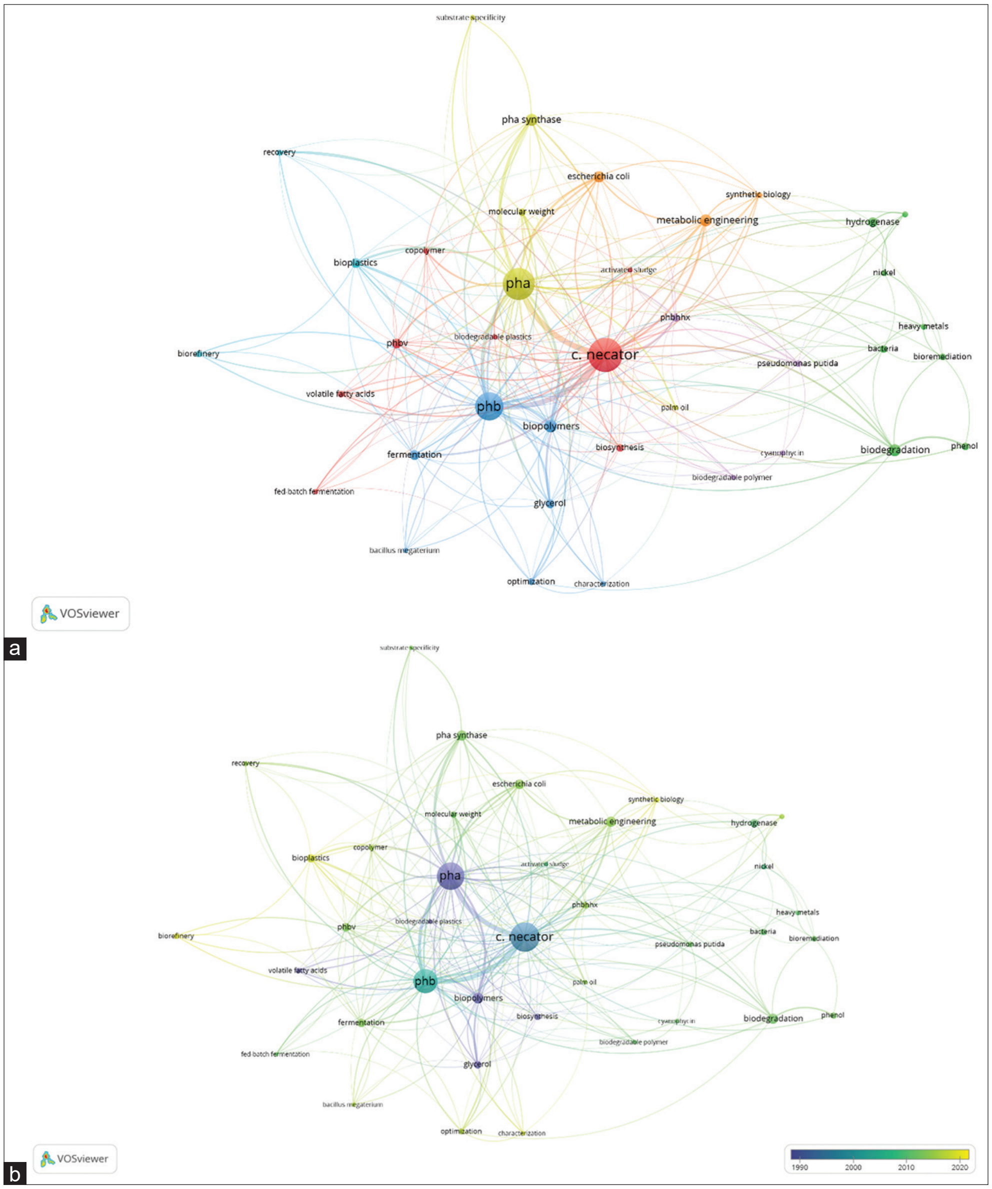

Figure 5: Bibliometric network of studies related to polyhydroxyalkanoates production by *Cupriavidus necator* between 2000 and 2022 in Web of Science (a) Network visualization of the research-topic map (b) Overlay visualization of the research-topic map. The minimum number of occurrences of a keyword is 15.

PHA. Recombinant strains of *C. necator* expressing genes *phaC*1437 from *Pseudomonas* sp. 6-19, *pct*540 from *Clostridium propionicum, sac* from *Mannheimia succinici producens* and *ldhA* from *E. coli* can produce poly (3-hydroxybutyrate-colactate) using sucrose as the sole carbon source [73].

The pathway for sucrose utilization was introduced in an engineered *C. necator* by introducing the *sacC* gene encoding the *β-fructofuranosidase* from *M. succiniciproducens.* The enzyme hydrolyzes sucrose into glucose and fructose and PHB yield reached 73% in cultivations with 20 g/L sucrose concentration. The same strain was cultivated using sugarcane molasses pre-treated with activated carbon as the carbon source to produce PHB and poly(3-hydroxybutyrate-co-lactate). The final PHB content achieved was 82.5% in batch fermentations [74].

Sugar-rich hydrolysates as inexpensive carbon sources have been also used for PHA production. Strains of *C. necator* have been used to synthesize PHB from wheat bran hydrolysates [75]. Likewise, recombinant strains of this same bacterium have been engineered to metabolize arabinose, by heterologous expression of a set of *E. coli* genes [76].

C. necator H16 and *C. necator* 5119 strains were co-cultured with *Bacillus subtilis* since it is a sucrose hydrolyzing organism resulting in 45% PHA production and propionic acid, which is a precursor for the hydroxyvalerate monomeric unit. Thus, the microbial consortia produced 66% poly(3-hydroxybutyrate-co-3-hydroxyvalerate) having 16 mol% hydroxyvalerate, showing that co-culture strategy allows overcoming the requirement of a previous strain engineering for sucrose utilization in PHA production [77].

Vinasse was also used as a basal medium for PHB production with *C. necator* L359PCJ, which uses glycerol from vinasse as a carbon source rather than residual sugars. Experiments in CSTR bioreactors using a medium concentrated vinasse based produced a PHB content

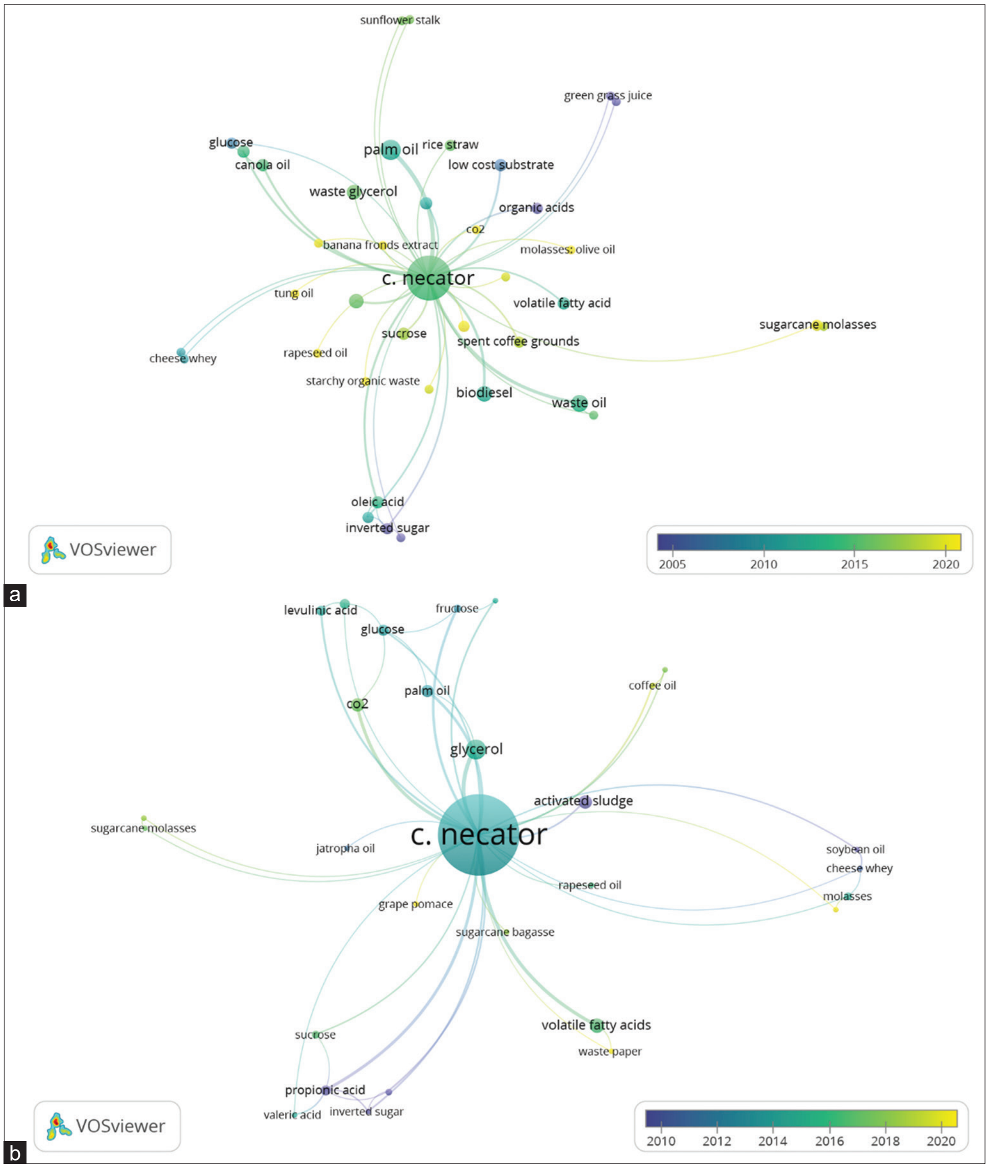

Figure 6: Overlay visualization of the research-topic map of studies of *Cupriavidus necator* related to carbon source to produce polyhydroxyalkanoates (a) Scopus and (b) Web of Science. The minimum number of occurrences of a keyword is 1.

of 66.3% [78]. Recently, *C. necator B-10646* was grown on sugar beet molasses previously hydrolyzed with β-fructofuranosidase, converting 89% of the sucrose (88.9%) into glucose and fructose. In that case, the maximum PHB content reached was 80% [79].

Starch is a high-quality glucose source with high availability and low cost. *C. necator* DSM 545 has been reported as unable to grow on starch. To overcome this limitation, a recombinant strain was constructed expressing glucodextranase *G1d* from *Arthrobacter globiformis I42* and the α-amylase *amyZ* from *Zunongwangia profunda* SM-A87. PHA yields were 34, 52, and 63% with purple sweet potato waste, broken rice, and raw corn starch, respectively [80]. Similar results were obtained in the *R. eutropha* DSM 545 strain using simultaneous saccharification and fermentation along with the addition of commercial amylases [81]. Furthermore, PHA production using cassava starch hydrolysate using *C. necator* KKU38 cultivated under N-limited conditions produced 61.60% of PHB. Cassava flour hydrolysates were also used in the cultivation of *C. necator* H16 yielding a PHA accumulation of 64% [82].

3.6. Perspectives for the Latin American Bioeconomy

Currently, green innovativeness is considered a significant component of economic progress, environmental sustainability, and improving wellness levels [83]. For the period studied, the results showed the global collaboration network of the PHA scientific ecosystem. Clearly, Germany, the USA, China, Japan, South Korea, France, England/United Kingdom, Malaysia, Belgium, and India, among others, show the strongest collaboration and higher number of contributions [Figure 7]. Most of EU countries are also part of intense collaboration, which remarks the compromise of the economic community in advancing toward a sustainable bioeconomy and particularly, in the substitution of petrochemical-based materials. As depicted in Figures 7a and 7b, countries that are not part of the most industrialized economies but are important in the primary sector and biomass resources such as Malaysia, India, and Latin America (with Brazil as the main contributor), also contribute significantly to the knowledge in PHA production.

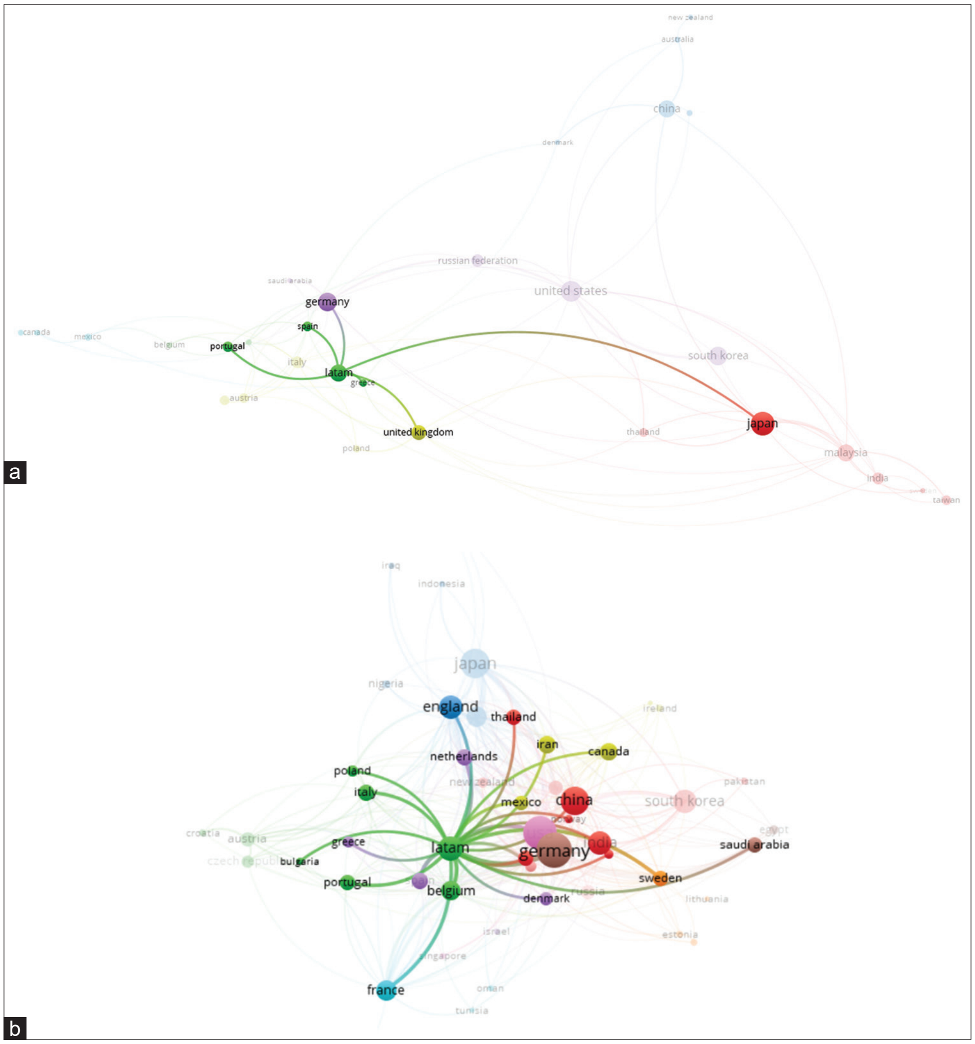

Figure 7: Latin American collaborations network of studies related to production polyhydroxyalkanoates by *Cupriavidus necator*, (a) Scopus and (b) Web of Science. The minimum number of occurrences of a keyword is 5.

Research in topics such as biomaterials and green chemistry is emerging and growing fast since those areas are expected to play an important role in a low-carbon economy and the generation of innovative bioindustries [1]. Concerning the large-scale production of bio-based chemicals, the OECD proposes that around 35% of industrial chemicals are substituted by bio-based chemicals by 2030. Latin America contributes approximately 4% of the global virgin plastics production, equivalent to 14.4 million tons, destined mostly for the domestic markets. As for 2022, the world's bioplastics production was 2.217 million tons, which is less than 1% of the total demand for plastics [8]. The share of bioplastics production with respect to fossil-derived materials in Latin America follows the same trend; currently, it is only 1.3%. Nevertheless, when observed the sole bioplastics market Latin America contributes 9% of the total bioplastics production, equivalent to 189 thousand tons [84].

The bioplastics industry is growing fast, with a projected growth rate of 3.7% for 2023, which means for Latin America a value of 2 billion USD [84]. In the current global plastics market, only Mexico is an important player, with 5% of the total polymer exports given its important refining capacity in the region. On the opposite side, Brazil is expected to become a big player in the biodegradable polymers industry with an important share in the market for bioplastics, considering its leadership in the sugar and oleaginous exportations with 20% and 30% of the global trade, respectively [85]. Apart from Brazil, Argentina is the 5th world exporter of oleaginous seeds, while Mexico, Colombia, and Guatemala are in the top 20 sugar exporters [85]. As it has been previously shown, those materials are the source of prospective inexpensive substrates for PHA production. The geographical and meteorological conditions favor the crops, plantations, and husbandry activities, which allows the continuous production of biomass during the whole year. These conditions might become Latin America an interesting hub for the production of PHA, bioplastics and, in general, many different bioproducts required for the transition towards a sustainable bioeconomy.

The world production of bioplastics is forecasted to triplicate in 2026 the production of 2021 up to 7.6 million tons, in which at less 70% would be biodegradable and the rest biobased non-biodegradable [8]. Nevertheless, this is still a very low percentage (2%) of global plastics production; hopefully, the growth would be higher as new regulations and restrictions on the use of nonbiodegradable plastics are introduced worldwide. Since Brazil is the world leader in the sugarcane industry and oleaginous seeds production, it has comparative and competitive advantages that can be also irradiated to its neighbor countries with similar geographic conditions. This also depends on effective economic integration between the South American countries and infrastructure developments that increase their competitiveness.

In the last years, Brazil has experienced the fastest industrial growth in bioplastics production in Latin America due to the very developed agro-industrial activity and big bioethanol distilleries that produce different kinds of biowaste with the potential for transformation into added-value bioproducts. Certainly, Brazil is called to lead the transition toward bioplastics in the continent; currently, this country accounts for more than 50% of the total bioplastics production in South America. An important pool of multinationals such as Amcor, Arkema, BASF, BioAmber, DowDuPont, Mitsubishi Chemical Corporation, NatureWorks LLC, Novamont, Solvay, and many others have a presence in the country, in addition to the local Braskem, which is the largest petrochemical company in Latin America. All of them have established plans in the country with the aim to develop bioplastic production facilities. Indeed, the UN Economic Commission for Latin America and the Caribbean (ECLAC) recognized in 2020 the production of a bioplastic developed by Braskem as one of the most outstanding cases of sustainable development in the continent.

In this interesting panorama, the PHA production is expected to multiply 10-fold the current small production of 56 thousand tons, by 2027 [8]. Latin America is a region with a high potential for biomass production given the availability of cultivable land, fertile soils, and water supply that favor the consolidation of production chains in food production, fibers and forestry, bioproducts, and bioenergy [86]. In addition, the availability of large amounts of waste biomass generated in the primary sector of the economy still lacks adequate waste management in many geographical areas.

Since the most prospective low-cost substrates, namely fats and oils, sugars, starch and their derivatives are readily available in Latin America from different sources, positive perspectives are envisioned for the establishment of processes for PHA and other bioplastics production in the continent. Some estimations indicate that Latin America could host up to 45-50% of the global bioplastics production. However, the funding of research in the region is considerably low when compared to USA, Asia, and Europe. The mean investment in science, technology, and innovation in the region is less than 1% of the GDP; this condition limits the scientific capacities of the Latin American countries, turning them into low-specialized economies that import technology, act as raw materials suppliers, or serves as a location for industrial outsourcing.

Recently, Moshood *et al*. [83] examined the biodegradable plastic product innovation across biodegradable plastic firms and non-governmental organizations (NGOs) emphasizing energy savings, public policies, and reductions in materials and pollution control as strategic points for business leaders, academics, and policymakers. The ECLAC has identified some common issues to be solved to promote the bioeconomy-related industries in Latin America: (i) absence of adequate regulatory frameworks, (ii) complexity of national regulatory processes, (iii) weak capacities to comply with external regulations in the target markets for bioproducts, (iv) incompatibility of regulations between conventional products and similar bioproducts and (v) difficulty in enforcing existing regulations [86]. The knowledge of the different kinds of biomass available, the formulation of precise public policies, the increase of the cooperation for the development of scientific and technological capabilities and the identification of the market potential, products, and applications would help to faster adoption of bioplastics in the region and towards the external markets.

3.7. Business Landscape in Colombia

Colombian's biomass residues account for about 20 million metric tons annually. However, the Colombian's government estimates this potential up to 43 million tons of biomass residues. Here, the agricultural sector plays an important role in Colombia´s bioeconomy, for example, 33 megatons of sugarcane were produced in 2019 [87]. The following are some of the productions in this sector (in metric tons): Coffee (720,000), corn (1.3 million), potatoes (3.1 million), palm oil (5.8 million), bananas (3.7 million), pineapples (900,000), avocado (325,000) [88]. Thus, the potential of Colombia, and other neighboring countries such as Ecuador, Peru, and Brazil, could contribute to low-cost coal sources for the production of PHA.

4. CONCLUSIONS

A clear scientific interest in the use of low-cost feedstocks (such as starch, waste fats and oils, molasses, and cellulose hydrolysates) for PHA production by *C. necator* arose during the last decade. The geographical and meteorological conditions of Latin America may open the opportunity to establish productive processes of PHA and bioplastics production in the region thanks to the high availability of biomass, products, and byproducts from agroindustry during the whole year. From regulatory and cooperation standpoints, efforts are required to establish a clear framework in Latin America for the development of bioeconomy initiatives. It is also necessary to intensify the research and strengthen the collaboration on this topic, especially in those regions that may act as potential hubs for the PHA and bioplastic production in the near future. Further studies and more intense scientific collaboration may contribute to achieving the objective of feasible and profitable PHA production as a real substitution alternative for conventional plastics.

5. ACKNOWLEDGMENTS

Martha L Ascencio-Galván acknowledges MinCiencias for funding her doctoral studies under the Bicentennial Doctoral Excellence Scholarship program.

6. AUTHORS' CONTRIBUTIONS

Conceptualization, V.A.L-A and H.R.-M.; methodology, M.L.A-G and H.R.-M.; software, M.L.A-G.; validation, M.L.A-G and H.R.-M.; formal analysis, M.L.A-G and D.G-R.; investigation, M.L.A-G.; resources, M.L.A-G.; data curation, M.L.A-G.; writing—original draft preparation, M.L.A-G.; writing—review and editing, D.G-R, V.A.L-A and H.R.-M.; visualization, M.L.A-G.; supervision, V.A.L.-A and H.R.-M.; project administration, H.R.-M. All authors have read and agreed to the published version of the manuscript.

7. FUNDING

The authors acknowledge the funding by Vicerrectoría de Investigaciones, Universidad del Valle, Project CI-21191.

8. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

9. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

10. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

11. PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

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How to cite this article:
Ascencio-Galván ML, López-Agudelo VA, Gómez-Ríos D, Ramirez-Malule H. A bibliometric landscape of polyhydroxyalkanoates production from low-cost substrates by *Cupriavidus necator* and its perspectives for the Latin American bioeconomy. J App Biol Biotech. 2024;12(2):48-61. DOI: 10.7324/JABB.2024.159864