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META-ANÁLISE-CRUZADA SOBRE O BIORREFINO DE POLICOSANOL: UM PROTOCOLO INOVADOR DE PROSPECÇÃO TECNOLÓGICA COM INSIGHTS IBERO-AMERICANOS.

CROSS-META-ANALYSIS ON POLICOSANOL BIOREFINING: AN INNOVATIVE TECHNOLOGY PROSPECTING PROTOCOL WITH IBERO-AMERICAN INSIGHTS.

METAANÁLISIS CRUZADO SOBRE LA BIORREFINACIÓN DE POLICOSANOL: UN PROTOCOLO INNOVADOR DE PROSPECCIÓN TECNOLÓGICA CON PERSPECTIVAS IBEROAMERICANAS.

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ABSTRACT

This Cross-Meta-Analysis, based on PROSPERO Protocol (CRD42023425955), addresses two gaps by conducting a regionalized and simultaneous analysis of articles and patents on the six main Policosanol biorefining routes - a multifunctional antihypercholesterolemic - within the dual context of the burgeoning global bioeconomy and strategies for the prevention and treatment of cardiovascular diseases, the leading cause of death worldwide. Most reviews focus on clinical applications, without comparing extraction methods and evaluating their uncertainties. This study employs extensive databases, and high-end bibliometric tools such as Bibliometrix and Orbit Business Intelligence, while examining 18 Ibero-American countries. The main inferences on efficiencies are the advances of Cuba, Spain, Brazil, Chile, Mexico and Portugal, as well as the need for greater academic-industrial coordination amongst themselves. Covering 16 raw materials, highlighting lacquer wax, sugar cane wax, rice bran wax and *Ericerus Pela* wax, yield analysis reveals: High ($0.511 \leq$ yield ≤ 0.700): three methods; Moderate ($0.381 \leq$ yield ≤ 0.510): four methods; Low ($0.251 \leq$ yield ≤ 0.380): seven methods. These yields signal clear directions for further research, according to biomes and local costs, being useful as a guide for laboratory research, industrial applications and decision makers.

Keywords: Policosanol Biorefining. Cardiovascular disease prevention/treatment. Ibero-American countries. Cross-Meta-Analysis. Uncertainty assessment.

RESUMO

Esta Meta-Análise Cruzada, baseada no Protocolo PROSPERO (CRD42023425955), aborda duas lacunas ao conduzir uma análise regionalizada e simultânea de artigos e patentes sobre as

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seis principais rotas de biorrefino do Policosanol – um anti-hipercolesterolêmico multifuncional – dentro do contexto duplo da crescente bioeconomia global e das estratégias para a prevenção e tratamento de doenças cardiovasculares, a principal causa de morte em todo o mundo. A maioria das revisões se concentra em aplicações clínicas, sem comparar métodos de extração e avaliar suas incertezas. Este estudo utiliza extensos bancos de dados e ferramentas bibliométricas de ponta, como Bibliometrix e Orbit Business Intelligence, ao examinar 18 países ibero-americanos. As principais inferências sobre eficiências são os avanços de Cuba, Espanha, Brasil, Chile, México e Portugal, bem como a necessidade de maior coordenação acadêmico-industrial entre eles. Abrangendo 16 matérias-primas, destacando cera de laca, cera de cana-de-açúcar, cera de farelo de arroz e cera de *Ericerus Pela*, a análise de rendimento revela: Alto (0,511 ≤ rendimento ≤ 0,700): três métodos; Moderado (0,381 ≤ rendimento ≤ 0,510): quatro métodos; Baixo (0,251 ≤ rendimento ≤ 0,380): sete métodos. Esses rendimentos sinalizam direções claras para pesquisas futuras, de acordo com os biomas e os custos locais, sendo úteis como um guia para pesquisas laboratoriais, aplicações industriais e tomadores de decisão.

Palavras-chave: Biorrefino de Policosanol. Prevenção/Tratamento de Doenças Cardiovasculares. Países Ibero-Americanos. Meta-Análise Cruzada. Avaliação de incerteza.

RESUMEN

Este Metaanálisis Cruzado, basado en el protocolo PROSPERO (CRD42023425955), aborda dos deficiencias mediante un análisis regionalizado y simultáneo de artículos y patentes sobre las seis principales rutas de biorrefinación del policosanol (un antihipercolesterolémico multifuncional), en el contexto de la creciente bioeconomía global y las estrategias para la prevención y el tratamiento de las enfermedades cardiovasculares, la principal causa de muerte en todo el mundo. La mayoría de las revisiones se centran en las aplicaciones clínicas, sin comparar los métodos de extracción ni evaluar sus incertidumbres. Este estudio emplea extensas bases de datos y herramientas bibliométricas de vanguardia como Bibliometrix y Orbit Business Intelligence, al tiempo que examina 18 países iberoamericanos. Las principales inferencias sobre la eficiencia son los avances de Cuba, España, Brasil, Chile, México y Portugal, así como la necesidad de una mayor coordinación entre el sector académico y la industria. El análisis de rendimiento, que abarca 16 materias primas, destacando la cera de laca, la cera de caña de azúcar, la cera de salvado de arroz y la cera de *Ericerus Pela*, revela: Alto (0,511 ≤ rendimiento ≤ 0,700): tres métodos; Moderado (0,381 ≤ rendimiento ≤ 0,510): cuatro métodos; Bajo (0,251 ≤ rendimiento ≤ 0,380): siete métodos. Estos rendimientos indican líneas claras para futuras investigaciones, según los biomas y los costos locales, y sirven como guía para la investigación de laboratorio, las aplicaciones industriales y los responsables de la toma de decisiones.

Palabras clave: Biorrefinación de policosanol. Prevención/tratamiento de enfermedades cardiovasculares. Países Iberoamericanos. Metaanálisis Cruzado. Evaluación de la incertidumbre.

INTRODUCTION

One of the main meeting points of the growing dynamics of the bioeconomy and strategies for prevention and treatment of cardiovascular diseases (PTCVD), is the bio-refining technological routes capable of generating - preferably with renewable, low-cost or easy-access raw materials - bio-products of high added value, with relevant nutraceutical or pharmacological properties, often multifunctional, among which the Policosanols (Pc) here examined. Globally, cardiovascular diseases represent the primary cause of mortality. This underscores the urgent need for bioproducts providing nutritional and pharmacological interventions for PTCVD (Galletti et al., 2019; Shen et al., 2019).

Policosanol (Pc), an aliphatic primary alcohol (CH_3-$(CH_2)_n$-CH_2OH, n=24-34), possesses anti-hypercholesterolemic properties, suitable for PTCVD (Al-Okbi et al., 2014a; Shen et al., 2019), obesity, diabetes, and atherosclerotic complications, among other functionalities (Antolín et al., 2008a; Berthold et al., 2006a; Castaño et al., 2005a; Martin-Ramos et al., 2008a; Menendez et al., 2005a; Shen et al., 2019; Talebi et al., 2020a). Policosanol (Pc) exists as a white powder or scaly crystal (Shen et al., 2019). It can be extracted from affordable raw materials, including beeswax, wheat straw and germ, sugarcane bagasse and skin, rice bran oil and wax.

This systematic review, based on PROSPERO Protocol (Primo et al., 2023), employs a innovative Cross-Meta-Analysis (CMA) approach to synthesize studies and patents in these six main methods for Pc extraction, across 18 Ibero-American countries and globally (Talebi et al., 2020b;.; Dhyani et al., 2019; Eck & Waltman, 2016; Jones et al., 2011; Ketenoglu & Tekin, n.d.; Pan'kiv, 2014; Venturelli et al., 2019): 1. Saponification: Alkaline digestion; 2. Solvent Extraction: Utilizes organic solvents (ethanol, hexane etc.); 3. Molecular Distillation: Advanced vacuum distillation (short-path evaporators, low pressure/temperature); 4. Transesterification: Oils/fats reaction with low-carbon alcohol solvent (octacosanol separation); 5. Supercritical CO_2 Extraction: Selective, non-toxic extraction (high-value compounds); 6. Ultrasonic-Assisted Extraction: Enhances bioavailability, avoids degradation, and targets hydroxylation.

The objectives are: 1. Ranking processes by yield; 2. Assessing uncertainty; 3. Detecting knowledge gaps; 4. Revealing new perspectives.

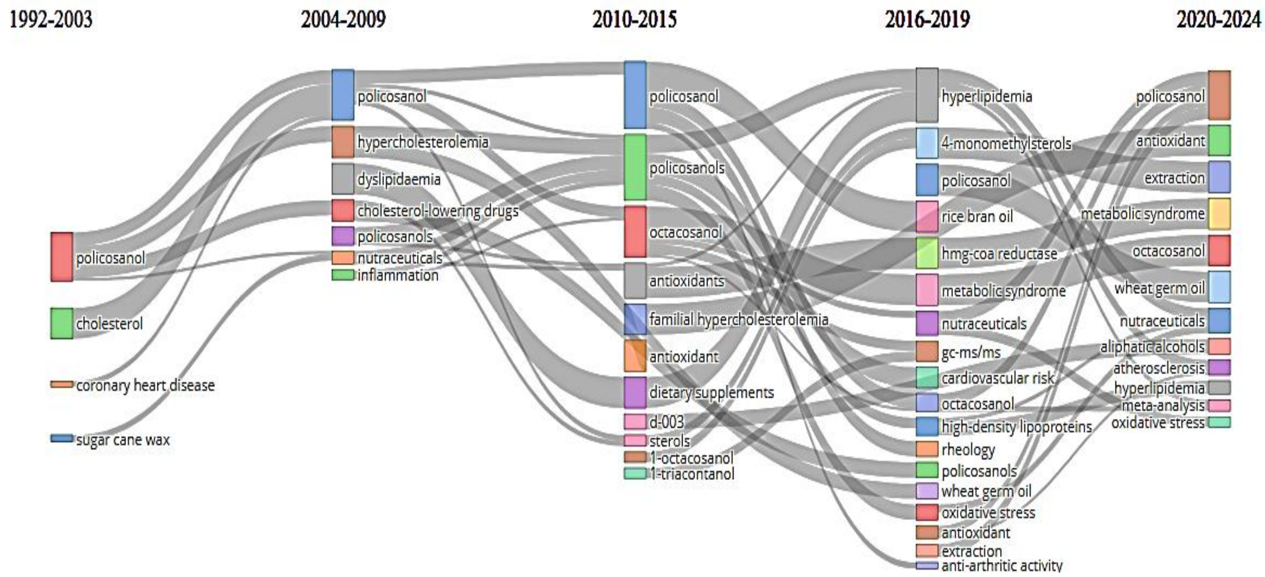
THEORETICAL FRAMEWORK

The 21st century has witnessed a fierce international race for the productivity of those 06 main methods of biorefining Pc, from 16 animal and plant raw materials, literature that has grown at a rate of 7.62% per year from 1992 to 2024, considering the two main databases (Scopus and WoS), and exceeding 13,750 peer-reviewed articles if we include the other databases available on the CAPES Journal Portal, in parallel with a related accumulation of 7,598 patent claims, according to the Orbit Intelligence search engine. Similar accumulations of research and patents, sometimes on applications, sometimes on extraction routes, require meta-analyses with robust tools.

Preceding their clinical and nutraceutical uses are their extraction methods, the focus of this study. Existing reviews on Policosanols (Pc) primarily focus on applications and testing, rather than extraction techniques, lacking regional perspectives and uncertainty assessments (Ameer et al., 2017; Arul Gnanaraj, 2012; Devi et al., 2022; Mohan et al., 2020; Osadnik et al., 2022; Paniwnyk, 2017; Sánchez et al., 2017; Shen et al., 2019; Singh et al., 2020; Wongwaiwech et al., 2022). This study addresses these gaps.

Figure 1

Transition of thematic axes in Pc studies (July 17, 2025).



Figures 1 and 2 illustrate the sustained interest in Pc therapeutic potential, particularly for hypercholesterolemia and dyslipidemia. Research converges on Pc-rich raw materials, nutraceuticals, and extraction methods, including mechanical wheat germ oil extraction, high-intensity ultrasound-assisted rice bran extraction, lipase-catalyzed methanolysis in supercritical CO_2, beeswax isolation, hydrolysis, and enzymatic transesterification, as well as Doppler-ultrasound studies on Pc therapy's effects on carotid-vertebral arteries (Al-Obaidi et al., 2013; Arul Gnanaraj, 2012; T. M. T. M. Attard et al., 2015; Batista et al., 1995; Brandolini & Hidalgo, 2012; J.-S. Choi et al., 2014; S. J. Choi et al., 2016; Cravotto et al., 2004; Dunford et al., 2010; García et al., 2003; Giuffrè et al., 2017; Gonzalez-Bravo et al., 1996; Haim et al., 2009; Ham et al., 2015; Jung et al., 2012; Kaewkool & Krisnangkura, 2010; Li et al., 2014; Ma et al., 2018; Morrison III et al., 2006; Murugasan et al., 2016; Ra et al., 2020; Ramos-Zambrano et al., 2019; Shen et al., 2019; Tung et al., 2010; Venturelli et al., 2019; L. Wang et al., 2008a; M.-F. Wang et al., 2007; Wongwaiwech et al., 2019).

Figure 2

Conceptual connections and convergences in the top ten countries (July 17, 2025).

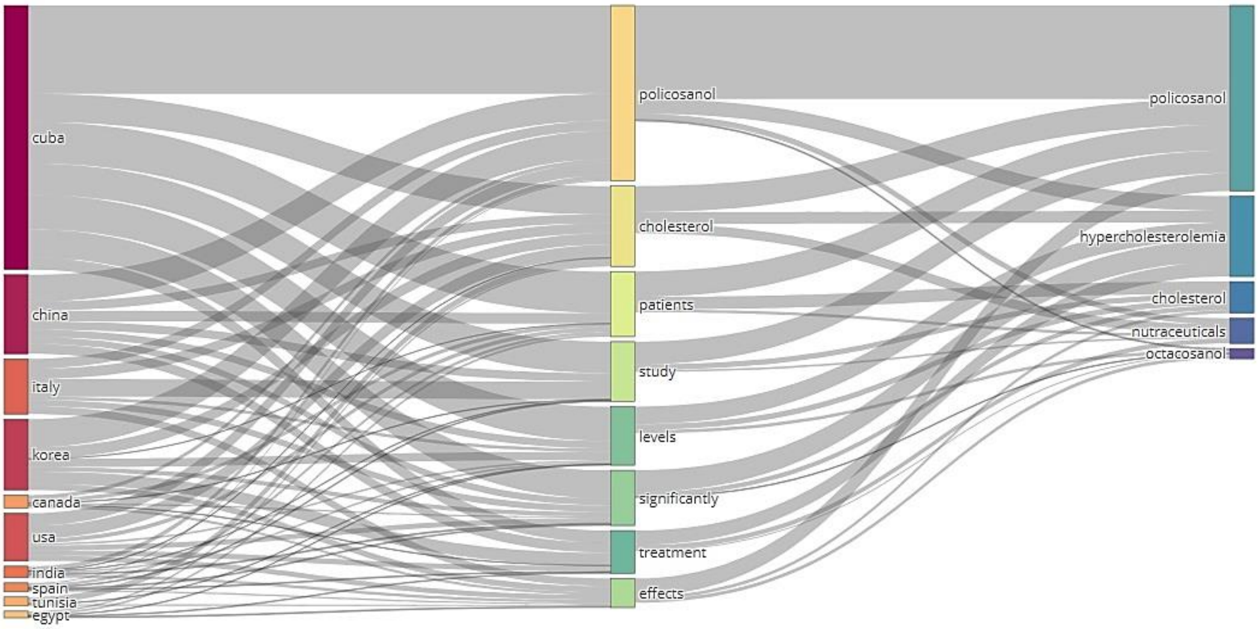


Figure 3 illustrates the evolving trend topics from 2000 to 2020, showcasing the top two annual themes with ≥ 5 abstract mentions. Notably, Pc and cholesterol research synchronized from 2006 to 2015. Subsequently, nutraceuticals (2017) and rice wax/oil (2016) emerged as prominent topics, reflecting renewed interest in raw materials previously highlighted (Afinisha Deepam et al., 2012; Africa et al., 2020; Al-Okbi et al., 2014b; Ham et al., 2015; Ishaka, Imam, Mahamud, Zuki, Maznah, et al., 2014; Kim et al., 2014; Lai et al., 2019; Peng et al., 2016;

Weerawatanakorn et al., 2017; Wong et al., 2016; Wongwaiwech et al., 2019; Xu et al., 2021).

Figure 3

Topic trending pairs on Pc extraction since 2000 to 2020, July 17.

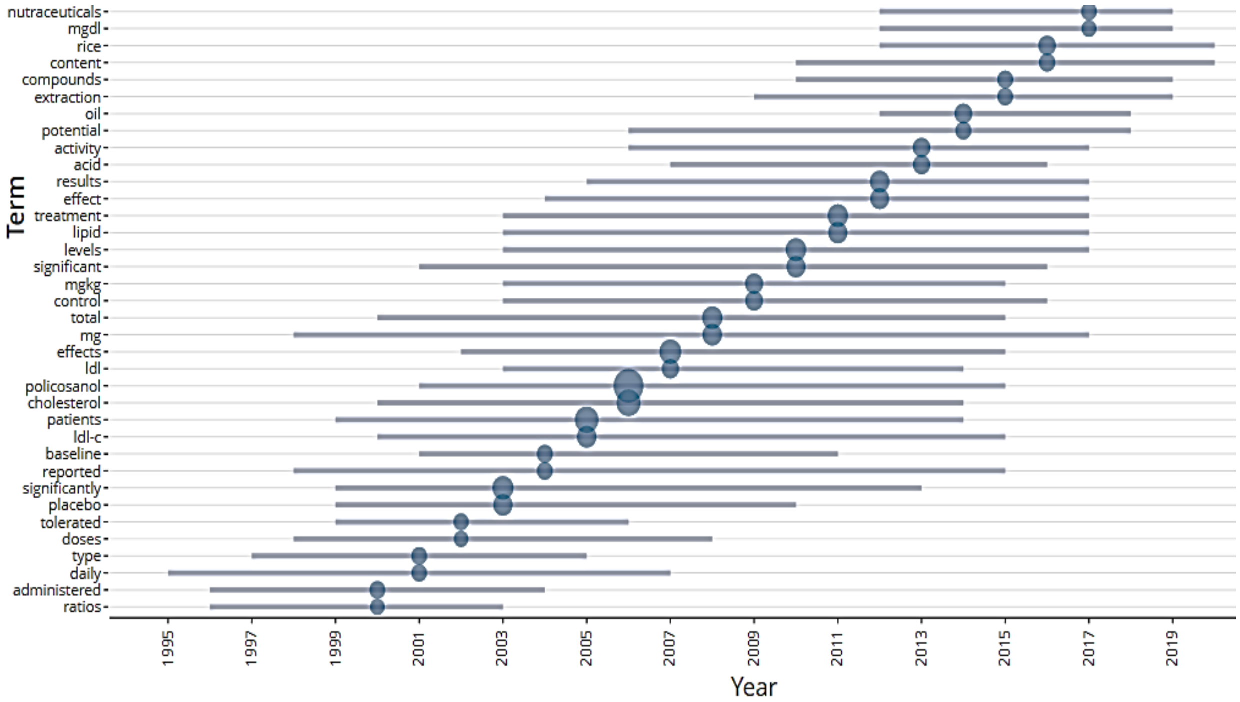


Figure 4

Networks between authors on Pc studies (July 17, 2025).

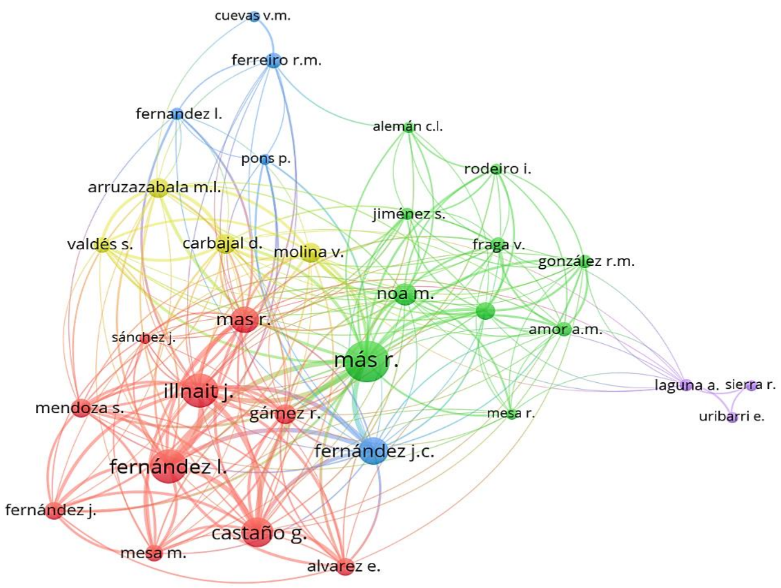


Figure 4 illustrates converging research interests among prominent author groups studying Policosanol and distinct clusters emerge:

a) Green Cluster - 1. Focuses on clinical applications: treating type II hypercholesterolemia, sugarcane wax acid research, and Pc's effects on lipid profiles and antiplatelet activity. 2. Features experiments on rats and rabbits (Alcocer et al., 1999; Alemán et al., 1994; Gamez et al., 2000; Mendoza et al., 2001; Noa & Mas, 2005).
b) Red Cluster - 1. Explores pharmacoepidemiology, lifestyle impacts, and Pc's efficacy/safety in patients with coronary disease or type II hypercholesterolemia. 2. Compares original Pc with other higher aliphatic primary alcohol mixtures (Castaño et al., 1995; Castano, Ferreiro, et al., 2001; Más et al., 1999; Pérez-Jiménez et al., 2018).
c) Yellow Cluster: Focuses on platelet aggregation, antiplatelet/antithrombotic effects, gastroprotection, venous thrombosis, and sugarcane wax compounds, with rabbit experiments (Arruzazabala et al., 1998, 2000; Carbajal et al., 1994; Carbajal Quintana et al., 2014; Rodriguez et al., 2004).
d) Blue Cluster: Explores Pc treatment for intermittent claudication, pharmacoepidemiology, sugarcane wax acids, efficacy/safety in hypercholesterolemia (particularly postmenopausal women), carcinogenicity in mice, and interactions with antiplatelet drugs (Carbajal Quintana et al., 2014; Castano et al., 2000; Castano, Ferreiro, et al., 2001; Castano, Mas, et al., 2001; J. C. Fernández et al., 2001; Janikula, 2002; Más et al., 1999).
e) Lilac Cluster: Investigates Pc's cholesterol-lowering effects, physicochemical characterization, compatibility studies, and interactions with excipients, featuring experiments on male monkeys (*macaca arctoides*) and rabbits (Cabrera, González, et al., 2002; Cabrera, Uribarri, et al., 2002; De Lourdes Arruzazabala et al., 1994; Martínez et al., 1999; Uribarri et al., 2002).

Pc Patents Around the World

Discarded the multiple uses of the Pc after its extraction, combined with other substances, as well as the generation processes of these new bioproducts using the previously extracted Pc, a relatively smaller number of patents resulting, due to the broad interests of the post-extraction Pc and, in another part, by the wide international domain of the main extraction techniques or routes examined.

Figure 5 illustrates the distribution of Policosanol patent filings across various technological domains, highlighting a pronounced concentration within the fields of pharmacology and food chemistry. In contrast, chemical engineering and fine organic chemistry account for a notably smaller share of the documented applications.

Figure 5

Patent families of Pc by technology domain since 2010 to 2020.

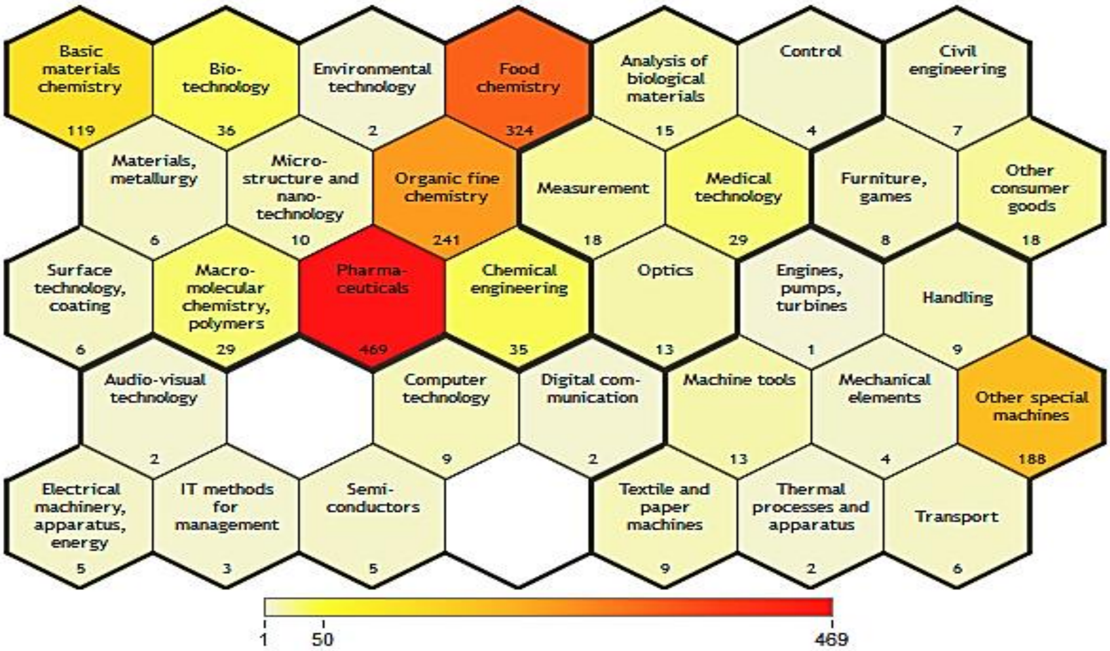


Figure 6

Connections between concepts and substances in Pc extraction patents (SciFinder, 2012 to 2022).

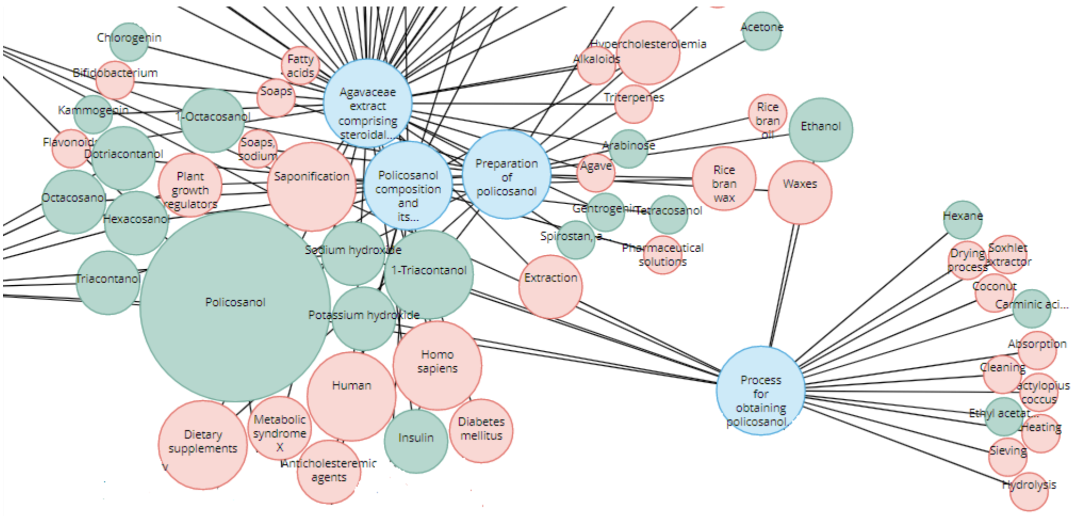


Figure 6 from SciFinder's Knowledge Graph reveals Pc variants' associations with hypercholesterolemia, anti-hypercholesterolemia, dietary supplements (nutraceuticals) and diabetes. Pc extraction, obtaining and preparation methods, frequently involving saponification, are highlighted. Rice bran wax emerges as the primary raw material, underscoring its significance in Pc-based pharmacological solutions.

Final Considerations on the Literature

The intersection of chemical engineering, biochemistry, agrotechnology, and related fields presents substantial bioeconomic potential for 2030-2050 (Jesús & Gil, 2009; Martin-Ramos & Martín-Gil, 2017; Schieb et al., 2015), driving innovation in sustainable bioproducts, biochemical processing, agro-industrial technologies, interdisciplinary collaborations and future-oriented technological advancements. Novel technological routes are being developed, prioritizing high-added-value product generation while minimizing ecological consequences (T. M. Attard et al., 2015; Budzianowski, 2016; Feng et al., 2014; Ghysels et al., 2020; Martin-Ramos & Martín-Gil, 2017; Routray & Orsat, 2017; Torres-Valenzuela et al., 2020). This study fits into this scenario and its ultimate objective is to serve as a guide for inventors, researchers, manufacturers and decision makers.

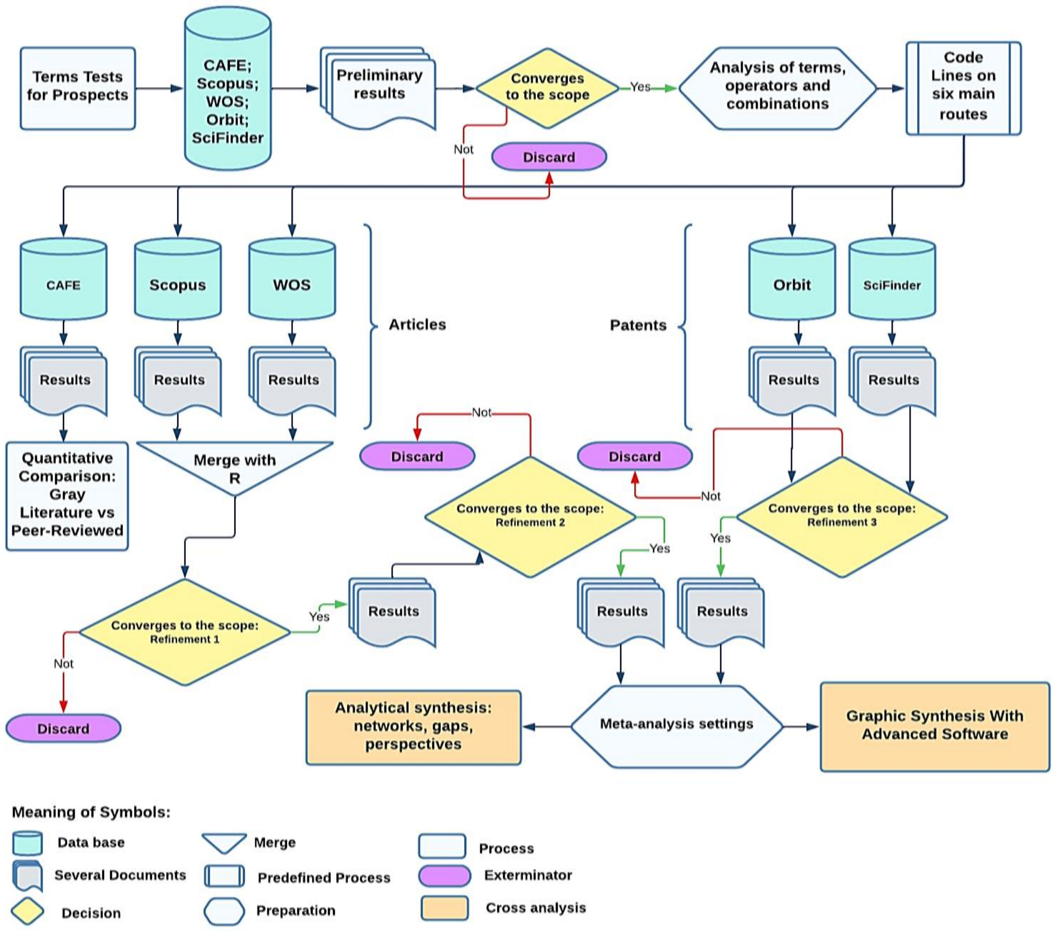
METHODOLOGY

The development and implementation of this innovative systematic review however reflects current methodological advancements in the field, particularly those promoted by initiatives such as PROSPERO and the PRISMA guidelines (Z. Chen et al., 2022; Okoli & Schabram, 2010; Schiavo, 2019; Shamseer et al., 2015).

This study adheres to a set of well-defined criteria to ensure analytical relevance and methodological rigor. Inclusion parameters encompass documents such as patents, and peer-reviewed research articles specifically addressing Pc extraction processes. Conversely, studies focused on applications of Pc rather than its extraction, as well as publications that have not undergone peer review, are excluded. The regional scope is limited to 18 Ibero-American countries—namely Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, the Dominican Republic, Ecuador, Spain, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Portugal, El Salvador, and Uruguay—to capture geographic diversity within a culturally and linguistically connected region. However, technical limitations were encountered: patent data were unavailable for Bolivia, Haiti, Paraguay, and Venezuela, and no relevant patent records were found for El Salvador, Guatemala, and Honduras, potentially affecting the comprehensiveness of regional patent mapping.

Figure 7

CMA Flowchart.



Source: (Primo et al., 2023) with application Lucid Visual Collaboration Suite®.

This study utilized four main databases (Figure 7): I - Modality Advanced Search and IP Business Intelligence of Orbit seekers (version 1.9.8) (35 technology domains); II - SciFinder, platform focused on the areas of Organic Chemistry, Biochemistry and Chemical Engineering; III - Portal Periódicos (537 bases) of Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), privileged institutional access by Federated Academic Community - CAFE; IV - Science Citation Index Expanded (SCI-E) (Web of Science - Core Collection - Clarivate Analytics – WoS) and Scopus (Elsevier). Aggregate results are presented in Tables I and II.

Table I

Analytical inventory on Pc (1992-2025, July 17).

Nº - Search (Substances / Routes)	ARTICLES (Peer reviewed)										PATENTS[c]							
	Portal Periódicos (CAPES-CAFE - 537 Bases / Expanded results)		Main Bases				Merged (WoS and Scopus)				Countries							
			Scopus		WoS		Documents Unique		National contributions by co-authorship		Substance				Extraction Method			
											World		Iberoamerican		World		Iberoamerican	
	General Results	Peer reviewed	World	Ibero-American	World	Ibero-American	World	Ibero-American	World	Ibero-American	Familie	Unique	Familie	Unique	Familie	Unique	Familie	Unique
00 PC	46 837	13 247	619	168	500	159	801	231	727	296	1 531	7 580	497	5 111	35	113	9	74
01 Saponification	181	83	10	1	9	2	14	2	15	4	142	743	34	477	10	27	5	12
02 Solvent extraction	401	177	14	4	11	3	19	6	19	9	908	5 660	246	3 901	27	68	6	34
03 Molecular distillation	17	5	7	5	3	0	9	5	12	2	77	238	31	158	2	3	0	0
04 Transesterification	48	20	7	8	6	0	7	8	9	8	55	359	28	282	1	1	1	1
05 Supercritical CO_2	56	16	25	2	12	1	33	2	45	2	101	695	59	589	6	30	3	22
06 Ultrasonic-assisted	131	62	52	7	9	3	56	10	112	11	277	1 824	66	1 201	4	20	1	13

Table II

Scientific production on Pc by Iberoamerican countries (1992-2025, July 17).

Country	Cuba	Spain	Brazil	Chile	Mexico	Portugal	Argentina	Colombia	TOTAL
Documents	230	28	15	8	8	5	1	1	296

The eliminate duplicates, bibliometric analysis and graphical presentation were conducted using Bibliometrix® (v. 4.1.1) and R Studio® (v. 2025.04.2+764), WoS® and Scopus® statistical tools, alongside VOSviewer® software (v. 1.6.15) (Van Eck & Waltman, 2020). For patent analysis, Orbit's® Advanced Search and IP Business Intelligence provided cientometric tools (Orbit Intelligence, 2021, 2022; Primo et al., 2023), while SciFinder's® Knowledge Graph enabled connections in organic chemistry, biochemistry, and chemical engineering (Primo et al., 2023). This approach promotes a comprehensive synthesis of findings while enabling the identification and mitigation of potential biases, facilitates the critical evaluation and refinement of procedures and criteria, thereby contributing to the objective appraisal of final syntheses. In doing so, it minimizes arbitrary decision-making, reduces the likelihood of rework, and fosters more effective collaboration.

Uncertainty Assessment

In quantitative research - particularly within industrial, health, and safety domains - explicit representation of data uncertainty is increasingly recognized as essential. Following a review of the metrological foundations and current best practices, the adopted methodologies and recommended procedures for uncertainty evaluation are outlined from now on (Primo et al., 2023). Regarding articles and reviews, in studies examining the yield of Pc extraction methods, measurement uncertainties are typically reported as standard deviations—often referred to as Type A standard uncertainties (Primo et al., 2023).

These studies generally omit assessments of Type B uncertainties, as well as evaluations of combined or expanded uncertainties and related coverage factors, thereby falling short of the metrological rigor required in various industrial, commercial, healthcare, and security contexts (Inmetro, 2012; IPQ & Inmetro, 2012). Given the practical constraints on time and resources, comprehensive statistical treatment of all influencing variables is seldom feasible; thus, uncertainty is more commonly estimated using mathematical models and the law of propagation of uncertainties (Hughes & Hase, 2010; Inmetro, 2012). Accordingly, this literature will present Type A standard uncertainties where such data are available or can be derived. For instance, M.-F. Wang et al. (2007) reported the standard deviation values for octacosanol and triacontanol concentrations explicitly; thus, $u_r = \sqrt{SD_1^2 + SD_2^2 + \dots + SD_n^2}$, where u is the Type A standard uncertainties and the subscript "r" indicates the technological route, the subscripts 1, 2, ... n indicate the specific standard deviations of component (Primo et al., 2023).

Regarding patents, practical constraints are only partly responsible for the limited treatment of uncertainty; equally influential is the insufficient dissemination of methodological norms for its evaluation, compounded by patent incentives that discourage the disclosure of reproducibility data. In this domain, patents rarely quantify uncertainty, though yield intervals are commonly reported as minimum and maximum bounds. When such bounds are the sole available metric, a provisional assumption of a symmetric uniform distribution is applied—implying a probability of one within the specified range and zero outside—to enable preliminary estimation of the standard uncertainty $u(x_i)$ (Primo et al., 2023). Formally, this function and probability density function (PDF) is conditioned as follows (Primo et al., 2023):

$$f(x) = \begin{cases} \dfrac{1}{a_+ - a_-}, a_- \leq x \leq a_+ \\ 0, a_- > x > a_+ \end{cases} \text{ and } P(x) = \int_{a_-}^{a_+} f(x)dx = \int_{a_-}^{a_+} \frac{1}{a_+ - a_-} dx = 1 \quad (1)$$

Where the extremes a_+ and a_- are, respectively, the limits of the right and left sides in relation to the midpoint 0 of the interval [Max, Min]. The expected value ($E[x]$) of the yield is

$$\mu_x = \int_{a_-}^{a_+} x f(x)dx = \frac{1}{a_+ - a_-} \cdot \left(\frac{x^2}{2}\right)\Big|_{-a}^{+a} = \frac{a_+ + a_-}{2} \qquad (2)$$

Remembering that

$$E[x^2] = \int_{a_-}^{a_+} x^2 f(x)dx = \frac{1}{a_+ - a_-} \cdot \left(\frac{x^3}{3}\right)\Big|_{-a}^{+a} = \frac{{a_+}^3 - {a_-}^3}{3(a_+ - a_-)} \qquad (3)$$

Then

$$u(x_i) = \sqrt{E[x^2] - \{E[x]\}^2} = \sqrt{\frac{{a_+}^3 - {a_-}^3}{3(a_+ - a_-)} - \left(\frac{a_- + a_+}{2}\right)^2} = \sqrt{\frac{(a_+ - a_-)^2}{12}} \qquad (4)$$

If (a_+ - a_-) is designated by 2a, becomes $u(x_i) = \frac{a}{\sqrt{3}}$ (Inmetro, 2012; Primo et al., 2023).

When yield variability is derived from applicants' experimental data, the corresponding standard uncertainty $u(x_i)$ is provisionally classified as Type B, consistent with metrological conventions (Inmetro, 2012). This classification holds until supplementary data becomes available—particularly crucial when procedural factors exert substantial influence on the uncertainty. Relative to Type A estimates reported in scholarly sources, such Type B uncertainties from patent documentation may exhibit reduced reliability, notably where few statistically independent observations are available. In select instances, published data may warrant similar treatment. (Inmetro, 2012; Primo et al., 2023).

RESULTS AND DISCUSSIONS

Table III ranks the top 25 countries by publication, highlighting Ibero-American nations in bold.

Table III

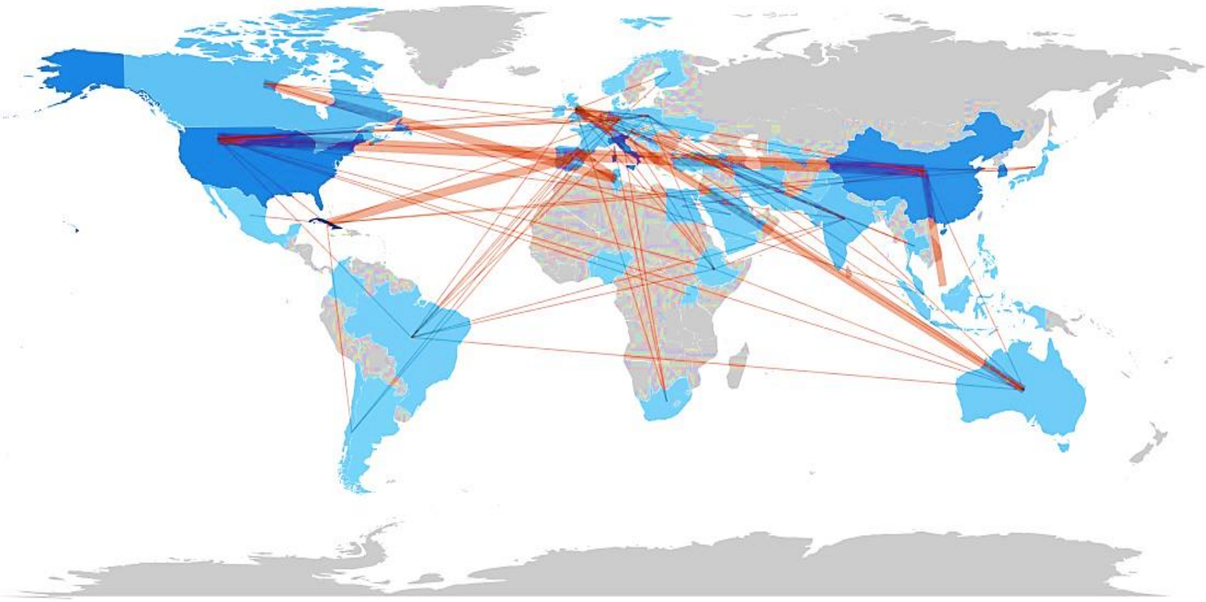
Scientific Production Accumulated by top 25 Countries.

Cou-	**Cuba**	USA	China	Italy	South	India	Ca-	**Spain**	UK	Egypt	Japan	**Brazil**	Ger-	Thai-	Aus-	Poland	Tuni-	**Chile**	**Me-**	France	Croa-	Iran	Net-	**Portu-**	Tur-
Articles	**230**	135	118	113	96	42	35	**28**	22	17	16	**15**	15	15	12	10	9	**8**	**8**	7	6	6	5	**5**	4

Cuba's prominence in Pc research stems from two key factors: 1. International collaborations (MCP): Partnerships such as Cuban Institute for Research on Sugarcane Derivatives - ICIDCA's with Spain's Universidad de Castilla-La Mancha enhanced supercritical extraction techniques, achieving 78.24% purity (vs. 22% with organic solvents) (de Lucas et al., 2007). 2. Domestic networking (SCP): such as ICIDCA's collaborations with Faculty of Chemical Engineering of the Technological University of Havana - CUJAE, National Center for Scientific Research - CNIC and others optimized sugarcane wax extraction using ethanol, yielding high-quality Policosanol (Díaz De Los Ríos et al., 2022), CNIC's innovative approach earned two WIPO gold medals (I. Fernández, 2015).

Figure 8

Countries' Collaboration World Map of ***Scientific Production on Policosanol.***



The mapping analysis (Figure 8) reveals China's dominance in international collaborations (MCP) on Policosanol research, closely followed by the USA and Spain. Intra-country collaborations (SCP) are led by Cuba, followed by the USA and Italy. Italy tops the citation count with 5,283, ahead of the USA (3,181), Croatia (2,606), and Cuba (1,937).

Hierarchy of Yields by Technological Route and Raw Materials

Table IV ranks physical productivity, detailing uncertainties, routes, raw materials, and references across five tiers.

Table IV

More expressive productivity in PC extraction (Articles in blue and Patents in white).

Pc Yield (Y) Range / (g/g)	DOCUMENT				
	Reference	**Route**	**Raw Material**	**Pc Yield / (g/g)**	**u**
0.511 ≤ Y ≤ 0.700	(Srivastava et al., 2017)	Saponification	Lac wax	0.70	0.06
	(Rozário et al., 2008)	Saponification	Sugar cane wax (and others)	0.70	0.18
	(Ganesh et al., 2019)	Solvent Extraction	Crude rice bran wax (RBW)	0.70	0.17
0.381 ≤ Y ≤ 0.510	(F. Chen et al., 2005)	Transesterification + Molecular Distillation	RBW	0.511	UNR*
	(Qi & Ji-Fu, 2004)	Saponification	Wax by Ericerus Pela	0.50	0.07
	(Srivastava et al., 2017)	Saponification	Lac wax	0.50	0.06
	(Rozário et al., 2008)	Saponification	Sugar cane wax (and others)	0.40	0.18
0.251 ≤ Y ≤ 0.380	(Ganesh et al., 2019)	Solvent Extraction	Crude RBW	0.38	0.02
	(Qi & Ji-Fu, 2004)	Saponification	Wax by Ericerus Pela	0.35	0.07
	(Granja et al., 1999)	Saponification	Sugar cane wax (and others)	0.30	0.18
	(Ganesh et al., 2019)	Solvent Extraction	Crude RBW	0.30	0.02
	(M.-F. Wang et al., 2007)	Saponification	RBW	0.280	0.000
	(Somaiya et al., 2016)	Saponification	Sugar cane press mud	0.26	0.18
	(Zhijuan et al., 2007)	Saponification	Wax by Ericerus Pela	>0.25	0.07
0.182 ≤ Y ≤ 0.250	(M.-F. Wang et al., 2007)	Saponification	RBW	0.210	0.069
	(F. Chen et al., 2007)	Transesterification	RBW	0.210	0.000
	(M.-F. Wang et al., 2007)	Saponification	RBW	0.202	0.030
	(Ganesh et al., 2019)	Solvent Extraction	Crude RBW	0.20	0.01
	(Leticia et al., 2021)	Transesterification	Cochineal scarlet wax (*dactylo-pius coccus*)	0.19	0.11
0.005 ≤ Y ≤ 0.181	(M.-F. Wang et al., 2007)	Saponification	RBW	0.181	0.000
	(Shen et al., 2019; Song et al., 2008)	Transesterification	Sugarcane wax	0.173	UNR
	(Leticia et al., 2021)	Transesterification	Cochineal scarlet wax (*dactylo-pius coccus*)	0.16	0.15
	(Ganesh et al., 2019)	Solvent Extraction	Crude RBW	0.15	0.01
	(Ganesh et al., 2019)	Solvent Extraction	Crude RBW	0.11	0.17
	(Ishaka, Imam, Mahamud, Zuki, & Maznah, 2014)[a]	Ultrasonic	RBW	0.108	0.040
	(Ishaka, Imam, Mahamud, Zuki, & Maznah, 2014)[a]	Ultrasonic	Rice bran oil	0.098	0.044

Table IV

More expressive productivity in PC extraction (Articles in blue and Patents in white).

Pc Yield (Y) Range / (g/g)	DOCUMENT				
	Reference	**Route**	**Raw Material**	**Pc Yield / (g/g)**	**u**
	(Rao, 2007)	Supercritical CO_2	Sugarcane pressmud-biomass	0.087	0.022
	(Heping, 2012)	Saponification	Domestic cane wax	0.06	0.18
	(Ou et al., 2012)	Solvent Extraction	Waxes of sugarcane juice	0.048	0.021
	(Laura Capriotti et al., 2023)	Ultrasonic	Industrial hemp (Cannabis sativa L.)	0.043	0.004
	(L. Wang et al., 2008b)	Supercritical CO_2	Distillers dry grain with solubles	0.034	UNR[b]
	(Ou et al., 2012)[a]	Supercritical CO_2	Waxes of sugarcane juice	0.030	0.015
	(Laura Capriotti et al., 2023)	Ultrasonic	Industrial hemp (Cannabis sativa L.)	0.028	0.004
	(Afinisha Deepam et al., 2012)[a]	Saponification	Crude rice bran oil	0.026	0.000
	(Ou et al., 2012)	Solvent Extraction	Waxes of sugarcane juice	0.023	0.012
	(Irmak et al., 2006)[a]	Solvent Extraction	Beeswax (brown)	0.012	0.006
	(Afinisha Deepam et al., 2012)[a]	Saponification	Refined rice bran oil	0.012	0.000
	(Rao, 2007)	Supercritical CO_2	Sugarcane pressmud-biomass	0.010	0.022
	(Irmak et al., 2006)[a]	Solvent Extraction	Beeswax-yellow	0.005	0.000

* UNR - Uncertainty not reported by authors. INF - Information not found.
a - The standard uncertainty of type A was measured by the authors for relative % of the constituents and here propagated for the yield.
b - Uncertainty indicated graphically.

Notably, patents dominate the upper tiers, while articles prevail in lower tiers. Notably, solvent extraction patent claims in the Americas, Europe, Asia, and Australia are dominated by Coca Cola and Purecircle, holding eight-fold market strength over competitors. Conversely, the broader competitive landscape exhibits balance, encouraging innovation and leadership among companies.

The viability of industrial and research applications hinges on access to raw materials, enabling technologies, and experimental conditions, which are, in turn, shaped by local market dynamics, ecological biomes, the prevailing scientific-industrial culture, and the degree of both internal integration and external connectivity.

CONCLUSIONS

This CMA identified biorefining pathways—particularly those focused on extracting high-value-added bioproducts targeted at the PTDCV, such as policosanol—as critical domains for research and investment in the 21st century.

Despite a pronounced gap in systematic literature reviews, Ibero-American countries—particularly Cuba, Spain, Brazil, Chile, Mexico, and Portugal—have made noteworthy strides in experimental research and patent development. These patterns of innovation highlight the critical need for deeper international scientific integration and more robust linkages between academic institutions and national biorefinery initiatives. The progress witnessed in Cuba, Brazil, and Spain serves as compelling evidence of the transformative potential inherent in such synergistic collaborations.

This study categorizes these experiments into five yield ranges, from 16 diverse raw materials, and experiments exhibiting high physical yields (Y) were identified.

a) $0.511 \leq Y \leq 0.700$: 2 Saponification, 1 Solvent Extraction;
b) $0.381 \leq Y \leq 0.510$: 3 Saponification, 1 Transesterification + Molecular Distillation;
c) $0.251 \leq Y \leq 0.380$: 5 Saponification, 2 Solvent Extraction;
d) $0.182 \leq Y \leq 0.250$: 2 Saponification, 1 Solvent Extraction, 2 Transesterification;
e) $0.005 \leq Y \leq 0.181$: 4 Saponification, 2 Transesterification, 6 Solvent Extraction, 4 Ultrasonic Extraction, 4 Supercritical CO_2 Extraction.

Significant research gaps persist in the field, particularly concerning the paucity of peer-reviewed investigations into the use of Ericerus pela wax as a raw material and the limited patent activity involving the application of transesterification and molecular distillation techniques for policosanol (Pc) extraction. Addressing these underexplored domains will require strengthened collaboration between scientific researchers and inventive stakeholders to foster innovation and advance the biorefining landscape.

Future research should prioritize the economic viability of Pc extraction processes. A systematic review of the economic criteria utilized in both academic studies and registered patents will be essential for identifying current gaps and opportunities. Further investigation should concentrate on evaluating key advantages that influence the economic potential of Pc production, including solvent and energy efficiency, process intensification and speed, scalability for commercial deployment, and overall industrial attractiveness. In addition, research should address opportunity costs and market competitiveness to ensure the long-term sustainability and profitability of these biotechnological approaches.

Simultaneously, environmental sustainability must be rigorously assessed. This involves conducting comprehensive environmental impact assessments of various Pc production methods to determine ecological footprints and areas for mitigation. Life Cycle Assessment (LCA) combined with mass balance analysis will provide quantifiable insights into resource utilization and emissions throughout the production chain. Moreover, exploring cleaner production strategies is imperative for aligning Pc extraction technologies with global environmental goals and regulatory standards.

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