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Global trends and future prospects of lactic acid production from lignocellulosic biomass

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Lignocellulosic biomass (LCB) stands as a substantial and sustainable resource capable of addressing energy and environmental challenges. This study employs bibliometric analysis to investigate research trends in lactic acid (LA) production from LCB spanning the years 1991 to 2022. The analysis reveals a consistent growth trajectory with minor fluctuations in LA production from LCB. Notably, there's a significant upswing in publications since 2009. *Bioresource Technology* and *Applied Microbiology and Biotechnology* emerge as the top two journals with extensive contributions in the realm of LA production from LCB. China takes a prominent position in this research domain, boasting the highest total publication count (736), betweenness centrality value (0.30), and the number of collaborating countries (42), surpassing the USA and Japan by a considerable margin. The author keywords analysis provides valuable insights into the core themes in LA production from LCB. Furthermore, co-citation reference analysis delineates four principal domains related to LA production from LCB, with three associated with microbial conversion and one focused on chemical catalytic conversion. Additionally, this study examines commonly used LCB, microbial LA producers, and compares microbial fermentation to chemical catalytic conversion for LCB-based LA production, providing comprehensive insights into the current state of this field and suggesting future research directions.

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Introduction

In a world grappling with pressing challenges such as environmental sustainability and an increasingly urgent energy crisis, the vast abundance of lignocellulosic biomass (LCB) on our planet offers a beacon of hope. Plants, which dominate terrestrial ecosystems, account for a staggering 80% or 450 gigatons of carbon to the total global biomass, making them an unparalleled wellspring of LCB resources.¹ This vast reserve of renewable resources includes the fibrous components of plants, such as cellulose, hemicellulose, and lignin. LCB, sourced from a diverse array of origins, including agricultural residues, forest waste, and specialized energy crops, represents an untapped reservoir that, if effectively harnessed, could help mitigate the energy crisis that looms over us.² The increasing interest in the production of value-added organic acids from LCB stems from the fact that these acids retain a substantial portion of critical elements like carbon and oxygen, aligning seamlessly with the high atomic economy principle.³

Beyond its pivotal role in the energy landscape, lactic acid (LA), a versatile and valuable compound, holds a critical place in various industries. The majority of non-polymer grade LA and its salts find extensive use in the food industry. LA also serves as a foundational element for the synthesis of various chemicals, including acrylic acid, acetaldehyde, pyruvic acid, 2,3-pentanedione, 1,2-propanediol, LA esters, and polylactic acid.⁴ Polymer-grade LA plays a crucial role in biomedical research and applications, serving as an essential raw material for the production of eco-friendly polylactic acid plastics. The multifaceted utility of LA underscores its significance as a highly sought-after product in today's global market.⁵

To unlock the full potential of LCB and meet the increasing demand for LA, researchers have directed their focus towards two promising methodologies: microbial fermentation and chemical catalytic conversion. These pioneering approaches provide environmentally sustainable and economically viable routes for converting LCB into LA. Microbial fermentation harnesses the capabilities of microorganisms to provide a sustainable and biologically efficient method for LA production.⁶ Microorganisms excel at efficiently utilizing the various sugars found in LCB hydrolysates, including glucose and xylose.⁷ This makes them particularly well-suited for the conversion of LCB into LA. However, industrial microbial fermentation for LA production is still in its first generation, primarily utilizing starch as the raw material. Challenges must be overcome, including the hydrolysis process, as well as the

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separation and purification processes, in order to achieve cost-effective LA production from LCB (a second-generation substrate).^{8,9} Conversely, chemical catalytic conversion, utilizing catalysts and precise reaction conditions, offers an alternative pathway to convert LCB into LA.¹⁰ It can efficiently convert monosaccharides into LA¹¹ and achieve direct catalytic conversion of cellulose and hemicellulose into LA,^{12,13} significantly simplifying the LCB pretreatment process. Nevertheless, the industrial application of chemical catalytic conversion for LCB-based LA production is still in its early stages, and there's a need for improvement in the selectivity and yield of catalytic conversion for complex substrates.¹⁴

Bibliometric analysis stands as a potent instrument, offering valuable insights into the trajectory and progression of research across diverse scientific domains.^{15–17} This paper employs bibliometric analysis to provide a comprehensive overview of current research on LA production from LCB. We focus on publication characteristics, keywords, and co-citation to uncover research trends and current standing in this field. Our objective is to offer insights into the present research landscape and potential future directions, contributing to more efficient and sustainable LA production from LCB, addressing environmental concerns, and enabling cost-effective processing.

Methods

Data sources

Scientific output data were retrieved from the Science Citation Index Expanded (SCIE) database and the 2021 Journal Citation Reports (JCR) of Web of Science on July 7th, 2023. The 2021 JCR encompasses 21 494 journals spanning 254 scientific disciplines across 111 countries/regions. For this study, specific keywords (“cellulose*” or “lignocellulose*” or “straw” or “stalk” or “stover” or “bagasse” or “corn cob”) and (“lactate” or “lactic acid”) were employed to focus on the period between 1991 and 2022. To ensure precise analysis of LA production from lignocellulose materials, articles pertaining to “bacterial cellulose production” were excluded. A total of 2847 publications concerning LA production from LCB were initially identified in the SCIE. Given that articles constituted the primary document category, the subsequent analysis focused on 2576 articles.

Content analysis

CiteSpace, developed by Chen,¹⁸ is a visual analytic tool employed in this study to analyze trends and patterns within the scholarly literature of specific disciplines during a defined timeframe. In particular, this article utilized CiteSpace Software (version 6.2.R4 Advanced (64-bit)) to generate comprehensive knowledge maps within the LA production from LCB. These maps elucidate research overviews, trends, and focal points through constructs such as co-citation networks and citation bursts. Furthermore, Gephi (version 0.9.7) was utilized to visualize networks depicting co-authors' affiliations and co-authors' country/region associations. This visualization was facilitated using the Force Atlas2 layout.¹⁶ The reported journal impact factors were sourced from the 2021 JCR. In the context of gauging the influence of

institutions or countries within a specific research domain, the *h*-index was employed as a commonly accepted indicator. The *h*-index was defined based on the total articles (TA) with at least *h* citations each and the remaining (TA-*h*) articles with a maximum of $\leq h$ citations each.^{16,19}

Results and discussions

Publication characteristics

Characteristics of publication outputs. The inaugural article on this subject, titled “formation and consumption of lactate during methane fermentation of cellulose” was published in the *Microbiology* journal in 1978. The author investigated the buildup and utilization of lactate during the extensive degradation of cellulose, as well as in the phase of vigorous gas production. This observation provided insights into the mechanisms underlying LA production and consumption within a mixed culture system.²⁰ Fig. 1 illustrates the progression of publications related to LA production from LCB spanning from 1991 to 2022. Initially, from 1991 to 2008, the number of relevant research publications exhibited a gradual increase marked by fluctuations, with a modest growth rate of 1.51 articles per year. This phase was characterized by the nascent stage of research activities in this domain. Post-2009, the annual count of publications underwent a dramatic surge, registering a growth rate of 20.19 articles per year. This accelerated growth can be attributed to an increasing focus among researchers on pivotal areas such as strain screening and modification,²¹ substrate pretreatment and degradation,²² and byproduct utilization and pollution reduction.²³ Throughout the period from 1991 to 2021, the annual tally of publications soared from 39 to 333. Notably, the ratio of annual articles to the overall annual publications remained consistently high, with the annual article/annual all publications ratio reaching an impressive 86.49% in 2022.

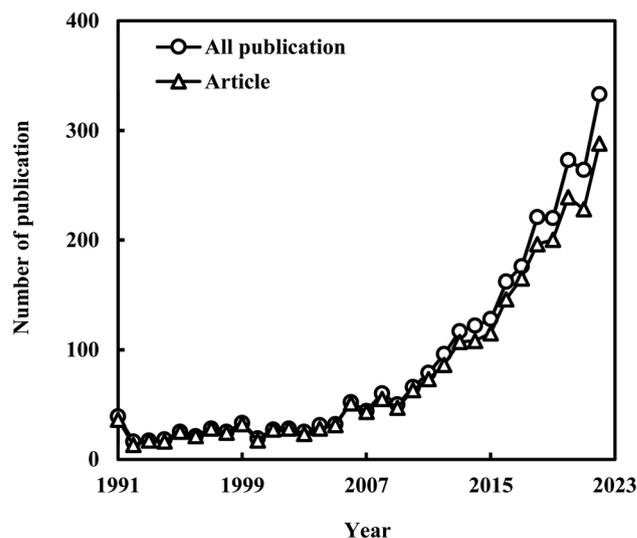


Fig. 1 Publication count of lactic acid production from lignocellulosic biomass (1991–2022).



The distribution of journals. A total of 2576 articles were published across 690 journals, although the majority of these journals (669 or 96.95%) featured fewer than 20 articles each concerning LA production from LCB. The performance analysis presented in Table 1 pertains to the top 10 most productive journals. This analysis encompasses metrics such as total publications, *h*-index, citations per article, journal impact factor, and the country of publication. Due to the significant variation in publication frequencies among these journals, the utility of the *h*-index as a research level indicator may be compromised. In light of this, the citations per article metric is employed for meaningful inter-journal comparisons. In the realm of the top ten productive journals, three hail from the UK and the Netherlands, two from the United States, and one each from Germany and Switzerland. This underscores the prevailing prominence of developed countries in journal publications. Together, these top 10 journals were responsible for 19.76% of the entire compilation of LA production from LCB articles.

Bioresource Technology stands out as the foremost journal, having published 180 (6.99%) articles. It is followed by *Applied Microbiology and Biotechnology* with 48 (1.86%) articles, *Biotechnology for Biofuels* with 42 (1.63%) and *Applied Biochemistry and Biotechnology* with 41 (1.59%). Through a comparative analysis of *h*-index, citations per article, and journal impact factor, intriguing patterns and phenomena can be unveiled. In an intriguing twist, *Green Chemistry* and *Applied and Environmental Microbiology*, though ranked fifth and eighth in terms of total publications, clinch the third and fifth spots in *h*-index, boasting 23 and 21 respectively. Moreover, they secure the top and third positions in citations per article values, standing at 75.24 and 47.52 correspondingly. This phenomenon underscores that *Green Chemistry* and *Applied and Environmental Microbiology* hold undisputed status as the most impactful and widely recognized journals for LA production from LCB. In a similar vein, *Carbohydrate Polymers*, securing the tenth rank with a modest 29 articles, manages to attain a relatively high *h*-index of 19 (6), an impressive citations per article value of 49.52 (2), and a substantial journal impact factor of 11.2. This outcome illuminates that while *Carbohydrate Polymers* may encompass a smaller quantity of LA production from LCB articles, these articles command considerable attention and acclaim.

The output of institutes. A total of 2520 articles containing author address information from 2325 institutes were published between 1991 and 2021. Table 2 presents the top 10 most productive institutions. Among these, seven were from China, while Denmark, the USA, and Spain each represented one, highlighting the prominent role of Chinese institutes in LA production from LCB. Leading the pack is the Chinese Academy of Sciences, China, securing the top position in total publications (92), collaborated institutions (108), and *h*-index (31), while ranking sixth in citations per article (33.98). It embarked on research in LA production from LCB relatively early, with its first article published in 1998. Ranked second in total publications (54) and *h*-index (21) is Nanjing Agricultural University, China. However, it holds the sixth, fifth, and seventh spots in terms of the year of first occurrence (2007), collaborated institutions (34), and citations per article (24.37), respectively. This demonstrates its substantial output quantity but relatively weaker influence in LA production from LCB. A noteworthy mention goes to the Technical University of Denmark, Denmark, securing the seventh position. With the earliest year of first occurrence (1995) and the highest citations per article (41.78), it showcases an extensive research history and high-quality output in LA production from LCB. Betweenness centrality gauges the impact of research entities across the entire field, with higher values indicating greater influence. By this measure, the Chinese Academy of Sciences, China, ranks first with a value of 0.27, thus exerting a considerable influence on LA production from LCB. Following suit is the Technical University of Denmark, Denmark (0.07) and China Agricultural University, China (0.06) underscoring the significant influence of these institutions in the domain of LA production from LCB.

Contribution of country/region. Between 1991 and 2021, a total of 2520 articles with author address information were published across 87 countries/regions. Table 3 highlights the top 10 high-productivity countries in LA production from LCB, contributing a combined 81.63% of the total publications. Notably, China emerges as the foremost contributor, publishing a substantial 736 articles, surpassing other countries by a considerable margin. The USA holds the top position in the year of first occurrence (1991), *h*-index (65), and citations per article (47.50), signifying its comprehensive impact and high-

Table 1 Performance analysis of the top 10 high-productivity journals^a

Journal	TP (%)	<i>h</i> -Index (R)	TC/TP (R)	JIF	Country
<i>Bioresource Technology</i>	180 (6.99)	53 (1)	44.78 (4)	11.4	Netherlands
<i>Applied Microbiology and Biotechnology</i>	48 (1.86)	24 (2)	35.52 (5)	5.0	Germany
<i>Biotechnology for Biofuels</i>	42 (1.63)	22 (4)	35.10 (6)	6.3	UK
<i>Applied Biochemistry and Biotechnology</i>	41 (1.59)	19 (6)	25.39 (7)	3.0	USA
<i>Green Chemistry</i>	37 (1.44)	23 (3)	75.24 (1)	9.8	UK
<i>Industrial Crops and Products</i>	35 (1.36)	16 (8)	22.89 (8)	5.9	Netherlands
<i>Animal Feed Science and Technology</i>	33 (1.28)	16 (8)	21.12 (9)	3.2	Netherlands
<i>Applied and Environmental Microbiology</i>	33 (1.28)	21 (5)	47.52 (3)	4.4	USA
<i>Frontiers in Microbiology</i>	31 (1.20)	13 (10)	15.71 (10)	5.2	Switzerland
<i>Carbohydrate Polymers</i>	29 (1.13)	19 (6)	49.52 (2)	11.2	UK

^a TP: total publication; R: the rank, out of the top 10 most productive journals; TC/TP: total citation/total publication; JIF: journal impact factor.



Table 2 Performance analysis of the top 10 high-productivity institutions^a

Institution	TP (%)	YFO	BC	CI	<i>h</i> -Index (R)	TC/TP (R)
Chinese Acad. Sci., China	92 (3.65)	1998	0.27	108	31 (1)	33.98 (6)
Nanjing Agr. Univ., China	54 (2.14)	2007	0.04	34	21 (2)	24.37 (7)
China Agr. Univ., China	47 (1.87)	2006	0.06	54	20 (3)	19.98 (9)
Beijing Forestry Univ., China	38 (1.51)	2011	0.02	30	18 (4)	38.58 (2)
Nanjing Forestry Univ., China	32 (1.27)	2012	0.02	25	14 (7)	20.09 (8)
Univ. Chinese Acad. Sci., China	28 (1.11)	2010	0.02	40	14 (7)	35.32 (5)
Tech. Univ. Denmark, Denmark	27 (1.07)	1995	0.07	36	17 (5)	41.78 (1)
East China Univ. Sci. & Technol., China	27 (1.07)	2013	0.03	20	11 (10)	12.93 (10)
Univ. Georgia, USA	25 (0.99)	1997	0.01	18	14 (7)	36.00 (3)
Univ. Vigo, Spain	24 (0.95)	1999	0.01	20	17 (5)	35.58 (4)

^a TP: total publication; YFO: year of first occurrence; BC: betweenness centrality; CI: collaborated institution number; R: the rank, out of the top 10 most productive institutions; TC/TP: total citation/total publication.

Table 3 Performance analysis of the top 10 high-productivity Countries^a

Country	TP (%)	YFO	BC	CC	<i>h</i> -Index (R)	TC/TP (R)
China	736 (29.21)	1997	0.30	42	62 (2)	24.15 (7)
USA	370 (14.68)	1991	0.20	41	65 (1)	47.5 (1)
Japan	197 (7.82)	1991	0.10	22	44 (3)	29.24 (5)
India	152 (6.03)	1992	0.03	26	30 (6)	21.33 (9)
Germany	132 (5.24)	1991	0.29	41	38 (4)	38.71 (2)
Spain	130 (5.16)	1996	0.12	28	34 (5)	31.82 (4)
South Korea	102 (4.05)	1997	0.01	16	28 (7)	24.98 (6)
Brazil	93 (3.69)	1994	0.12	21	26 (9)	21.6 (8)
Italy	73 (2.90)	1996	0.13	31	22 (10)	19.62 (10)
UK	72 (2.86)	1991	0.10	32	28 (7)	37.78 (3)

^a TP: total publication; YFO: year of first occurrence; BC: betweenness centrality; CC: collaborated country number; R: the rank, out of the top 10 most productive countries; TC/TP: total citation/total publication.

quality output in this domain. Remarkably, despite being ranked fifth, Germany secures the second position in betweenness centrality value (0.29), collaborated country count (41), and citations per article (38.71). These rankings underscore Germany's relatively modest research volume but extensive international collaboration and significant influence. India, positioned fourth in terms of total publications (360), occupies the ninth spot in betweenness centrality value (0.03) and citations per article (21.33). This outcome suggests the need for strengthening research quality within the Indian context.

Fig. 2 illustrates three distinct clusters that vary in terms of countries/regions and publication volumes. Cluster I stands out as the largest and most intricate group, encompassing 18 countries/regions, with China, the USA, Japan, and South Korea emerging as the most prolific contributors. In Cluster II, which comprises 16 countries/regions, Germany, Spain, and Brazil serve as the central nodes. Meanwhile, Cluster III consists of 25 countries/regions, predominantly from Europe and Asia, where France, the Netherlands, the UK, and India hold central positions. In terms of collaborative efforts, the China-USA partnership claims the top spot with 58 cooperative publications. Following closely are China-Japan (38), China-Canada (14), and China-Australia (12) collaborations.

Research tendencies and hotspots

Author keywords analysis. Examining author keywords constitutes a vital facet of bibliometric research, offering invaluable insights into the research interests and thematic focus of authors within a specific field or discipline. These keywords are usually selected by authors themselves, reflecting their personal interpretation of the primary topics and concepts addressed in their work. Serving as a focal point of information within an article, author keywords facilitate the extraction of research trends.²⁴ Table 4 showcases the temporal progression of the 30 most frequently employed author keywords across four distinct periods, along with the corresponding year of their inaugural appearance.

In this paper, the data was collected by including “lactate” and “lactic acid” as essential components of the search phrase. This approach resulted in notable frequencies for terms such as “lactic acid”, “lactic acid bacteria”, “polylactic acid”, “L-lactic acid”, “lactic acid fermentation”, and “D-lactic acid”. The term “lactic acid” consistently emerges as the most frequently used keyword across all periods, boasting a frequency of 316 and a relative occurrence ranging from 3.56% to 5.21%. Ranked second among author keywords, “lactic acid bacteria” ascended from the 11th position in the years 1991–1998 to claim second place during 1999–2006, maintaining its fourth-place ranking ever since. “Polylactic acid”, holding the third position among author keywords, represents a thermoplastic polyester formed through the condensation of LA with water release. Remarkably, this keyword was absent before 2007. However, its ranking has substantially risen, securing second and fourth positions during the periods 2007–2014 and 2015–2022, respectively. As for “L-lactic acid” and “D-lactic acid”, the two isomers of LA, they did not feature before 1999. Yet, their rankings quickly ascended to 11th and 14th places, respectively, during the period 2015–2022. This trend underscores the growing research focus on the production of optically pure L- or D-LA from LCB. Additionally, “lactic acid fermentation”, ranking 15th among author keywords, made its debut in 1992 and has consistently maintained high-frequency usage. This underscores the extensive research concentration on microbial fermentation of LCB into LA.



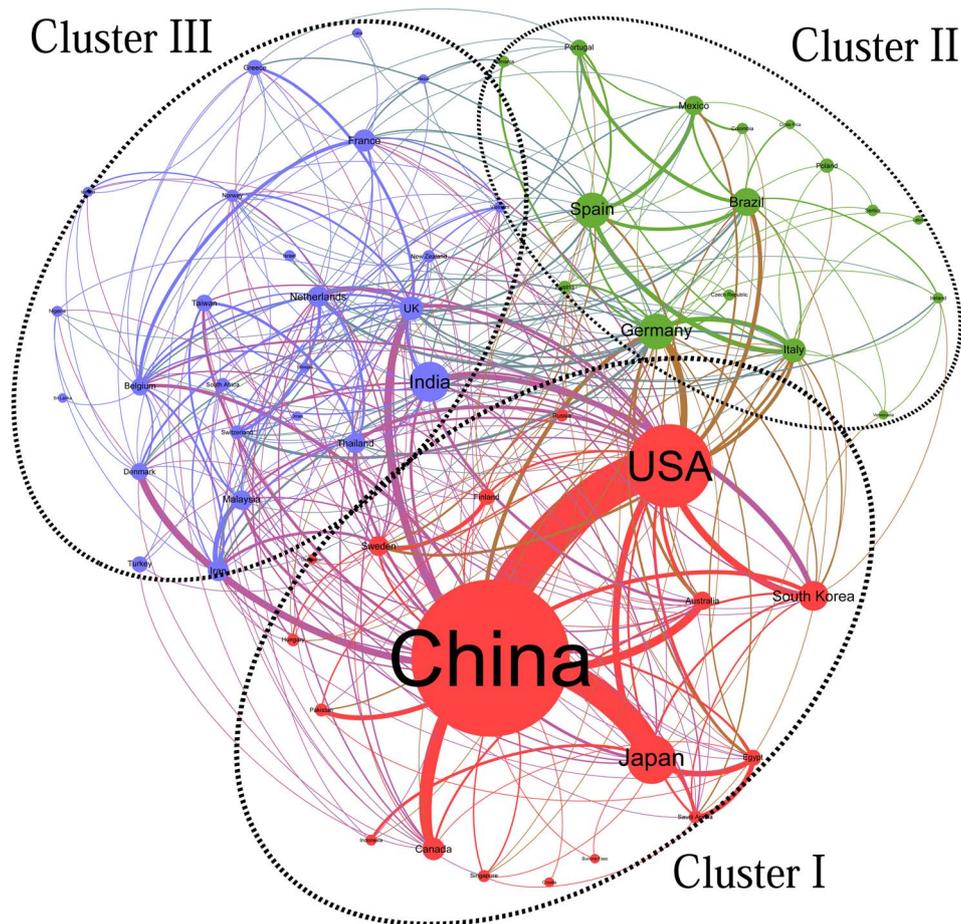


Fig. 2 Network diagram illustrating cooperation between countries/regions.

Through the inclusion of crucial elements such as “cellulose*”, “lignocellulose*”, “straw”, “stalk”, “stover”, “bagasse”, and “corn cob” in the search phrase, the focus of the analysis was achieved. Notably, author keywords like “lignocellulosic biomass”, “corn stover”, “rice straw”, “sugarcane bagasse”, “wheat straw”, and “sugar beet pulp” have garnered substantial attention in recent years. Both “lignocellulosic biomass” and “corn stover”, ranked fourth and seventh among author keywords, respectively, did not make appearances between 1991 and 1998. Nevertheless, their frequency and ranking have consistently increased in subsequent periods. The terms “rice straw”, “sugarcane bagasse”, “wheat straw”, and “sugar beet pulp” exhibit a similar pattern, with their rankings displaying certain fluctuations over the four stages. The pretreatment of LCB, a bottleneck in LA production, has garnered substantial attention from researchers. Notably, representative methods like enzymatic hydrolysis and deep eutectic solvents (DESs) have emerged as key focal points, ranking fifth and sixth, respectively. Enzymatic hydrolysis of LCB refers to the process of liberating monomeric sugars from the structural carbohydrates cellulose and hemicellulose.²⁵ DESs, on the other hand, constitute systems formed by a eutectic mixture of Lewis or Brønsted acids and bases, which can encompass a range of anionic and/or cationic species.²⁶

DESs made their debut in 2017, subsequently experiencing an explosive growth in related articles. This surge indicates the extensive research interest in utilizing DESs for the pretreatment of LCB.

Microbial fermentation, serving as the primary pathway for LA production from LCB, has garnered significant attention, with related author keywords attracting substantial focus. Notably, “*Bacillus coagulans*”, which has been reclassified as *Weizmannia coagulans*,²⁷ emerged in 2007 and subsequently experienced explosive growth in related articles, securing the eighth position between 1991 and 2022. *W. coagulans*, a LA-forming bacterial species with a history spanning over a century since its first report, has found extensive application in the production of l-LA.²⁸ Furthermore, author keywords like “metabolic engineering”, “*Saccharomyces cerevisiae*”, and “*Escherichia coli*” hold the 10th, 11th, and 24th rankings, respectively. Of notable significance, extensive research has been undertaken on the production of LA from LCB through metabolically engineered *S. cerevisiae*^{29,30} and *E. coli*.^{31–33} Additionally, LA often emerges as a byproduct in systems where *S. cerevisiae* produces ethanol from LCB.³⁴

Ranked 21st among author keywords, “*Lactobacillus plantarum*” has found wide application in the production of silage through the fermentation of LCB such as corn stalk and rice



Table 4 Top 30 most frequently used substantives in author keywords across five periods^a

Keywords	TP	YFO	91–22 R (%)	91–98 R (%)	99–06 R (%)	07–14 R (%)	15–22 R (%)
Lactic acid	316	1995	1 (4.67)	1 (3.56)	1 (4.02)	1 (5.21)	1 (4.63)
Lactic acid bacteria	77	1998	2 (1.14)	11 (0.40)	2 (1.28)	4 (0.99)	4 (1.21)
Polylactic acid	75	2007	3 (1.11)	NA	NA	2 (1.41)	4 (1.21)
Lignocellulosic biomass	67	2004	4 (0.99)	NA	47 (0.18)	10 (0.63)	3 (1.25)
Enzymatic hydrolysis	62	1999	5 (0.92)	NA	7 (0.55)	3 (1.13)	6 (0.94)
Deep eutectic solvents	61	2017	6 (0.90)	NA	NA	NA	2 (1.34)
Corn stover	45	1997	7 (0.66)	11 (0.40)	15 (0.37)	7 (0.70)	7 (0.70)
<i>Bacillus coagulans</i>	41	2007	8 (0.61)	NA	NA	5 (0.78)	8 (0.66)
Rice straw	41	2001	8 (0.61)	NA	15 (0.37)	7 (0.70)	10 (0.64)
Metabolic engineering	39	2010	10 (0.58)	NA	NA	10 (0.63)	8 (0.66)
L-Lactic acid	36	2003	11 (0.53)	NA	15 (0.37)	10 (0.63)	11 (0.55)
<i>Saccharomyces cerevisiae</i>	36	2000	11 (0.53)	NA	4 (0.73)	5 (0.78)	14 (0.46)
Simultaneous saccharification and fermentation	35	1997	13 (0.52)	11 (0.40)	2 (1.28)	10 (0.63)	17 (0.40)
Mechanical properties	30	1997	14 (0.44)	11 (0.40)	7 (0.55)	14 (0.56)	17 (0.40)
Fermentation quality	27	1999	15 (0.40)	NA	47 (0.18)	39 (0.21)	13 (0.48)
Lactic acid fermentation	27	1992	15 (0.40)	5 (0.79)	47 (0.18)	15 (0.49)	17 (0.40)
Microbial community	27	2007	15 (0.40)	NA	NA	24 (0.28)	12 (0.51)
Sugarcane bagasse	26	2005	18 (0.38)	NA	15 (0.37)	24 (0.28)	16 (0.44)
D-Lactic acid	25	2006	19 (0.37)	NA	47 (0.18)	39 (0.21)	14 (0.46)
Lactate dehydrogenase	23	1991	20 (0.34)	2 (2.77)	4 (0.73)	39 (0.21)	31 (0.20)
Acetic acid	22	2002	21 (0.32)	NA	15 (0.37)	7 (0.70)	29 (0.22)
<i>Lactobacillus plantarum</i>	22	2000	21 (0.32)	NA	15 (0.37)	65 (0.14)	17 (0.40)
Wheat straw	21	2002	23 (0.31)	NA	15 (0.37)	24 (0.28)	21 (0.33)
<i>Escherichia coli</i>	19	1998	24 (0.28)	11 (0.40)	15 (0.37)	20 (0.35)	25 (0.24)
Consolidated bioprocessing	18	2010	25 (0.27)	NA	NA	15 (0.49)	25 (0.24)
Anaerobic digestion	17	1995	26 (0.25)	11 (0.40)	NA	24 (0.28)	22 (0.26)
<i>Clostridium thermocellum</i>	16	1994	27 (0.24)	11 (0.40)	NA	17 (0.42)	31 (0.20)
<i>Rhizopus oryzae</i>	16	1999	27 (0.24)	NA	15 (0.37)	17 (0.42)	39 (0.18)
Sugar beet pulp	16	2001	27 (0.24)	NA	47 (0.18)	17 (0.42)	31 (0.20)
Cellulose acetate	15	1995	30 (0.22)	11 (0.40)	15 (0.37)	65 (0.14)	29 (0.22)

^a TP: total publication; YFO: year of first occurrence; R: the rank; NA: not appear.

straw.^{35,36} Additionally, metabolically engineered *L. plantarum* exhibits the ability to utilize xylose, achieving efficient D-LA production from LCB.³⁷ Since its initial appearance in 1999, “fermentation quality” has consistently attracted attention, signifying a considerable body of research focused on enhancing the fermentation quality of silage feed.³⁸ At the 27th rank among author keywords, “*Clostridium thermocellum*” displays the capability to degrade lignocellulosic materials to generate hydrogen, lactate, and ethanol. Moreover, it enhances the enzymatic hydrolysis of cellulosic substrates, playing a pivotal role in the consolidated bioprocessing of lignocellulose into lactate and ethanol.^{39,40} “*Rhizopus oryzae*”, first appearing in 1999, demonstrates the ability to secrete cellulase and hemicellulase, utilizing glucose, xylose, and sucrose for the production of L-LA.⁴¹ These attributes position *R. oryzae* as a potential candidate for generating L-LA from LCB. The fifteenth-ranked author keyword, “microbial community”, has garnered considerable attention in recent decades. This trend underscores the extensive research focus on mixed culture systems for LA or silage production through the fermentation of LCB.^{42,43}

Ranked 13th among author keywords, “simultaneous saccharification and fermentation (SSF)” stands out as distinct from separate hydrolysis and fermentation (SHF), as it

combines saccharification and fermentation processes at the same location. The SSF system offers a shorter time period and reduced feedback inhibition compared to SHF.⁴⁴ Presently, this mode constitutes the primary fermentation approach for producing LA from LCB. “Anaerobic digestion”, which first appeared in 1995, disappeared during the subsequent period of 1999–2006. However, it experienced a resurgence since 2007, quickly becoming a research hotspot. Notably, LA fermentation strains are typically either obligate anaerobes or facultative anaerobes. Analyzing the author keywords provides an overview of the research on LA production from LCB.

Co-citation reference analysis. The CiteSpace software was utilized to construct a co-citation network based on articles published between 1991 and 2022, with each year representing a discrete time slice (Fig. 3). The modularity score and silhouette score serve as two extensively employed metrics for evaluating the effectiveness of clustering algorithms.⁴⁵ The modularity score assesses the significance and meaningfulness of the clustering arrangement, with values exceeding 0.3 indicating a pronounced clustering structure.^{46,47} Conversely, the silhouette score measures the resemblance among data points within a cluster and the dissimilarity across various clusters; values surpassing 0.7 denote a clustering structure of high reliability.⁴⁸ In the context of this study (Fig. 3 and Table 5), the



CiteSpace, v. 6.2.R4 (64-bit) Advanced
 August 23, 2023 at 8:22:58 AM CST
 WoS: C:\Users\15652\Desktop\Lactic acid\Data
 Timespan: 1991-2022 (Slice Length=1)
 Selection Criteria: Top 100.0% per slice, up to 100, LRF=3.0, L/N=10, LBY=5, e=1.0
 Network: N=8491, E=30138 (Density=0.0008)
 Nodes Labeled: 1.0%
 Pruning: None
 Modularity Q=0.9609
 Weighted Mean Silhouette S=0.964
 Harmonic Mean(Q, S)=0.9625

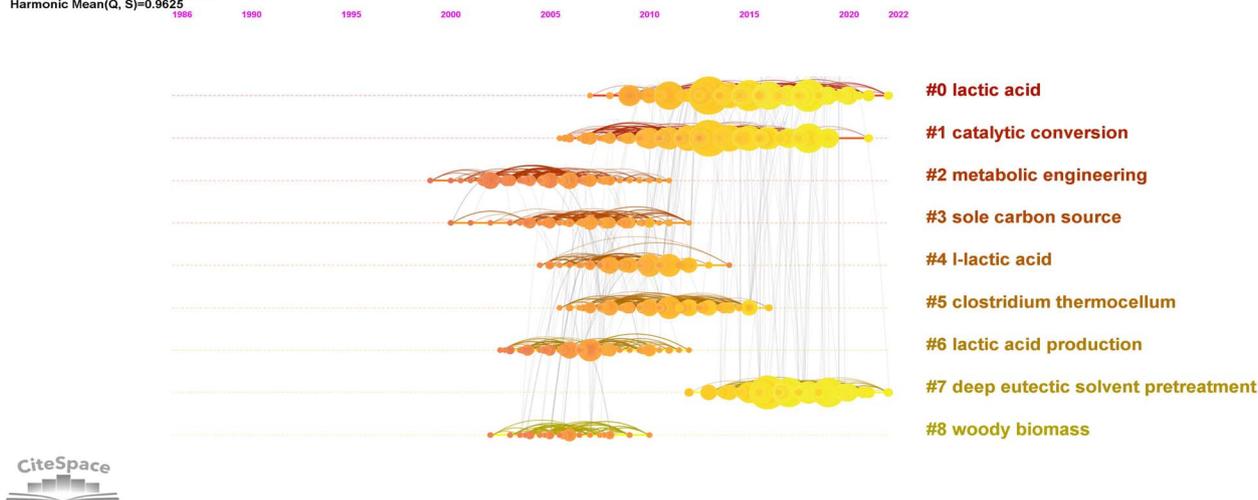


Fig. 3 Timeline-based reference network visualization of lactic acid production from lignocellulosic biomass (lighter colors indicate closer time, darker colors indicate distant time).

clustering structure holds significance, and the clustering is characterized by both rationality and high reliability. Table 5 provides insights into the top nine co-citation clusters, encompassing four key research trends. Among these trends, three are linked to microbial conversion, involving substrate pretreatment and degradation, microbial selection and engineering, and fermentation process optimization, while the remaining trend pertains to chemical catalytic conversion.

The research trend identified concerns substrate pretreatment and degradation consisting of four clusters with the average publication timeframe spanning from 2006 to 2017. The clusters were characterized by their silhouette score, size, and mean year of publication. Cluster #3, designated as “sole carbon source” (silhouette score = 0.931; 183; 2007), highlights

enhancing LA fermentation *via* efficient LCB pretreatment. *Bacillus* strains show promise for LA production. Recombinant cellulolytic *B. subtilis* integrates cellulose hydrolysis and fermentation, simplifying the process for potential ethanol production and comprehensive biorefinery approaches.⁴⁹ Cluster #6, identified as “lactic acid production” (silhouette score = 0.956; 150; 2007), reflects a modern approach to LA production. It emphasizes efficient pretreatment and degradation of LCB, particularly recycled paper sludge, to enhance sustainable LA fermentation from various sources, promoting eco-friendly and resource-efficient processes.^{50,51} Cluster #8, denoted as “woody biomass” (silhouette score = 0.973; 146; 2006), signifies the focus on woody biomass pretreatment for LA production, employing techniques such as hot water, sulfuric

Table 5 Analysis of co-citation clusters in references

Cluster ID	Size	Silhouette	Mean (year)	Latent semantic indexing (LSI)
0	374	0.933	2015	Lactic acid; lactic acid production; <i>Bacillus coagulans</i> ; lignocellulosic biomass; L-lactic acid production
1	330	0.902	2012	Lactic acid; catalytic conversion; direct conversion; organic acid; levulinic acid
2	217	0.959	2005	Metabolic engineering; thermophilic bacterium; high yield; ethanologenic bacteria; engineering biocatalyst
3	183	0.931	2007	Sole carbon source; other organic nutrient; recombinant cellulolytic <i>Bacillus subtilis</i> ; one-step production; ethanol production
4	182	0.918	2009	L-Lactic acid; efficient production; <i>Bacillus coagulans</i> ; lactic acid; biomass-derived xylose
5	154	0.983	2010	<i>Clostridium thermocellum</i> ; hydrogen production; major catabolic pathway; linking genome content; production yield
6	150	0.956	2007	Lactic acid production; lactic acid; new trend; renewable biomass; recycled paper sludge
7	148	0.986	2017	Deep eutectic solvent pretreatment; wheat straw; acidic deep eutectic solvent pretreatment; bioethanol production; enhanced enzymatic saccharification
8	146	0.973	2006	Woody biomass; sweet sorghum stalk; fuel ethanol production; cellulosic material; yeast fermentation



acid, enzymatic degradation, and ammonia recycle percolation.^{52–54} Cluster #7, labeled as “deep eutectic solvent pretreatment” (silhouette score = 0.986; 148; 2017), the most recent cluster for substrate pretreatment. Typically, DES is created by blending quaternary ammonium halide salts with a neutral organic hydrogen bond donor, resulting in a complex of halide ions and solvent molecules.⁵⁵ Prior research has demonstrated the effective pretreatment capabilities of DES on lignocellulosic materials. It facilitates the efficient separation of cellulose and lignin,^{56,57} establishing a basis for subsequent enzymatic cellulose hydrolysis to yield sugars and microbial fermentation for LA production.^{22,58}

The microbial selection and engineering can be classified into two distinct clusters. Cluster #2, named “metabolic engineering” (silhouette score = 0.959; 217; 2005), signifies the substantial research conducted on producing LA from LCB using genetically modified strains. The isolation of acid-tolerant, thermophilic strains such as *B. coagulans*,⁵⁹ and the application of metabolic engineering to modify strains such as *S. cerevisiae*⁶⁰ and *L. delbrueckii*,⁶¹ have both proven effective in facilitating microbial strains to utilize LCB for LA production. Cluster #5, designated “*Clostridium thermocellum*” (silhouette score = 0.983; 154; 2010), has gained prominence for its remarkable capacity to efficiently break down LCB. Researchers have conducted extensive studies on the metabolic pathways of *C. thermocellum*,⁶² employing genetic engineering to enhance LA and ethanol production. This approach has proven highly efficient in the production of LA and ethanol from LCB.^{63,64}

The research on the fermentation process optimization consists of two clusters, with the average publication years of 2009 and 2015, respectively. Cluster #4, referred to as “L-lactic acid” (silhouette score = 0.918; 182; 2009), highlights the importance of refining the fermentation process for the efficient production of L-LA from LCB. By optimizing fermentation parameters, such as pH control and fermentation mode, and employing strains like *B. coagulans* and *Lactobacillus* sp., a significant enhancement is observed in the conversion of pentose and hexose obtained from LCB into high-purity L-LA.^{65–67} Cluster #0, labeled as “lactic acid” (silhouette score = 0.933; 374; 2015), represents the largest cluster in the production of LA from LCB. The prior research achievements, including the adoption of SSF,⁶⁸ detoxification of lignocellulosic hydrolysates,⁶⁹ and the production of LA under non-sterile conditions,⁷⁰ have collectively facilitated the economically viable and efficient fermentation of LA from LCB.

The identified research trend focuses on chemical catalytic conversion, represented by a cluster with an average publication year of 2012. Cluster #1, denoted as “catalytic conversion” (silhouette score = 0.902; 330; 2012), the second-largest cluster with 330 publications, underscores the increasing attention towards the direct catalytic conversion of LCB to LA and its derivatives, signifying a relatively recent area of significant interest. Chemical catalysis can be broadly categorized into photochemical catalysis,⁷¹ biocatalysis,⁷² acid–base catalysis, metal catalysis,⁷³ and more. It typically involves acid–base or metal catalysis to transform LCB into LA under specific temperature, pressure, and atmospheric conditions.⁷⁴

Importantly, the transition of LCB into LA encompasses sequential stages such as LCB pretreatment, cellulose and hemicellulose hydrolysis, and catalytic conversion of monosaccharides into LA (Fig. 4).^{74–76} The conversion of glucose and xylose, the primary monosaccharides in LCB hydrolysates, into LA entails a series of catalytic processes. Glucose’s catalytic conversion involves its isomerization into fructose, retro-aldol condensation of fructose to produce dihydroxyacetone, followed by dehydration, hydration, and isomerization, resulting in LA production.^{3,76} Conversely, xylose’s catalytic conversion includes retro-aldol condensation, yielding dihydroxyacetone. Dihydroxyacetone then undergoes tautomeric isomerization and dehydration to produce 2-hydroxypropenal, followed by keto–enol tautomeric isomerization, hydration, and isomerization, ultimately resulting in LA production.⁷⁵

The inception of this field initially focused on achieving the homogeneous catalytic conversion of triose sugars into LA derivatives.⁷⁷ Pioneering research in this domain established the foundation for the direct catalytic synthesis of LA from LCB.^{78,79} Numerous metal cations, including Pb(II), Al(III), Bi(III), In(III), Zn(II), Sn(II), Co(II), Ni(II), Fe(II), and Mn(II), have been recognized for their catalytic roles in converting cellulose into LA. Notably, Pb(II) demonstrated an exceptional LA yield of 68% under anaerobic conditions (N₂ atmosphere of 3 MPa, temperature: 463 K, time: 4 hours).¹² In a similar vein, Tang *et al.* (2014) reported the efficacy of homogeneous vanadyl cations as catalysts for transforming ball-milled cellulose into LA, achieving a yield of 54% under anaerobic conditions (N₂ atmosphere of 2 MPa, temperature: 453 K, time: 2 hours).⁸⁰ However, aerobic conditions led to the formation of formic acid instead of LA. Recent research underscores the effectiveness of dual-metal cations like Al(III)–Sn(II), Al(III)–In(III), Al(III)–Mn(II), Al(III)–Cu(II), and Al(III)–Ni(II) over single metal cations for cellulose-to-LA conversions. Among them, Al(III)–Sn(II) (ratio = 1 : 1) displayed optimal performance, yielding 65% LA from ball-milled cellulose under anaerobic conditions (N₂ atmosphere of 3 MPa, temperature: 463 K, time: 2 hours).³ Additionally, the direct separation of LA from synthetic solutions derived from LCB has become a noteworthy subject of investigation.⁸¹

Lignocellulosic biomass. LCB primarily consists of cellulose, hemicellulose, and lignin, constituting over 90% of its dry matter, along with smaller quantities of minerals, oils, and other constituents.⁶ Fig. 5a illustrates the most frequently used LCB sources for LA production, ranked in descending order of prevalence: corn waste, wheat straw, rice straw, and sugarcane bagasse. Whether employing microbial fermentation or chemical catalysis for LA production, LCB pretreatment is essential to overcome its recalcitrance. The elevated lignin content has adverse effects on the pretreatment process.⁸² These highly utilized LCB sources share common characteristics, including high cellulose (25–45%) and hemicellulose (23–36%) content, and low lignin content (6.1–25%), making them more advantageous compared to pine, spruce, and grasses.⁸³ Furthermore, these lignocellulosic biomasses are cost-effective and readily accessible.

Corn waste, including corn stalks and cobs, has been the subject of growing interest in recent years, with a total of 437



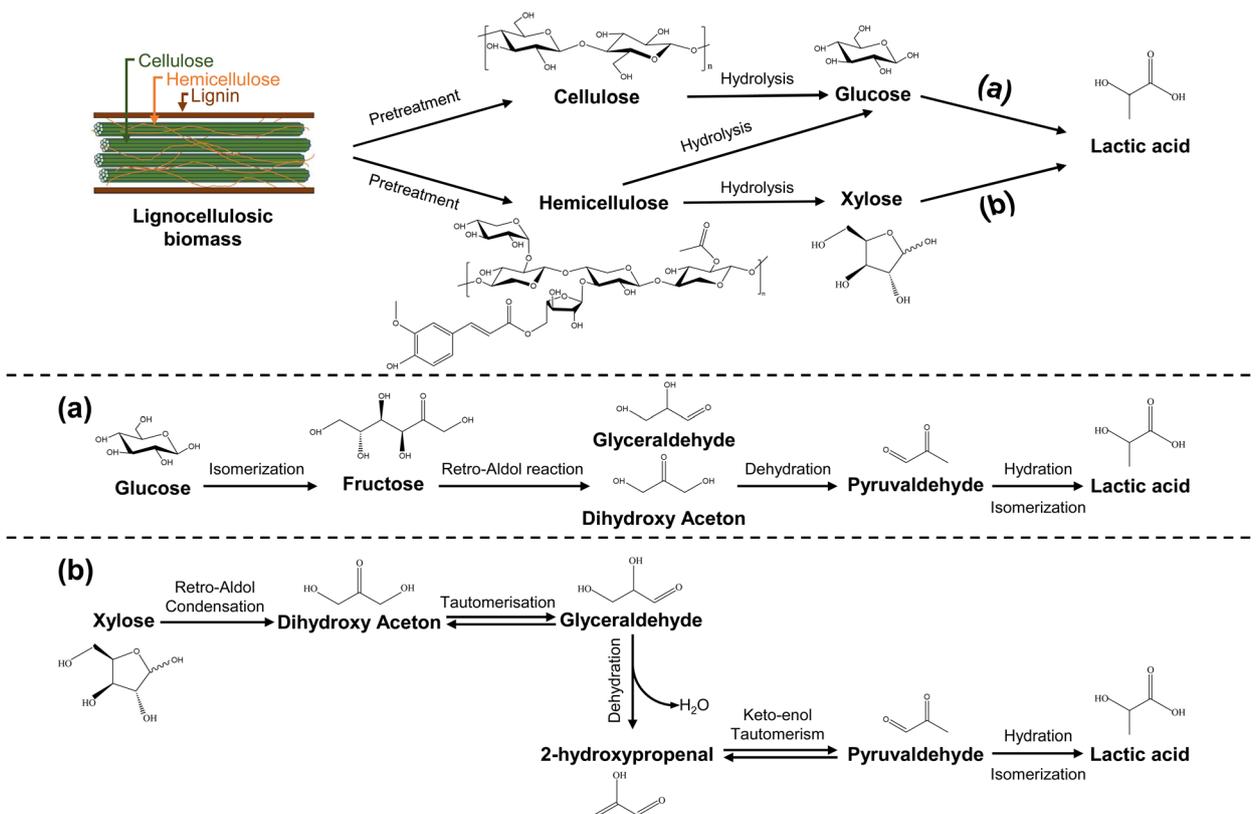


Fig. 4 Proposed reaction mechanisms for the conversion of lignocellulosic biomass to lactic acid, including (a) the transition of glucose to lactic acid and (b) the transition of xylose to lactic acid (adapted from ref. 75 and 76).

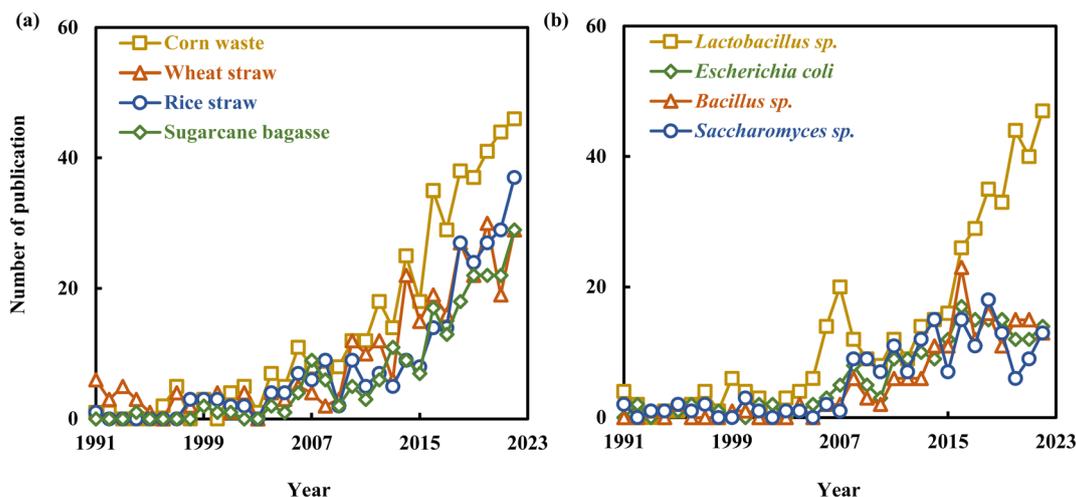


Fig. 5 Growth trends of hotpot-related articles of lactic acid production from lignocellulosic biomass: (a) raw materials, (b) microorganisms from 1991 to 2022.

articles published on the topic. Liu *et al.* (2015) achieved a remarkable L-LA yield of 0.715 g per g-cellulose by employing engineered *Pediococcus acidilactici* with detoxified corn stalk as the substrate.⁸⁴ Corn stalk hemicellulose derivatives were processed to produce LA, achieving a high yield of 0.796 g per g-hemicellulose with 90% selectivity through MgO catalysis.¹³ The number of related articles on wheat straw increased from 6

in 1991 to 29 in 2022, with a total of 296 articles published on the topic. A recently discovered strain, *B. coagulans* IPE22, has demonstrated impressive capabilities in fermenting pentose, hexose, and cellobiose, achieving a LA yield of 0.461 g-LA per g-dry wheat straw.⁶⁹ Research related to rice straw has seen a continuous increase in recent years, with the number of relevant articles reaching 37 in 2022. Kuo *et al.* (2015)



documented the development of an innovative engineered strain, *L. paracasei* 7BL, characterized by high inhibitor tolerance and the production of optically pure L-LA. This strain achieved an impressive productivity rate of $5.27 \text{ g L}^{-1} \text{ h}^{-1}$ when utilizing detoxified rice straw hydrolysate as its substrate.⁸⁵ These studies collectively highlight the extensive utilization of LCB in both fermentation and chemical catalysis for LA production.

Microbial lactic acid producers. The production of LA is achievable through a range of microorganisms, encompassing bacteria, fungi, yeast, cyanobacteria, and algae. Each of these biocatalysts brings distinct advantages, such as a wider substrate utilization range, improved yield and productivity, reduced nutritional requirements, or enhanced optical purity of LA.⁵ Fig. 5b depicts the microorganisms most commonly utilized for LA production from LCB. These microorganisms are listed in descending order of their prevalence and include *Lactobacillus* sp., *E. coli*, *Bacillus* sp., and *Saccharomyces* sp. It's noteworthy that bacteria (*Lactobacillus* sp., *E. coli*, and *Bacillus* sp.) and yeast (*Saccharomyces* sp.) are the predominant strains employed for LA production from LCB.

Bacteria that produce LA from LCB primarily fall into three categories: lactic acid bacteria (LAB, mainly *Lactobacillus* sp.), *Bacillus* strains (mainly *B. coagulans*), and *E. coli*. The number of articles related to *Lactobacillus* sp. has seen a significant increase, rising from 4 in 1991 to 47 in 2022, with a total of 425 articles published on the topic. *Lactobacillus* sp. can be classified into either homofermentative or heterofermentative types based on the different end products of fermentation. *L. plantarum* is a homofermentative bacterium that primarily produces LA through the pentose phosphate pathway. However, like many strains within the *Lactobacillus* genus, it produces racemic mixture of LA, containing both the L- and D-LA enantiomers.^{37,86} The engineered *L. plantarum* (with a deficient L-lactate dehydrogenase gene or expressing L-lactate oxidase gene) has been extensively utilized for the production of D-LA, exhibiting excellent utilization capabilities for pentoses and hexoses, as well as high D-LA yields.^{37,87,88} Research related to *Bacillus* strains did not appear until 1993, and it reached a maximum of 23 articles per year, accumulating a total of 167 articles on the topic. *B. coagulans* has the capability to grow and ferment both hexoses and pentoses present in LCB, yielding high-purity L-LA under non-sterilized conditions. These characteristics have continually enabled *B. coagulans* to achieve new breakthroughs in utilizing LCB for L-LA production.^{68,89} *E. coli*, owing to its rapid metabolism of hexoses and pentoses, coupled with its simple nutritional requirements, engineered *E. coli* demonstrates significant potential for efficient LA production from LCB.³¹ Nevertheless, efforts are needed to enhance its LA productivity and acid tolerance.⁹⁰

Wild-type yeasts typically produce minimal LA as a primary fermentation product. However, because of their robust acid resistance and the simplicity of their cultivation medium, significant efforts have been invested in engineering yeasts to enhance LA production.⁵ Novy *et al.* (2017) reported the utilization of *S. cerevisiae* IBB14LA1_5 for L-LA production, achieving impressive LA yields of 0.67 g per g-glucose and 0.80 g

per g-xylose. This study demonstrates that the engineered strain holds significant promise for L-LA production from LCB.⁹¹ Sornlek *et al.* (2022) conducted genetic engineering on *S. cerevisiae*, which involved the integration of the D-lactate dehydrogenase gene from *Leuconostoc mesenteroides*, the deletion of *gpd1*, *gpd2*, and *adh1* genes to reduce glycerol and ethanol production, and hybridization with the weak acid-tolerant *S. cerevisiae* BCC39850 strain. The engineered strain, when subjected to SSF using alkaline-pretreated sugarcane bagasse, achieved an impressive D-LA yield of 0.33 g per g-glucan.³⁰ This outcome underscores its potential for the production of industrially valuable products. The genetic-engineering approaches have been exploited in a big way for the improvement of LA yield and optical purity by various microbial producers. Furthermore, mixed culture systems, which harness consortia of microorganisms for fermentation, present a promising alternative to monocultures for intricate biotransformations. They offer inherent advantages, including the distribution of metabolic burdens through division of labor, improved efficiency in converting complex substrates, and modularity.^{27,92} The co-culture of *B. coagulans* and *L. rhamnosus* for LA production from cassava bagasse resulted in significantly improved LA concentration, productivity, and yield, reaching 112.5 g L^{-1} , $2.74 \text{ g L}^{-1} \text{ h}^{-1}$, and 0.88 g g^{-1} , respectively, surpassing the outcomes of mono-culturing each bacterium.⁹³ Collectively, previous studies indicate that genetic engineering approaches and mixed culture systems play a significant role in enhancing both the productivity and yield of LA.

Microbial versus chemical catalytic for lignocellulosic biomass to lactic acid. The production of LA from LCB can generally be divided into two categories: microbial fermentation and chemical catalytic conversion. It is noteworthy that research related to microbial fermentation for LA production is much more extensive than that of chemical catalytic conversion, which also directly reflects their respective applications. Fig. 6 depicts the processes of microbial fermentation and chemical catalysis for LA production from LCB, the application areas of the resulting products, as well as the respective advantages and disadvantages of these two methods. The process of microbial fermentation for LA production from LCB mainly involves the pretreatment of LCB, cellulose and hemicellulose hydrolysis, LA production, and LA extraction.⁹⁴ Similar to microbial fermentation, chemical catalysis for LA production from LCB also involves pretreatment of LCB. However, subsequent processes like cellulose and hemicellulose hydrolysis, sugars isomerization, retro-aldol reaction, and hydration rearrangement all occur under catalytic conditions.⁷⁴

Microbial fermentation generates a substantial amount of waste, including waste fermentation broth and gypsum waste.⁹⁵ The formation of gypsum is primarily a result of neutralization processes. The purification of LA from the fermentation broth can be quite intricate, as the LA fermentation process often yields by-products like acetic acid and formic acid.⁹⁰ Moreover, microbial fermentation tends to be time-consuming, with the fermentation process typically spanning from hours to days. In contrast, chemical catalytic conversion can overcome these problems. Chemical catalytic conversion generally takes only



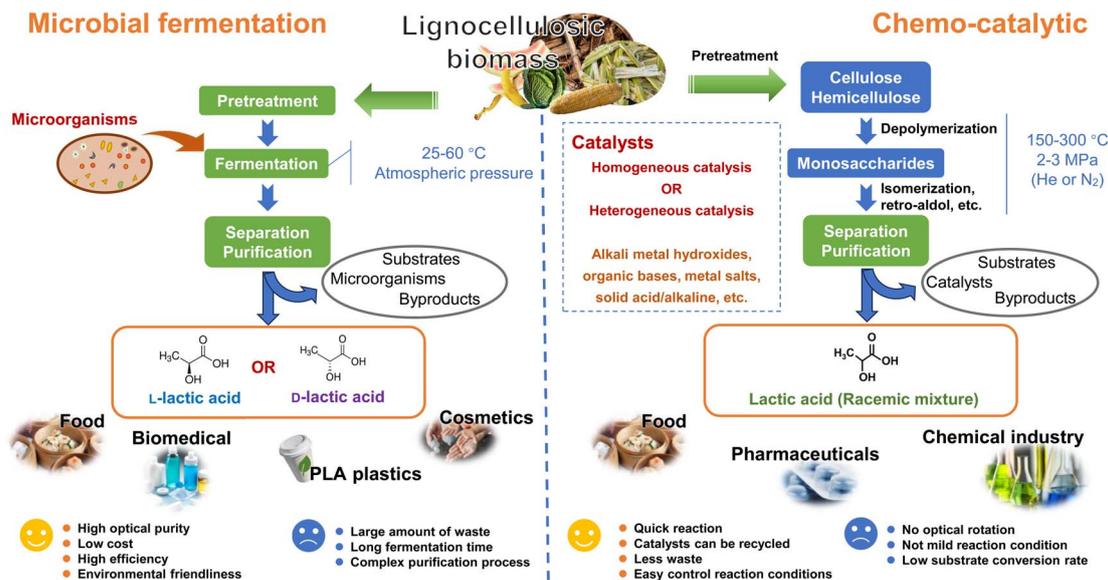


Fig. 6 Comparative lactic acid production from lignocellulosic biomass: microbial fermentation vs. chemical catalytic conversion.

several hours to complete, generates fewer wastes, and allows for easy recycling of catalysts from the system.⁹⁶ However, chemical catalysis has a low substrate conversion rate, and the process typically requires harsh conditions, often conducted at temperatures between 150–300 °C and pressures of 2–3 MPa.⁹⁷ A recent report indicated that, under a pressure of 0.1 MPa at room temperature, glucose can be selectively converted to LA with a yield of 95.4%. However, this process takes a longer time, spanning 48 hours.⁹⁸ Thus, the development of novel catalysts and the exploration of new catalytic systems would contribute to enhancing the efficiency of utilizing LCB resources in the catalytic production of LA.

Optically pure LA has been widely utilized in the production of polylactic acid, which is recognized as a crucial raw material for biomedical applications and the manufacturing of polylactic acid plastics. This application carries significant economic added value.⁷⁴ The production of enantiomerically pure L-LA or D-LA depends on the microbial strains used in the fermentation process. Microbial fermentation possesses the capability to achieve high optical purity in LA production, a feat not attainable through chemical catalysis. This is a key factor in why microbial fermentation is widely utilized for LA production, despite its various limitations. Chemical catalysis can only produce a racemic mixture of L- and D-LA.⁸³ To address this challenge, numerous studies have focused on utilizing membrane technology,^{99,100} porous ceramic discs,¹⁰¹ and high-performance chromatography¹⁰² to achieve enantiomeric resolution. However, most of these studies are still in the research stage, and the separation costs are relatively high. There is still a considerable gap to bridge before these methods can be applied on a large scale.

Based on our research findings, we have identified several promising future research directions in the field of microbial fermentation, which encompass the following key points: research is expected to continue focusing on the development

and enhancement of microbial strains to improve LA production efficiency. Genetic engineering will play a pivotal role in optimizing metabolic pathways and fermentative performance. Another avenue of research involves enhancing the tolerance of microbial strains to inhibitors commonly present in LCB hydrolysates, thereby reducing the need for detoxification procedures. An emerging field of study centers on mixed microbial cultures, aiming to optimize the synergistic interactions among various microorganisms, ultimately enhancing LA production efficiency. Shifting to the realm of chemical catalytic conversion, ongoing research will emphasize the development and optimization of catalysts for the conversion of LCB into LA. This will include the exploration of novel catalyst materials and structures, as well as improvements in catalytic efficiency through catalyst modification and reaction engineering. Looking forward, there is a growing interest in integrating LA production into lignocellulosic biorefineries, aligning the production of LA with other high-value chemicals derived from biomass components like lignin. Concurrently, attention will be devoted to developing more cost-effective and environmentally friendly downstream processing methods for the separation and purification of both D- and L-LA. In conclusion, the future of LA production from LCB will require interdisciplinary collaboration across fields such as microbiology, chemistry, engineering, and environmental science. This collaborative approach will strongly emphasize sustainability, efficiency, and cost-effectiveness.

Conclusions

This paper presents a comprehensive overview of research in the field of LA production from LCB. It encompasses publication characteristics, author keywords analysis, co-citation reference analysis, and research hotspots. From 1991 to 2022, there was a significant surge in annual publications, growing



from 39 to 333. Notably, *Bioresource Technology* and *Applied Microbiology and Biotechnology* emerged as the two most prolific journals in this domain. Chinese Acad. Sci., China held the top spot with the highest total publications (92), betweenness centrality value (0.27), collaborations (108), and an *h*-index of 31, signifying excellence in LA production from LCB. China ranks first in total publication count (736), betweenness centrality value (0.30), and the number of collaborating countries (42), reflecting its substantial influence and contributions in LA production from LCB. Author keywords analysis emphasized the pivotal role of microbial fermentation in LA production from LCB. Co-citation reference analysis delineated four key domains within LA production from LCB: substrate pretreatment and degradation, microbial selection and engineering, fermentation process optimization, and chemical catalytic conversion. Furthermore, the paper delves into commonly used LCB and microbial LA producers, highlighting the diversity of microbial and extensive studies involving various LCB sources for LA production. Moreover, the study performed a comparative analysis of microbial fermentation and chemical catalytic conversion for the production of lactic acid from LCB, elucidating their distinct strengths and weaknesses. The paper also delved into recent research endeavors aimed at addressing these challenges and underscored potential future research directions.

Author contributions

All authors contributed to the conception and design of the study. Dr Min Zhang and Dr Siyuan Yue were responsible for data collection and analysis. Dr Siyuan Yue took the lead in writing the draft of the manuscript, while Dr Min Zhang reviewed and corrected it. The final manuscript was reviewed and approved by all authors.

Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

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