Kojic Acid as an Emerging Biotechnological Product: Advances in Production, Applications, and Optimization Based on Scientific Output Analysis

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Abstract

Kojic acid (KA) is a fungal secondary metabolite with recognized applications in cosmetics, pharmaceuticals, and food due to its antioxidant, antimicrobial, and depigmenting properties. However, industrial production remains limited by low fermentation yields and high costs. To assess the research landscape, a bibliometric analysis was performed using the Scopus database (1993–2025), focusing on original research articles with the keywords “kojic acid” and “production.”

Findings reveal a sustained rise in publications since 2010, with marked growth after 2017, led by Asian countries such as South Korea, China, and Japan. Network and cluster analyses identify two main axes of research: process optimization through microbial fermentation and genetic engineering, and biomedical applications related to tyrosinase inhibition.

This study consolidates fragmented knowledge, highlights key contributors and trends, and points to future directions such as hybrid bioprocesses and synthetic biology, which are critical to achieving competitive industrial-scale production and expanding KA’s market potential.

Keywords: Biotechnological production; microbial fermentation; Aspergillus; process optimization; genetic engineering, tyrosinase inhibition; bibliometric analysis.

Introduction

Kojic acid (KA) is an organic compound characterized by an oxo group at position 4, a hydroxyl group at position 5, and a hydroxymethyl group at position 2 (Figure 1). Although discovered in in Japan in 1907, this bioproduct has recently attracted interest due to its diverse potential applications in the cosmetic, pharmaceutical, and food industries. Its name derives from the *koji* fermentation process of malted rice, from which it was initially isolated. Across the *in-vitro* studies, the KA has been recognized for its antioxidant, antibacterial, and skin-lightening properties, which support its potentialities for several industries (Sharma et al., 2023).

From a mechanistic standpoint, KA is a fungal secondary metabolite whose biosynthesis remains incompletely understood(Feng et al., 2019). Its principal biological activities are mediated by chelation of divalent ions, free radical scavenging, and inhibition of tyrosinase (Couteau & Coiffard, 2016)(Khezri et al., 2021). By binding copper ions at the active site of tyrosinase (Bashir et al., 2021)(Mohiuddin, 2019), KA disrupts the conversion of L-tyrosine to L-DOPA and subsequent oxidation to o-quinones (Hashemi, 2015)(Deri et al., 2016). Importantly, KA acts during melanin synthesis rather than before or after, making it a direct regulator of melanogenesis (Chang, 2009). Although its precise inhibitory mechanism is still under investigation, evidence suggests KA binds near the enzyme’s active site entrance, interacting with intermediate conformations (Deri et al., 2016).

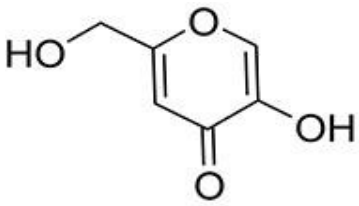

Figure 1. Chemical structure of kojic acid.

The production of kojic acid is carried out mainly through an aerobic fermentation process, in which microorganisms belonging to the genus *Aspergillus* play a crucial role (Abd El-Aziz, 2013) organisms are typically cultivated in media containing carbon sources such as glucose, sucrose, and starch, along with various nitrogen sources such as yeast extract, peptone, and corn steep liquor, among others. At present, the limited development of this bioprocess is reflected in the low yields achieved in fermentations with producing strains, which range between 0.1 and 0.5 g/L (Mohamad et al., 2010), thereby increasing the cost of the final product. Although aerobic fermentation is one of the most commonly employed methods, factors such as culture medium composition, oxygen concentration, and pH directly impact production efficiency. Furthermore, despite technological advances, kojic acid production has not been sufficiently optimized for industrial scale-up, which restricts its competitiveness in the global market. In fact, its current cost of approximately USD 20 per kilogram remains an obstacle to the expansion of this market, particularly in comparison with more affordable alternatives(Alibaba, 2024). Although demand is high and the market is projected to grow to approximately USD 39 million by 2026(Felipe et al., 2023), the lack of detailed information sources and limited research on efficient production technologies continue to pose barriers to large-scale commercialization. Furthermore, knowledge on the production methods, scalability, and emerging applications of this compound remains fragmented and poorly systematized.

In this context, bibliometric methods have become powerful tools for mapping the scientific landscape of specific research fields, identifying knowledge gaps, and guiding future investigations (Ascencio-Galván et al., 2024). Unlike traditional narrative reviews, bibliometric analyses enable the quantitative and qualitative assessment of scientific production, co-citation networks, and thematic evolution, thereby providing an evidence-based understanding of the dynamics of knowledge creation. Applying these methodologies to kojic acid research is particularly relevant given the growing demand for sustainable bioprocesses and the need for more efficient production technologies(Ramírez-Malule et al., 2023)

This study applies a bibliometric approach to analyze the evolution of scientific research on kojic acid, focusing on production technologies, biological applications, and market perspectives. Specifically, it aims to: (i) identify the main research fronts and trends over time; (ii) highlight the most influential authors, institutions, and journals in this field; and (iii) examine the thematic structure and potential future directions of kojic acid research. By combining bibliometric indicators with network analysis, this work seeks to provide a comprehensive overview that contributes to consolidating and expanding the knowledge base on kojic acid, with implications for both scientific development and industrial implementation.

Materials and methods

Data source and search strategy

This study was conducted as a bibliometric analysis employing quantitative and systematic tools to map the evolution, structure, and trends of research on kojic acid production, thus visualizing the knowledge clusters, and tracking thematic evolution over time through co-authorship, co-citation, and co-word analyses(Galeano et al., 2024). The data were obtained through a systematic search in the Scopus database, chosen for its broad coverage and rigorous indexing of scientific literature. The search was carried out using the specific keywords *"kojic acid"* and *"production"*, and it was limited to the period between 1993 and 2025. This time frame was selected based on two criteria: first, to encompass both pioneering studies and more recent developments; and second, to establish a starting point at which sustained growth in scientific output on this topic began to be observed. Similarly, the search was restricted exclusively to scientific articles, excluding other types of documents such as books, conference papers, or reviews, in order to focus the analysis on original research.

The search strategy was structured around four main thematic areas—Biochemistry, Genetics and Molecular Biology; Agricultural and Biological Sciences; Chemical Engineering; and Immunology and Microbiology— and search queries were constructed to reflect these domains, enabling a focused yet inclusive collection of relevant studies.

Database	Search equations	Date of search
Scopus	"Kojic Acid"	08/10/2024
Scopus	"Kojic acid" and "production"	08/10/2024
Scopus	"Kojic acid" and "fermentation"	08/10/2024

Screening and data analysis

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol was applied rigorously for article screening. As depicted in Figure 2, the procedure involved duplicate removal, title and abstract screening, and application of inclusion and exclusion criteria. By adhering to PRISMA, we ensured transparency and reproducibility in our selection process (Gómez-Ríos et al., 2024).To maintain consistency, the entire screening process was executed by a single researcher.

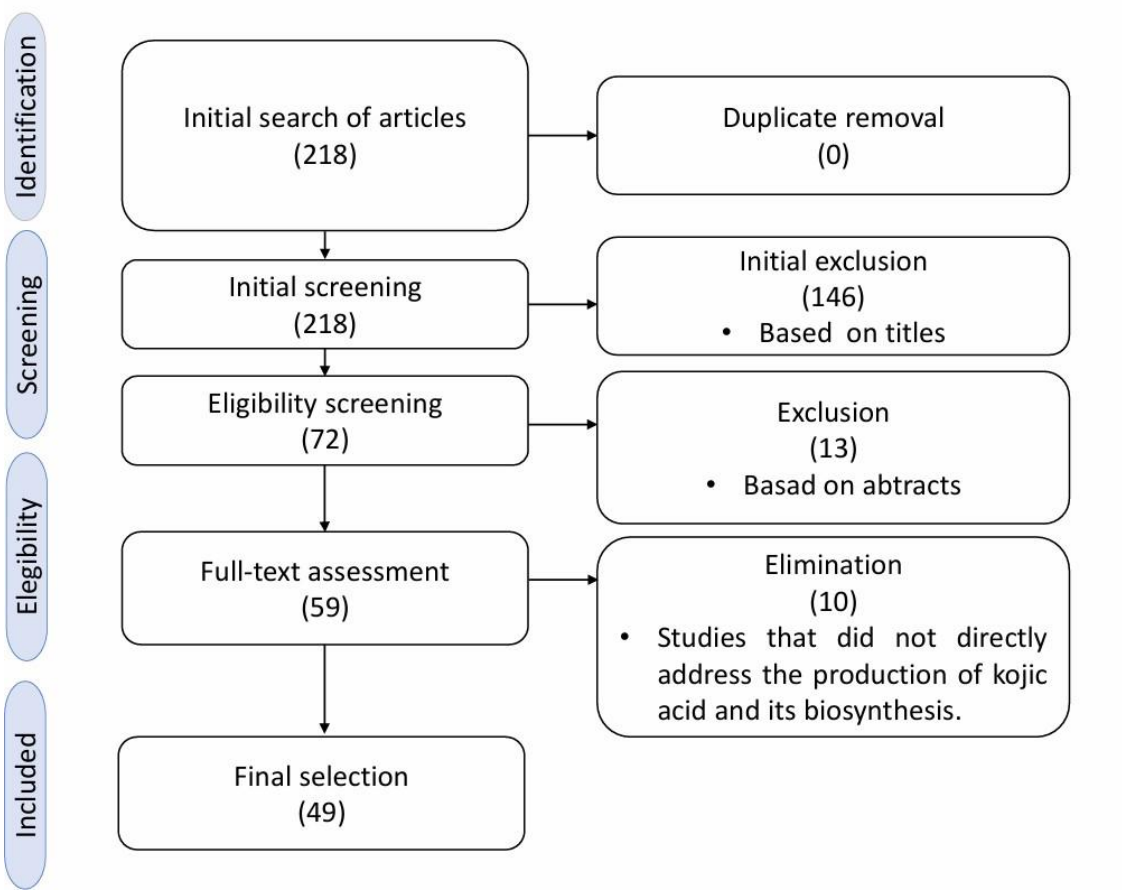

Figure 2. Screening (PRISMA) protocol for article selection.

Data processing was conducted in Rstudio, while data visualization and construction networks were performed in the VOSviewer free software.

Results

Evolution in the number of publications

The evolution of the total number of scientific publications per year related to kojic acid production shows a sustained increase starting in 2010, with a more pronounced rise from 2017 onwards. The highest peak was recorded in 2023, with more than 30 publications. This trend reflects the growing scientific interest in kojic acid research, which is likely associated with advances on industrial bioprocessing , as well as its expanding applications in the cosmetic, pharmaceutical, and food industries.

To gain a clearer understanding of how research on kojic acid has developed over time, the annual growth rate of publications was calculated. This analysis enabled the quantification of the steady increase in scientific output within this field. By applying the compound annual growth rate (CAGR) formula, an annual growth rate of 5.74% was observed which is modest in comparison with other mature fields, highlighting the emergent character of the research

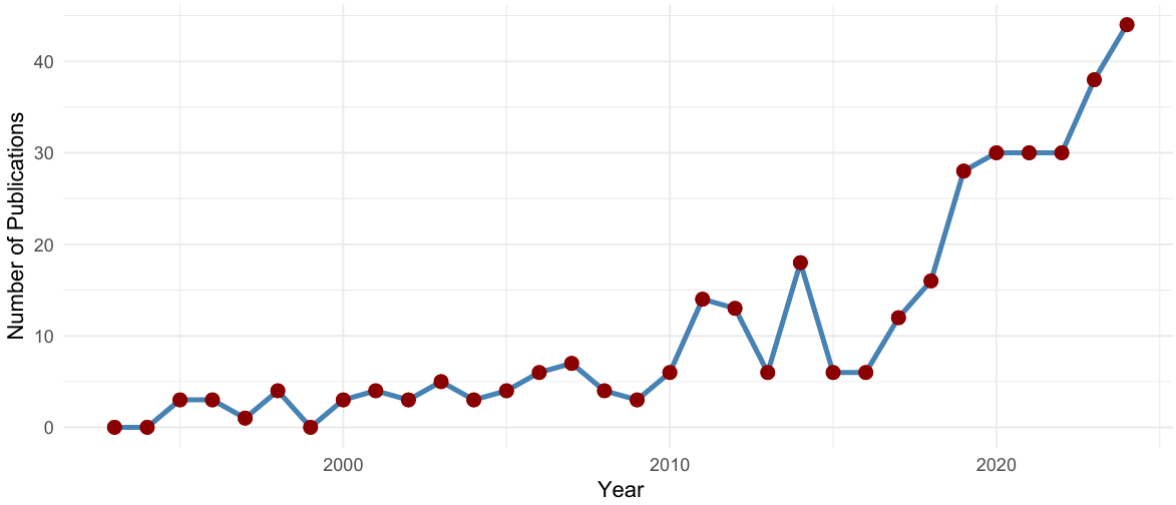

Figure 3. Evolution of the number of publications for Equation (2): Kojic acid and production

Bibliometric Study

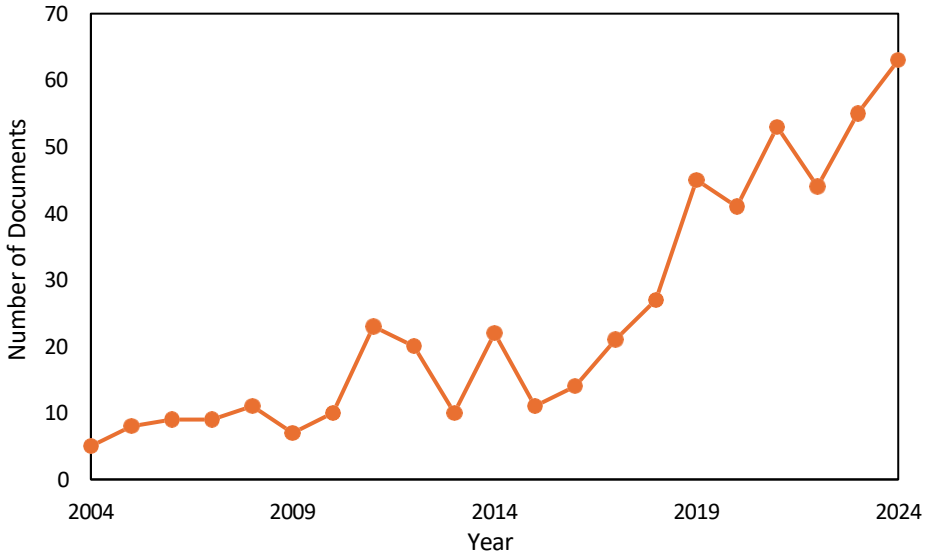

Figure 4. Research documents by year for "Kojic Acid Production" between 2004 and 2024

Figure 4 shows the number of research documents by year for "Kojic Acid Production" between 2004 and 2024. The temporal distribution shows a sustained increase in research output, from five documents in 2004 to sixty-three documents in 2024, for a total of 508 documents over the 21-year period (mean = 24.2 documents per year; median = 20). The compound annual growth rate (CAGR) from 2004 to 2024 is approximately 13.5%, and the five-year mean for 2020–2024 (51.2 documents per year) is roughly twice the long-term average, indicating a marked acceleration of publication activity after 2018. Between 2004 and 2019, the number of research documents published on kojic acid production remained relatively low, averaging about 16 documents per year, with values fluctuating between 5 and 45. This period reflects modest but gradually increasing interest in the topic. In 2020, coinciding with the onset of the COVID-19 pandemic, the number of publications decreased slightly from 45 in 2019 to 41, suggesting a temporary disruption likely related to

laboratory closures, funding reallocation, and delays in publishing processes. However, from 2021 onward, a clear shift is observed: publications increased sharply to 53 in 2021, and the trend continued with 44 in 2022, 55 in 2023, and a peak of 63 in 2024. This indicates not only a rapid recovery after the initial pandemic impact but also a sustained acceleration of research activity in this field. The post-pandemic average (2022–2024, 54 documents per year) is more than three times higher than the pre-pandemic average (2004–2019, 16 documents per year). While the timing suggests that the pandemic may have acted as a catalyst for renewed scientific interest, possibly through the promotion of bioprocess innovations, bioactive compounds, and applied research funding, this relationship should be interpreted with caution since correlation does not prove causation. Overall, the data highlight a notable turning point around 2021, marking the beginning of a strong upward trajectory that culminates in the highest publication output of the series in 2024.

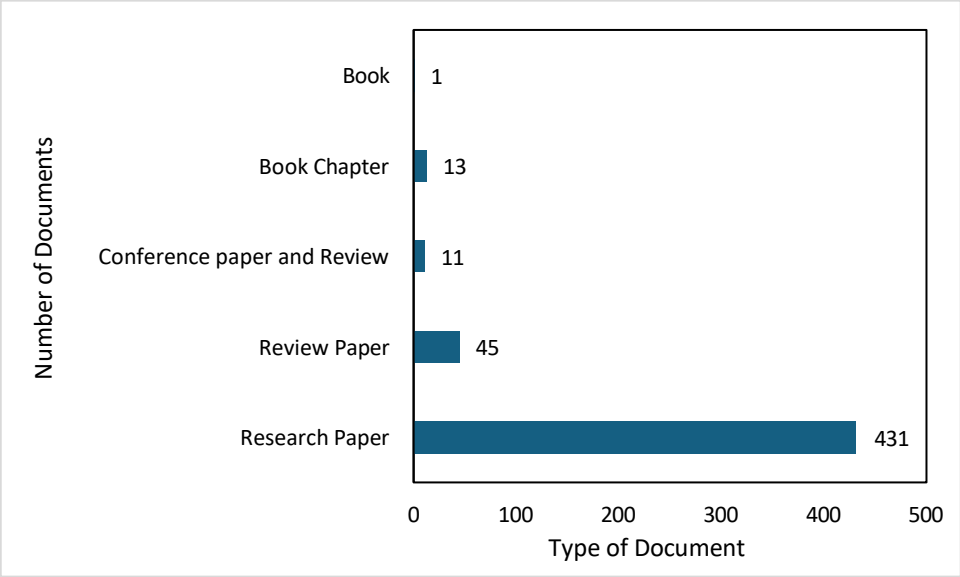

Figure 5. Documents by type published regarding Kojic Acid Production between 2004 and 2024.

The data from 2004 to 2024 show a clear dominance of research papers (431) in the publication output related to kojic acid production (Figure 5), representing the primary format for disseminating new experimental and applied findings. Review papers (45) constitute a smaller but significant share, indicating that as the research field matured, efforts were made to synthesize and consolidate knowledge. Book chapters (13) and conference contributions (11) remain comparatively minor, reflecting a limited role of broader dissemination formats or early-stage reports in this specific area. Only one book was identified in Scopus database, suggesting that while kojic acid production has been actively studied, it has not yet reached the level of a highly consolidated research field that generates dedicated monographs.

When contrasted with research trends, the predominance of research papers aligns with the strong growth in annual publication numbers observed after 2018 and especially after 2021. This pattern highlights that the field is still in an expansionary phase, driven mainly by empirical and process-focused studies rather than by large-scale theoretical synthesis. The increase in review papers during the later years may reflect the need to summarize and guide rapidly accumulating knowledge, which is consistent with a research area transitioning from niche interest to broader industrial and academic

relevance. The COVID-19 pandemic and global economic changes also had a visible effect. The initial dip in publications in 2020 was likely linked to restricted laboratory access and economic uncertainty. However, the subsequent surge in research papers after 2021 shows how the reopening of research activities, combined with increased interest in sustainable bioprocesses and bioactive compounds, fueled renewed growth. Moreover, economic shifts—such as rising demand for natural and multifunctional products in cosmetics, food, and pharmaceuticals—likely contributed to sustaining interest in kojic acid production. Review papers published during or after the pandemic may also represent efforts to consolidate fragmented progress during disrupted years, offering roadmaps for post-pandemic research strategies.

Figure 6. Research papers by country regarding Kojic Acid Production between 2004 and 2024.

The publication trend by country on kojic acid production from 2004 to 2024 shows a strong concentration in Asia, led by South Korea (89), China (69), Thailand (41), Japan (40), India (39), Malaysia (20), and Indonesia (16) (Figure 6). This reflects both the geographical distribution of research capacity and the industrial demand for kojic acid. South Korea and Japan have long-standing investments in biotechnology and the cosmetic industry, sectors where kojic acid is widely used as a skin-whitening and antioxidant agent. Their strong R&D expenditures relative to GDP and the presence of globally competitive cosmetic and pharmaceutical companies explain their leadership. China, with the second-highest output, also reflects its rapid growth in R&D spending (now one of the highest in the world) and its dual focus on pharmaceuticals and functional foods. India's rising output mirrors its expanding pharmaceutical and generic drug industry, along with growing domestic demand for cosmetic and food additives.

Thailand, Malaysia, and Indonesia's significant contributions, despite lower overall R&D investment compared to developed economies, can be linked to the abundant availability of agricultural feedstocks (e.g., rice, sugarcane, palm oil residues) that serve as substrates for kojic acid fermentation. Their active food and cosmetic sectors, coupled with interest in value-added bioproducts, have positioned them as important regional contributors. Brazil similarly leverages its strong agricultural

base and biotechnology research networks, supported by initiatives in bioprocesses and food innovation.

Among Western economies, the United States (57) stands out as the leader, consistent with its global role in pharmaceuticals, cosmetics, and biotechnology, backed by the highest absolute R&D spending worldwide. European countries such as Italy (22), the United Kingdom (14), and Germany (13) show moderate but steady engagement, likely driven by specialized pharmaceutical and cosmetic applications rather than large-scale feedstock-based production. These contributions align with their advanced economic development, but the smaller numbers compared to Asia suggest that kojic acid research is more strategically relevant in regions with direct industrial or market drivers. The presence of Egypt (21), Iran (16), and Turkey (14) indicates growing engagement from emerging economies, where investment in applied biotechnology and affordable cosmetic/pharmaceutical products is expanding. Their involvement may also be supported by cost-effective labor and increasing emphasis on regional self-sufficiency in health and personal care products.

Figure 7. Research documents by country for the top 5 countries in Central and South America

The Central and South American publication trend on kojic acid production shows a clear concentration in Brazil (23 documents), while Mexico (3), Argentina (2), Chile (2), and Colombia (2) have only minimal contributions (Figure 7). Brazil's leadership reflects its relatively higher investment in research and development (R&D) compared to other countries in the region and the direct relevance of kojic acid to its industrial profile. Brazil hosts one of the world's largest cosmetics and personal care markets, where kojic acid is used as a skin-lightening and antioxidant agent, as well as an expanding pharmaceutical sector and a strong agro-industrial base. Its abundant agricultural feedstocks, such as sugarcane, coffee, corn, and soy residues, create favorable conditions for fermentation-based production processes, which explains why Brazil is the regional hub for this research.

In contrast, Mexico, Argentina, Chile, and Colombia contribute only sporadically, reflecting structural limitations. These countries allocate lower percentages of GDP to R&D and their pharmaceutical and cosmetic industries, though present, are smaller and less integrated into global value chains compared to Brazil. Although they also possess rich agricultural resources that could serve as feedstocks for

kojic acid production, the absence of strong industry pull factors, limited innovation funding, and weaker academia-industry collaboration have constrained research outputs. For instance, Mexico's growing pharmaceutical manufacturing sector and Chile's biotechnology niche could support more activity, but kojic acid has not emerged as a strategic priority. Similarly, Argentina and Colombia have active agricultural and food industries but limited translation of these resources into biotechnological applications like kojic acid production. The trend suggests that in Central and South America, the development of research on kojic acid production is strongly associated with the intersection of economic development, industrial demand (especially in cosmetics and pharmaceuticals), higher R&D investment, and feedstock availability. Brazil meets all these conditions and therefore dominates the regional output, while other countries, despite having potential, remain underrepresented. This gap highlights opportunities for diversification of biotechnological research in the region, especially in countries with strong agricultural sectors but low scientific production on this topic.

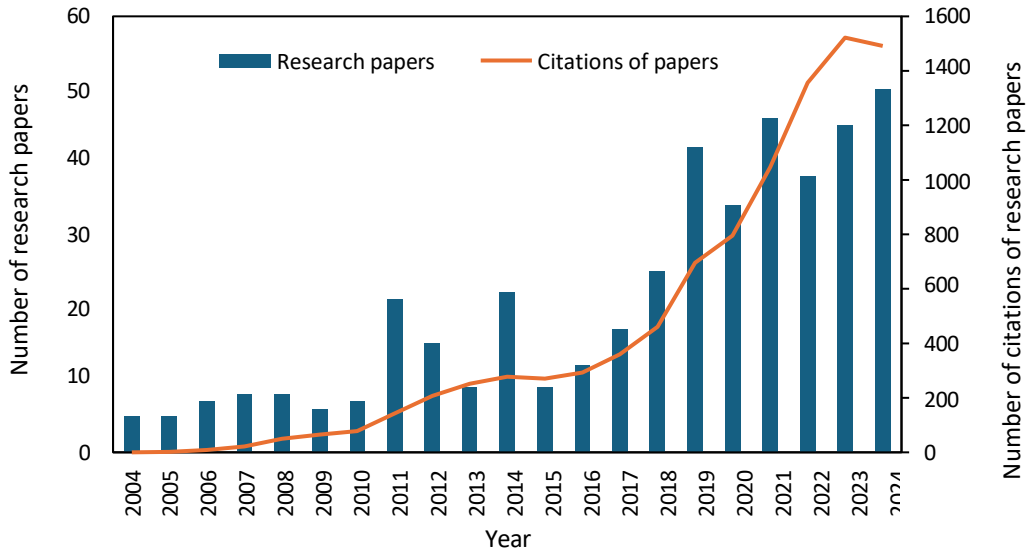

Figure 8. Number of Research papers published in contrast to number of citations of research papers for Kojic Acid Production from 2004 to 2024.

In terms of publication of research paers, output remained modest until 2010, with fewer than 10 papers annually, followed by a sharp increase beginning in 2011 (21 papers) and continuing upward, peaking at 50 papers in 2024. The growth is especially visible after 2017, when the annual output consistently surpassed 20 papers, reflecting a surge of interest and research activity in the field (Figure 8).

By contrast, citations show a steeper and delayed growth curve, highlighting the time-lag effect typical of academic influence. From 2004 to 2010, citations increased slowly (from 0 to 78), but from 2011 onward they grew rapidly, reaching 293 in 2016, 696 in 2019, and nearly doubling each year after 2020. The highest citation counts are seen in 2023 (1522) and 2024 (1492), indicating that recent publications are being referenced extensively and that kojic acid research has gained significant visibility and integration into broader scientific discussions. When contrasting the two trends, it is clear that while the number of papers has grown steadily, the citation rate has expanded

disproportionately, especially from 2018 onward. This suggests that not only is more research being conducted, but it is also being recognized as relevant across multiple fields, including pharmaceuticals, cosmetics, and food science. The rise in citations after 2020 may also reflect increased interest in natural bioactive compounds during and after the COVID-19 pandemic, as industries sought sustainable and multifunctional ingredients.

Thematic Cluster Analysis

The co-occurrence network (Figure 9) illustrates how the central concept *"kojic acid"* lies at the core of several research lines. The thematic cluster analysis revealed two major axes around which research on kojic acid has been structured: (i) the production of kojic acid from *Aspergillus* species, including studies focused on process optimization and (ii) tyrosinase inhibition and the biology of melanogenesis. Secondary clusters are around cytotoxic, antioxidant and anticancer activities, using both, experimental and computational approaches.

A microorganisms' cluster is identified around the genus *"Aspergillus"* and the producer strains *A. oryzae* and *A. niger* since those are the primary industrial producers of kojic acid via fermentation. This cluster also includes terms such as *"secondary metabolites"*, *"fungi"*, and *"endophytic fungi"* associated to the nature of both, the compound and the producer organisms.

A clearly distinguishable second cluster (blue) is dominated by the terms *"tyrosinase inhibition"* and *"anti-melanogenesis"*. This grouping reflects the biomedical and cosmetic interest in kojic acid, particularly as a tyrosinase inhibitor, a key enzyme in melanin biosynthesis. Related to this topic are the *"molecular docking"*, *"melanoma cells"*, *"anti-aging"*, and *"antioxidant activity"* studies, which reinforce its potential as an active ingredient in depigmenting, anti-aging, and antioxidant treatments. This cluster suggests the integration of both computational and cellular studies, demonstrating a multidisciplinary approach to its pharmacological evaluation.

A third, but minor cluster, represented in green, focuses on the role of kojic acid in relation to mycotoxins such as aflatoxins, ochratoxin A, and cyclopiazonic acid. The association with *"reactive oxygen species"* points to research addressing fungal defense mechanisms or detoxification strategies, in which kojic acid acts as a mitigating agent against hazardous fungal toxins, potentially through the formation of non-toxic complexes or adducts.

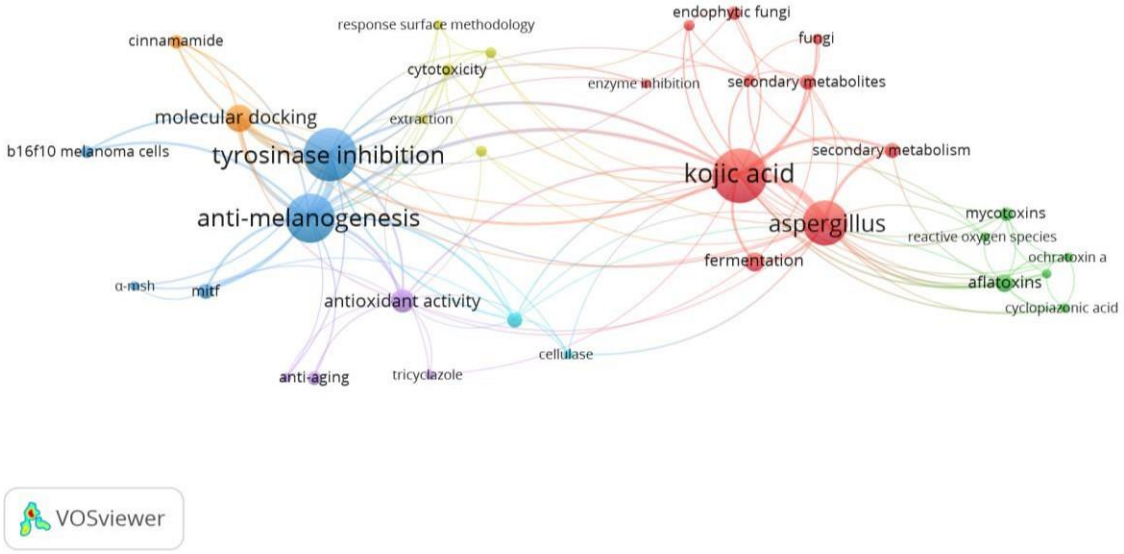

Figure 9. Network of keywords co-currence in kokic acid scientific publications.

The overlay visualization (Figure 10) provides insights into how research related to kojic acid have evolved over time. In the first years of the 2010-2020 period, research on kojic acid primarily focused on its production using *Aspergillus* fungi as well as its relationship with toxic compounds such as aflatoxins, ochratoxin A, and cyclopiazonic acid. This stage reflects a biotechnological and toxicological orientation, where the main interest lay in kojic acid's ability to act as an antifungal agent or mycotoxin inhibitor, as well as its production via microbial fermentation. Similarly, between 2014 and 2017, interest remained in the fermentative production and experimental approaches for process optimization .

From 2017 onwards, a notable change in research orientation is evident, focused on the pharmacological and cosmetic applications of kojic acid. Terms such as *tyrosinase inhibition*, *anti-melanogenesis*, *anti-aging*, *molecular docking*, and *antioxidant activity* demonstrate the increasing emphasis on its use as a depigmenting, antioxidant, and therapeutic agent, particularly in dermatological treatments. Furthermore, the emergence of terms associated with cellular studies, such as *B16F10 melanoma cells* or *α-MSH*, suggests a progression toward more specific and controlled molecular investigations on anticancer and antioxidant activity, highlighting possibilities in oncology and regenerative medicine.

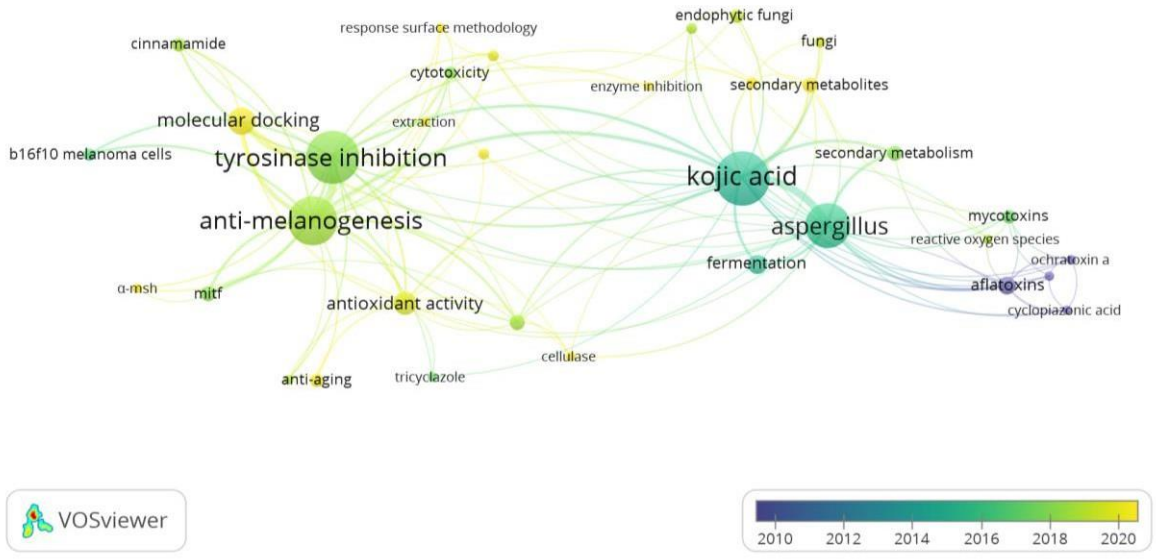

Figure 10. Time overlay of keywords on kojic acid research.

International Collaboration in Kojic Acid Research

The network of international collaboration on kojic acid research is shown in Figure 11. In this network, each node represents a country, where node size indicates the relative volume of publications, connections illustrate collaborations between countries, and darker colors denote earlier research, while lighter shades correspond to more recent studies. South Korea, the United States, and China stand out as the principal centers of scientific production in the topic.

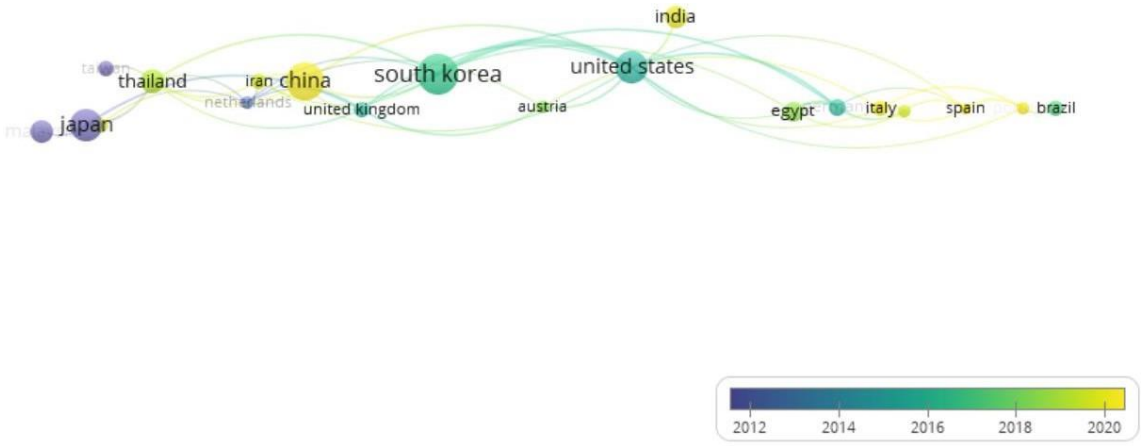

Figure 11. Network of co-authorships by country in kojic acid research.

Institutional and Individual Contributions to Kojic Acid Research

The institutional origin of kojic acid research, presented in Table 2, reveals that the five institutions with the highest number of publications are exclusively based in Asian countries, highlighting the

strong geographical concentration of this field. Institutions such as Pusan National University and Inje University, both located in South Korea, lead the ranking with 24 and 17 publications, respectively, spanning the periods 2010–2025 and 2012–2025. The interest of South Korean institutions on KA is likely driven by the global leadership of the national cosmetic industry, which is well recognized for its innovation and focus on market priorities like antioxidant and antimelanogenic compounds. Moreover, the top five most prolific authors in kojic acid research (see Table 3) are associated to South Korean universities. Moon, Hyungryoung (21 publications) is the main contributor, following is Chun, Pusoon (17 publications), Jung, Hee-jin (13 publications), Park, Yujin (13 publications), and Chung, Hae-young (11 publications).

By contrast, Universiti Putra Malaysia reports 14 publications over a broader timeframe (1996–2024), suggesting a longer but possibly more intermittent trajectory. In China, government institutions like Ministry of Education of the People's Republic of China and the Chinese Academy of Sciences also appear among the top contributors with more recent publications, consistent with the strong governmental support for biotechnology and health-related research.

Table 2. Leading institutions in scientific publications on kojic acid.

Rank	**Institution**	**Number of publications**	**Years**
1	Pusan National University	24	2010-2024
2	Inje University	17	2012-2024
3	Universiti Putra Malaysia	14	1996-2024
4	Ministry of Education of the People's Republic of China	11	2011-2024
5	Chinese Academy of Sciences	10	2014-2024

Table 3. Leading contributors on kojic acid research.

Rank	**Author**	**Number of publications**	**h-index**	**Affiliation**
1	Moon, Hyungryoung	21	38	Pusan National University
2	Chun, Pusoon	17	25	Inje University
3	Jung, Hee-jin	13	14	Pusan National University

4	Park, Yujin	13	15	Daegu-Gyeongbuk Medical Innovation Foundation
5	Chung, Hae-young	11	15	Pusan National University

Table 4 highlights the scientific journals most frequently publishing on kojic acid production and applications. Molecules emerges as the leading platform, with 20 articles, followed by the International Journal of Molecular Sciences, with 15 publications and the highest impact factor among the listed journals (IF = 9.0). The journal Antioxidants, ranked third with 7 publications and the highest SCImago Journal Rank (SJR = 1.484) and an elevated impact factor (12.4). Those are followed by Bioorganic & Medicinal Chemistry and Bioorganic & Medicinal Chemistry Letters, each with 7 publications. Most of these journals are positioned in the SJR Q1 quartile of their respective subject categories.

Table 4. Leading journals on publications related to kojic acid research.

Rank	**Journal**	**Number of publications**	**Journal Rank SJR 2024**	**Journal impact factor**
1	Molecules	20	(0.865) Q1	8.6
2	International journal of Molecular Sciences	15	(1.273) Q1	9.0
3	Antioxidants	7	(1.484) Q1	12.4
4	Bioorganic and Medicinal Chemistry	7	(0.608) Q2	6.7
5	Bioorganic and Medicinal Chemistry Letters	7	(0.472) Q2	5.1

Tabla 5. Most cited publications on kojic acid research.

Rank	**Publication**	**Authors**	**Cites**	**Year**	**Ref**
1	Improvement of kojic acid production in Aspergillus oryzae AR-47 mutant strain by combined mutagenesis	Feng W.; Liang J.; Wang B.; Chen J.	34	2019	23

2	Single production of Kojic acid by Aspergillus flavus and the revision of flufuran	Ola A.R.B.; Metboki G.; Lay C.S.; Sugi Y.; De Rozari P.; Darmakusuma D.; Hakim E.H.	30	2019	50
3	Synthesis and cytotoxic evaluation of kojic acid derivatives with inhibitory activity on melanogenesis in human melanoma cells	Karakayaa G.; Ercanb A.; Onculb S.; Aytemira M.D.	26	2018	29
4	Aspergillus oryzae nrtA affects kojic acid production	Sano M.	25	2016	56
5	Improved production of kojic acid by mutagenesis of Aspergillus flavus HAk1 and Aspergillus oryzae HAk2 and their potential antioxidant activity	Ammar H.A.M.; Ezzat S.M.; Houseny A.M.	25	2017	4
6	Identification and functional characterization of glycerol dehydrogenase reveal the role in kojic acid synthesis in Aspergillus oryzae	Fan J.; Zhang Z.; Long C.; He B.; Hu Z.; Jiang C.; Zeng B.	23	2020	21
7	Anti-inflammatory Effects of a P-coumaric Acid and Kojic Acid Derivative in LPS-stimulated RAW264.7 Macrophage Cells	Lee M.; Rho H.S.; Choi K.	23	2019	35
8	Evaluation of kojic acid production in a repeated-batch PCS biofilm reactor	Liu J.-M.; Yu T.-C.; Lin S.-P.; Hsu R.-J.; Hsu K.-D.; Cheng K.-C.	22	2016	39
9	Zn(II) and Cd(II) thiosemicarbazones for stimulation/inhibition of kojic acid biosynthesis from Aspergillus flavus and the fungal defense behavior against the metal complexes' excesses	Mahmoud G.A.-E.; Ibrahim A.B.M.; Mayer P.	19	2020	41
10	Overexpression of a novel gene Aokap2 affects the growth and kojic acid production in Aspergillus oryzae	Li Y.; Zhang H.; Chen Z.; Fan J.; Chen T.; Xiao Y.; Jie J.; Zeng B.; Zhang Z.	17	2022	37

The Top 10 most cited articles on kojic acid research (see Table 5) represent the most influential and widely referenced contributions to the field. Most of these studies were published between 2016 and 2020. The most cited work, with 34 citations, is a 2019 study by Feng et al., which focused on improving kojic acid production through mutagenesis in *Aspergillus oryzae*. Other highly cited contributions include studies by (Ola et al., 2019) and (Sano, 2016) , which also centered on optimized production using *Aspergillus* species. Several of the most referenced papers highlight the molecular and bioactive properties of kojic acid, such as its role as a cytotoxic or antioxidant compound and its effectiveness as a tyrosinase inhibitor. Additional influential works address structural characterization, metal-assisted biosynthesis, and genetic determinants of production.

As noted in the Table 5, the most influential publications and the largest research activity in KA is production and optimization. Since 2014 onwards, experimental and genetic strategies have been explored driven by the need to develop scalable, cost-effective, and industrially robust processes, as well as to favor a reliable KA supply for expanding market in the pharmaceutical and cosmetic applications. In tables 7 and 8 the relevant publications in KA production and optimization are presented as the most active knowledge cluster in KA research. Table 7 compiles studies focusing on the cultivation of different *Aspergillus* strains under diverse fermentation conditions, highlighting the range of substrates, culture systems, and process configurations. Table 8 presents studies addressing genetic and molecular interventions to enhance KA production in submerged cultures, especially with *Aspergillus* species

Table 7. *Studies on the cultivation of different strains for kojic acid production*

Strain	**Type**	**Scale**	**Volume (L)**	**Substrate/Medium**	**KA Yield**	**Ref**
A. oryzae, Epicoccum dendrobii	Batch	Flask	0.1	Glucose and potato starch	1.10 g/L	61
A. flavus BU20S	Batch	Flask	0.05	Glucose + inorganic nitrogen (ammonium chloride)	2.52 ± 0.56 g/L (NH_4Cl), 2.02 ± 0.06 g/L (yeast extract)	60
A. oryzae / A. tamari	Batch	Flask	–	10% cane molasses + yeast extract, KH_2PO_4, $MgSO_4$	25.91 g/L (A. oryzae), 18.95 g/L (A. tamari)	46
A. niger M4	Batch	Flask	0.02	Glucose ($ZnSO_4$) + yeast extract	0.552 g/L (72 h), 0.510 g/L (96 h)	64

A. flavus	Batch	Flask	0.36	Rice	1.2 g/L	49
A. flavus	Batch	Solid state	5 g (solid)	Sago fiber, urea, KH2PO4 (0.2% w/v), MgSO4·7H2O, yeast extract	2.75 g/L	3
A. oryzae	Batch	Flask	0.1	5% reduced sugars molasses, NaNO3, KH2PO4, MgSO4·H2O	8.01 g/L	32
A. flavus	Batch	Flask	0.1	Glucose, KH2PO4, NaNO3, KCl, MgSO4·7H2O, FeSO4	62.23 ± 0.69 g/L	41
A. oryzae	Batch	Flask	0.1	Glucose + yeast extract + mineral salts (KH2PO4, MgSO4·7H2O)	139.24 g/L	43
A. flavus	Batch	Flask	0.07	Glucose + yeast extract	31.00 g/L	55
A. flavus	Batch	Bioreactor	3.0	–	11.1 g	34

Table 8. *Studies on genetic modifications for kojic acid production*

Strain	**Genes targeted**	**Intervention**	**KA Yield**	**Ref**
A. niger	*kojA, nrkA, nrkB, nrkC, nrkD*	Overexpression and deletion (plasmid transformation)	25.71 g/L	64
A. oryzae	*Δgld3 – OE-kojR*	Overexpression (CRISPR/Cas9)	0,12 g/L	21
A. oryzae NSAR1	*Ao_mcrA*	Overexpression (CRISPR/Cas9)	2.52 g/L	16
A. oryzae 10H3	*Random*	Protoplast formation + UV mutagenesis	7.3 g/L	48
A. oryzae	*Aokap5, kojT*	Deletion and overexpression (CRISPR/Cas9)	32 g/L	36
A. oryzae	*HirA*	Deletion (plasmid transformation)	1.8 g/L	31

A. oryzae 3.042	*Aokap6*	Overexpression and deletion (CRISPR/Cas9)	15 g/L	13
A. flavus	*HAk1*	Gamma radiation mutagenesis	4.5 g/L	4
A. terreus	*kojA, kojR, kojT*	UV mutagenesis	109 g/L	58
A. oryzae AR-47	–	ARTP mutagenesis	96.5 g/L	23
A. oryzae	*Aokap2*	Overexpression (CRISPR/Cas9)	3.2 g/L	37
A. oryzae	*Aokap1*	Deletion (CRISPR/Cas9)	2.1 g/L	38

Discussion

The bibliometric mapping of kojic acid research reveals two dominant axes that have structured scientific activity in this field. The first encompasses studies on biological activities and applications, where KA biochemical properties are examined as an antioxidant, antimicrobial, depigmenting, and pharmacologically active compound, particularly in relation to tyrosinase inhibition and its biomedical and cosmetic uses. The second axis centers on production optimization, which integrates both bioprocess engineering and strain improvement strategies. This line of research reflects a sustained effort to expand the applications spectrum of this bioproduct along with enhance yields, reduce costs by employing approaches ranging from fermentation design to advanced genetic and molecular interventions.

Biological activities of kojic acid

As evident in the thematic clustering, KA exhibits several biological activities of scientific interest, including anti-tyrosinase, anti-melanin, antimicrobial and antioxidant capacities. KA possesses potent antibacterial and antifungal properties(Owolabi et al., 2020). Early studies demonstrated that it is generally more effective against Gram-negative bacteria than against Gram-positive species (Aytemir et al., 2012). Experimental tests confirmed the antimicrobial efficacy of KA against *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (Nurunnabi et al., 2018) (Mohamad et al., 2010) as well as fungi including *Fusarium oxysporum*, *Rhizoctonia solani*, *Pythium graminicola, A. Flavus, A. Niger and Fonsecaea* spp. (Rudhra et al., 2024) (Pereira et al., 2022) (Eslamifar et al., 2024).

KA also exerts moderate anti-inflammatory effects, which can be significantly enhanced through structural modification (Brtko et al., 2004). A notable example is the synthesis of KA derivatives with *p*-coumaric acid, where incorporation of a cinnamate moiety enhanced hydrophobicity and improved activity Similarly, hybrid compounds combining KA with p-coumaric acid exhibited synergistic anti-inflammatory effects via NF-κB suppression (Lee et al., 2019).

Nevertheless, the most extended use of KA is in the cosmetic industry, given its anti-melanogenic effect. The hyperproduction or abnormal accumulation of melanin is associated with several dermatological disorders, including melasma and post-inflammatory hyperpigmentation, as well as chronic infectious diseases such as chromoblastomycosis (El-Korany et al., 2020). Thus, tyrosinase inhibition has emerged as one of the most targeted approaches for depigmenting and therapeutic interventions. In this context, KA has emerged as a prospective bioproduct with tyrosinase inhibition capacity. as observed within the bibliometric landscape, clustering with anti-melanogenesis, and antioxidant activity.

Several compounds have been extensively investigated for their ability to inhibit tyrosinase. Hydroquinone, for instance, acts as a competitive inhibitor and induces melanocyte destruction, explaining its widespread use in depigmenting formulations, although safety concerns limit its long-term application. Ascorbic acid, beyond its antioxidant properties, can reduce the cupric ion of tyrosinase and revert dopaquinone oxidation, thereby decreasing preformed melanin(Santos et al., 2024) (El-Korany et al., 2020). Nevertheless, its instability under light and oxygen exposure requires stabilization to ensure effectiveness. KA, by contrast, exerts its effect through chelation of copper ions at the active site of tyrosinase, directly impairing catalytic activity. This mechanism, coupled with its antioxidant and anticancer properties, has led to its frequent incorporation in cosmetic formulations, where it is regarded as a safer alternative with balanced efficacy, despite its susceptibility to degradation under light, oxygen, and heat (Santos et al., 2024). Although KA is recognized as one of the most effective skin-lightening agents and it has a role in cosmetic dermatology in certain extent, still many studies remain the *in-vitro* stage. (Burnett et al., 2010) (Ando et al., 2010).

Clinical studies have consistently demonstrated the therapeutic potential of KA in treating skin pigmentation disorders. It has been shown in clinical trials that topical formulations including KA significantly improved pigmentation conditions and higher melasma clearance (up to 60%) than those without KA (Ando et al., 2010). KA combined with Vitamin C outperforms hydroquinone in reducing dyschromia with fewer side effects (Tetali et al., 2020). Split-face trials also confirmed that KA with glycolic acid was as effective as hydroquinone regimens(Gupta et al., 2006). More recently, multi-agent formulations containing KA showed marked improvements in pigmentation, skin texture, and tone uniformity (Desai et al., 2019). In chronic infections such as chromoblastomycosis caused by melanized fungi (*Fonsecaea* spp.), KA at low concentrations of (100 µg/mL) markedly reduced melanization, biofilm formation, and vesicular exocytosis of melanin, suggesting KA as a promising adjuvant in chromoblastomycosis therapy, where standardized treatments remain absent (Pereira et al., 2022). This capacity has been tested even in non-mammalian organisms such as the *Pteria penguin* in pearl aquaculture; in which a reduction in eumelanin oxidation products (by ~58%) and decreased tyrosinase activity (by ~55%) was demonstrated, enhancing nacre color uniformity for pearl quality (Yu et al., 2020).

As observed in Figure 4, the expanded the biomedical potential of KA beyond its use as a tyrosinase inhibitor, include the exploration of antioxidant and anticancer properties. In fungi, KA improved stress responses by reducing oxidative damage, highlighting its protective metabolic role (Zhang et al., 2017). Studies examining the relationship between anti-melanogenic and antioxidant activities revealed that both KA and its ester derivatives in concentrations ranging 1.95 and 1000 µg/mL exhibited mild free radical scavenging activity, but weaker than classical antioxidants (Lajis et al., 2012). However, some studies have reported that KA from *A. niger* has a strong antioxidant activity, comparable to this of the ascorbic acid and through structural modification, its antioxidant capacity

can be increased (Zhou et al., 2025). The synthesis of a KA dimer achieved superior antioxidant performance compared to vitamin C, in addition to neuroprotective effects and inhibition of β-amyloid deposition, positioning it as a candidate for neurodegenerative disease management (X. Liu et al., 2023). KA biosynthesized by *A. flavus* CL7, an endophytic and non-aflatoxigenic strain, along with other metabolites exhibited high antioxidant and antimicrobial activity, demonstrating the potential of endophytic isolates as safe biotechnological platforms (Balbinot et al., 2021).

The potential anticancer activity of KA has been less investigated than its other bioactive properties. KA produced by engineered *A. flavus* ASU45 showed cytotoxic activity against human cancer cell-lines (Mcf-7, HepG2 and Huh7), especially in human hepatocellular carcinoma (HepG2) cells (Mahmoud et al., 2024).Mannich derivatives of KA incorporating cyclic amines (morpholine, piperidine, pyrrolidine) also displayed strong cytotoxicity against melanoma cells, surpassing standard chemotherapeutics such as dacarbazine, while simultaneously inhibiting melanogenesis (Karakaya et al., 2018).

Kojic acid bioproduction and optimization

As observed in Figures 4 and 5, along with the cluster showing the current biomedical research associated with the potential bioactivity of KA, a cluster associated to KA production and optimization is evident. KA production has been historically linked to filamentous fungi of the genus *Aspergillus*, particularly *A. oryzae* and *A. flavus*. These species can be considered as the main industrial producers of KA, but the growing demand for KA from cosmetic industry, and the need to reduce production costs, has stimulated research in fermentation technology, strain engineering, and substrate utilization. The bibliometric analysis confirms this line as one of the two principal axes of research activity, highlighting the interest of microbial production strategies in the scientific landscape of KA research. Within this cluster, several sub-themes emerge: optimization of bioprocess parameters, utilization of agro-industrial residues and strain improvement through genetic engineering.

The choice of carbon and nitrogen sources has consistently been shown to modulate KA yields, which is critical when selecting media composition for achieving high synthesis rates. Nitrogen limitation induces morphological changes in the fungal hyphae of *A. oryzae* and *A. flavus*, correlating with the increased expression of kojA and kojT genes of the KA biosynthetic cluster. (J. M. Liu et al., 2016). It has been observed that nitrate metabolism mediated by the nrtA gene, also modulates KA production, linking primary nutrient acquisition to secondary metabolism (Sano, 2016). Achieving an adequate nutritional balance is even more important when using sustainable/low-cost substrates, where the possibilities of adjusting media composition are more limited.

Sugarcane molasses has proven to be a particularly effective substrate for KA production. Using sugarcane molasses as carbon source in *A. oryzae* and *A. tamari* cultures, yielded 25.91 g/L and 18.95 g/L, respectively (Mohamed et al., 2024). Fermentation of brewer's rice by *A. oryzae* not only yielded KA and ferulic acid but also significantly increased the phenolic and flavonoid content of the substrate. This process enhanced the bioactivity of the fermented material, with a 7-fold increase in tyrosinase inhibition and a 57-fold increase in elastase inhibition relative to unfermented extracts (Dang et al., 2019). Lignocellulosic components, particularly lignin, exert strong inhibitory effects on KA biosynthesis. In *A. flavus* BU20S, lignin derived from rice straw reduced KA production by more than 90% when added to glucose-, xylose-, or xylan-based media, showing the necessity of lignin remotion if KA production is intended for valorization of lignocellulosic residues(Sharma et al., 2024).

Optimization of fermentation conditions through pH control and immobilization techniques in batch fermentation yielded 18.61 g/L KA from *A. flavus* and 12.96 g/L from *A. oryzae* under dual pH control strategies (Lakhawat et al., 2018) Even higher yields were achieved using plastic composite supports for *A. oryzae* immobilization under nitrogen-limited conditions, producing 83.47 g/L with a productivity of 3.09 g/L/day (J. M. Liu et al., 2016). Solid-state fermentation has also emerged as an alternative strategy for residues valorization, particularly KA yields of 2.75 g/L were achieved using sago fiber as substrate (ALVIN MIAI SPENCER et al., 2019)

One innovative strategy has been the use of chemical and biological stressors to improve KA production. Exposure to citrinin, have been shown to upregulate KA biosynthetic genes in *A. oryzae* and *A. parasiticus*, indicating that KA may act as a defensive metabolite under oxidative stress (Ichinomiya et al., 2022). The cocultivation of *A. oryzae* with *Epicoccum dendrobii* produced KA at concentrations of 1.10 g/L, driven by competitive interactions that stimulated cryptic metabolic routes, unlocking secondary metabolites not observed under monoculture conditions(Shen et al., 2024).

Recently, the use of engineered strains emerged as an alternative for enhanced KA production. Heterologous expression of the kojA gene from *A. oryzae* in a non-producer strain of *A. niger* produced 25.71 g/L of KA, representing a 26.7% improvement compared to shake-flask cultures of A. Oryzae (Wu et al., 2023). Targeted deletion of genes such as msn2 in *A. oryzae* increased KA production by 81%, correlating with upregulation of kojR and LaeA genes (Shi et al., 2022). Similarly, manipulation of genes regulating glycerol metabolism (AoGld3) or global transcription factors (mcrA) demonstrated profound effects on KA biosynthesis (Fan et al., 2020)(Dao et al., 2021). Notably, zinc-finger proteins such as AoKap2 and AoKap6 have been identified as critical regulators of KA biosynthesis, with overexpression or deletion producing substantial shifts in kojA and kojR expression (Li et al., 2022) (Chen et al., 2022).

In the other hand, the traditional physical mutagenesis methods, including gamma irradiation and microwave/UV/plasma-based strategies, continue to be successfully applied for KA producers strain improvement. Mutants of *A. flavus* and *A. oryzae* showed up to 2.03-fold increases in KA production after gamma irradiation (Ammar et al., 2017), while combined mutagenesis strategies yielded the AR-47 strain with 96.5 g/L KA, representing a 292.3% increase over the parental strain (Feng et al., 2019) Response surface methodology applied to UV-induced *A. terreus* mutants further optimized production to 109 ± 10 g/L (Shakibaie et al., 2018). Those productivities are still higher than those achieved in engineered platforms, highlighting the relevance of classical mutagenesis in industrial biotechnology as a complementary approach to the application metabolic and genetic engineering tools.

Conclusions and future perspectives

Over the past two decades, kojic acid production has experienced remarkable progress, particularly in Asian countries where universities and research centers have led the development of biotechnological processes targeting this high-value compound. Microbial fermentation, especially under liquid-state batch and fed-batch modes, remains the primary strategy for its production, with *Aspergillus oryzae* and *A. flavus* serving as the most widely employed strains. Within these processes, operational variables such as pH regulation, substrate selection, and the type of nitrogen source have consistently proven to be critical factors in maximizing production yields.

In this context, the utilization of agro-industrial residues such as molasses, brewer's rice, or sago fiber has emerged as an attractive strategy, offering not only technical feasibility but also important contributions to sustainability and cost reduction in industrial settings. At the same time, the application of genetic engineering tools has significantly boosted kojic acid yields. Among the most impactful techniques are random mutagenesis (via UV or gamma irradiation), protoplast-based approaches coupled with selective screening, and precise genome editing using CRISPR/Cas9. These interventions have enabled the overexpression or deletion of key regulatory genes, including *kojA*, *kojR*, *kojT*, and *LaeA*, thereby enhancing metabolite biosynthesis and redirecting secondary metabolism toward KA accumulation.

Beyond its well-recognized depigmenting effect mediated by tyrosinase inhibition, kojic acid has demonstrated a broad spectrum of biological activities, including antioxidant, antimicrobial, anticancer, and anti-inflammatory properties. These bioactivities greatly expand its potential across medical, cosmetic, and pharmaceutical fields, consolidating KA as a multifunctional biocompound of growing interest in modern biotechnology.

Looking ahead, one of the most promising directions for kojic acid production lies in the development of hybrid bioprocesses that integrate chemo-enzymatic pathways with microbial fermentation. Such combined strategies could deliver more efficient, flexible, and scalable production systems capable of meeting the rising demands of the global market. In parallel, the application of genetic engineering within the framework of synthetic biology opens avenues for constructing artificial biosynthetic routes and introducing heterologous platforms into non-native hosts. This would allow for enhanced process control, higher product purity, and improved industrial scalability.

Moreover, the implementation of artificial intelligence tools, including machine learning–based predictive models, represents a powerful approach to accelerate medium design, optimize strain selection, and anticipate production yields under diverse operational conditions. These strategies could enable more precise decision-making and improve process efficiency by providing predictive insight into production outcomes.

In addition, progress in continuous fermentation systems, such as bioreactors with immobilized supports, offers a unique opportunity to establish stable production schemes with sustained high yields and reduced need for human intervention. Finally, it will be essential to deepen toxicological evaluations of kojic acid and its derivatives to ensure their safety in pharmaceutical and food applications. This entails not only acute and chronic toxicity studies but also strict compliance with international regulatory standards, which will ultimately enable their safe approval and commercialization across new global markets

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