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Advancements in Modern Biotechnology for Enhanced Kojic Acid Production in the Cosmetic Industry: A Review

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Abstract: Kojic acid (KA), a secondary metabolite from *Aspergillus* species, is widely used in the cosmetic industry as a skin-lightening agent, antioxidant, and anti-aging ingredient. With the growing demand for natural and effective skincare products, there is an increasing interest in sustainable and scalable KA production. Conventional fermentation methods remain limited by low yields, long incubation periods, and high costs. Advances in biotechnology now provide more efficient and reliable alternatives to overcome these challenges. This systematic review of studies published between 2020 and 2025 highlights recent developments in genetic engineering and process optimization for KA production. CRISPR/Cas9-based editing of regulatory genes such as *kojR* and the promoter region of *kojA* has improved production stability and yield, with increases reported up to 43 percent. Mutagenesis approaches using UV, gamma irradiation, microwave exposure, and atmospheric plasma have produced hyperproductive strains, with some reaching 96.5 g/L KA, representing a 293 percent increase compared with parental strains. In addition, novel regulatory proteins, including AoZFA and Aokap2, have been identified as key molecular factors controlling KA biosynthesis. Fermentation optimization also contributes significantly to efficiency. Adjustments in pH and temperature, the addition of metal ions such as Zn^{2+} and Pb^{2+}, and the use of alternative substrates like sugarcane bagasse or sorghum sheaf have been shown to improve yields and reduce costs. These strategies not only increase production but also align with the demand for sustainable raw materials. Overall, integrating advanced genetic tools with optimized fermentation systems provides a strong platform for industrial-scale KA production. Modern biotechnology demonstrates clear potential to meet the requirements of the cosmetic industry while ensuring product safety, consistency, and scalability.

Keywords: *Aspergillus*; Biotechnology; Kojic Acid; Production.

Introduction

Kojic acid was first discovered by Japanese microbiologist, Kendo Saito, in 1907 from cultures of *Aspergillus* species fungi used in the fermentation of traditional Japanese foods, such as miso and shoyu [1–3]. The name kojic acid is derived from the word "koji", which refers to a fermentation medium made from steamed rice [4]. Kojic acid is known to be a secondary metabolite that has various uses, including as a skin lightener, antioxidant, and antimicrobial [5–7].

Attention to kojic acid is increasing rapidly due to its commercial applications in industry, especially in the field of cosmetic industry [8]. The role of kojic acid in the world of cosmetics can be used as a skin care product that prevents exposure to UV radiation [9,10]. In addition, kojic acid is also used in the production of skin whitening creams, skin protection lotions and whitening soaps [8,11]. The way kojic acid works by suppressing hyperpigmentation in human skin is through the formation of melanin by inhibiting the formation of tyrosinase, which is the enzyme responsible for skin pigmentation [8,12–15].

To meet the growing demand in the cosmetic industry, biotechnology plays an important role in producing kojic acid more efficiently [16]. As an application of science, biotechnology helps improve quality and efficiency in various industries, including the production of cosmetic active ingredients such as kojic acid, through CRISPR/Cas9-based genetic engineering techniques, microbial fermentation, and mutagenesis techniques. These technologies enable more stable and affordable production yields [17,18]. For example, kojic acid can be produced through the fermentation of microorganisms such as *Aspergillus* [18] and using mutagenesis and genetic engineering techniques to increase its yield and stability [1][19]. With biotechnology, kojic acid production becomes more efficient, supporting the cosmetic industry in providing safe, effective, and affordable products [19,20].

In the last five years, modern biotechnology has provided powerful tools to overcome these limitations. Techniques such as CRISPR/Cas9 genome editing, recombinant DNA technology, and multi step mutagenesis have enabled the precise modification of key genes like *kojA* and *kojR*, leading to more stable and predictable yields. In parallel, fermentation optimisation strategies such as controlled aeration, supplementation with metal cofactors, and the use of agro-industrial residues have substantially improved efficiency and reduced costs. Despite these advances, no systematic review has yet been conducted that integrates genetic engineering breakthroughs with process innovations and

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directly relates them to the demands of the cosmetic industry.

The purpose of this review is to fill that gap by synthesizing the most recent developments in biotechnology for KA production from 2020 to 2025. By combining insights from molecular genetics and fermentation engineering, this article highlights how modern biotechnology can achieve higher and more consistent yields, ensure production stability, and enable sustainable scaling. The implications extend beyond academic research, offering clear pathways for the cosmetic industry to adopt biotechnology-based production of KA as a safe, efficient, and commercially viable active ingredient.

Research Methods

This review method uses a systematic literature review approach to collect and analyze literature related to advances in modern biotechnology for improved kojic acid production in the cosmetics industry. Literature was searched through scientific databases such as PubMed, Google Scholar, and Springer, using the keywords "kojic acid fermentation", "kojic acid production", and "biotechnology in cosmetics of kojic acid". The articles used were published from 2020 to 2025. From the search results, 1,849 articles were obtained. The articles were then selected based on title identification, resulting in 489 articles. The abstracts were reviewed, and 32 articles were selected. Ultimately, 10 articles were chosen. The articles were then briefly reviewed to ensure that the articles taken were in accordance with the population, intervention, comparison, outcome, timeframe, and setting (PICOTS) elements. The PICOTS results can be seen in Table 1. At the analysis stage, ChatGPT was used as a tool in the discussion. ChatGPT was used as a supporting tool to refine the discussion by improving clarity and structuring ideas.

Table 1. Inclusion criteria based on PICOTS elements

PICOTS	Inclusion Criteria
Population	The cosmetic industry that uses active ingredients such as Kojic Acid in skin care products
Intervention	Genetic engineering techniques or fermentation of microorganisms in the production process of Kojic Acid
Comparison	-
Outcome	Effectiveness and efficiency of Kojic Acid production on an industrial scale through modern biotechnology
Timeframe	Research published from 2020-2025
Setting	All countries

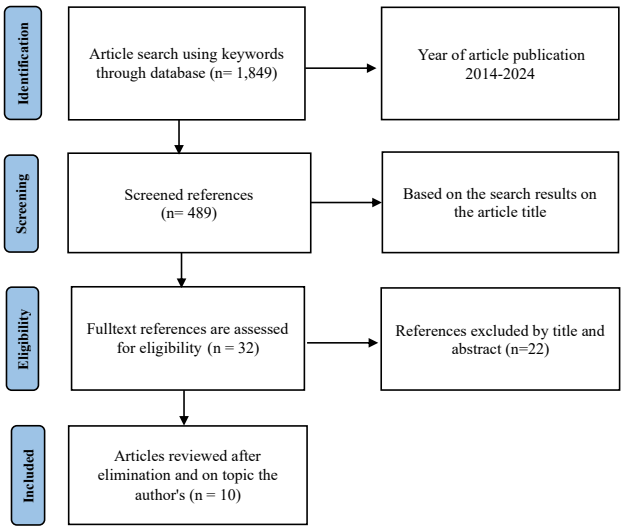

Figure 1. PRISMA diagram

Results and Discussion

The production of KA (Kojic Acid) is generally carried out using conventional methods through the fermentation process during a certain incubation period [18]. However, along with the times and increasing needs, this opens up opportunities for kojic acid production with modern biotechnological innovations, such as genetic engineering techniques, to increase kojic acid production [20]. Several studies have demonstrated an increase in kojic acid production through the application of genetic engineering and mutagenesis techniques to Aspergillus strains, as presented in Table 2.

Table 2. Research on kojic acid production using modern biotechnology to increase kojic acid

No.	Title	Country	Methodological Overview	Types of Biotechnology Techniques	Results	Source
1.	Enhancing Kojic Acid Production in Aspergillus oryzae: Leveraging Crude Cellulase from Achatina fulica for Strain Improvement via Protoplasting and UV Mutagenesis	Indonesia	Protoplasting *A. oryzae* menggunakan enzim selulase dari *Achatina fulica*, dilanjutkan mutagenesis UV (10, 15, 20 menit). Screening dengan FeCl3 dan pengukuran spektrofotometri.	Protoplasting, UV mutagenesis, penggunaan enzim selulase non-komersial	Mutant strain 10H3 produced the highest kojic acid concentration (7.339 g/L), which was 1.83× higher than the parent strain. Medium with molasses as a carbon source enhanced the yield of kojic acid compared to sucrose.	[22]
2.	Biotechnological Production of Kojic Acid Synthesized by Endophytic Fungi,	Egypt	Isolation of endophytic fungi from *Euphorbia peplis* (leaves, stems, roots). Identification of *A. oryzae* as the most	Endophyte isolation, agro-waste fermentation, bioprocess optimization,	*A. oryzae* strain produced maximum KA at pH 6.0, 28°C, and 20 days of incubation under shaking conditions. Sugarcane	[23]

	Aspergillus oryzae Isolated from *Euphorbia peplis*		potent KA producer. Fermentation is carried out using agro-waste (sugarcane bagasse, corn cobs, rice straw). Optimization of fermentation conditions (pH, temperature, incubation time, shaking vs static). Product analyzed using TLC, spectrophotometry, antioxidant assay (DPPH), and GC-MS.	analytical techniques (TLC, GC-MS).	bagasse was the best substrate. The ethyl acetate extract demonstrated strong antioxidant activity (IC50 = 5.7).	
3.	Kojic Acid Gene Clusters and the Transcriptional Activation Mechanism of *Aspergillus flavus* KojR on Expression of Clustered Genes	America	The CRISPR/Cas9 system is used to target and modify genes involved in kojic acid biosynthesis, specifically the promoter of the kojA gene. Identified KojR-binding motifs in the kojA and kojT promoter sequences. Overexpression of kojR gene using heterologous promoter from *Aspergillus nidulans* (gpdA) and homologous promoter from *Aspergillus flavus* (gpiA).	CRISPR/Cas9 technique to investigate the importance of the KojR-binding motif in the kojA promoter, which is crucial for K biosynthesis.	The kojic acid production of strain D-16 resulted in 438.0 ± 57.8 mg of kojic acid per gram of dried mushroom, an increase of 43% compared to the control (306.1 ± 187.0 mg). An important sequence was found in the kojA promoter, which aids kojic acid production.	[1]
4.	Production of Kojic Acid by *Aspergillus niger* M4 with Different Concentrations of Yeast Extract as a Nitrogen Source	Mexico	Submerged fermentation of *A. niger* M4 with varying yeast extract (0.05–2.5 g/L) as nitrogen source. Fermentation conditions optimized by adjusting pH (4.5–6.5), incubation time (up to 120 h), and addition of $ZnSO_4$. Kinetics of KA production were modeled and monitored spectrophotometrically.	Submerged fermentation, nutrient optimization, bioprocess modeling.	Maximum KA yield: 0.931 g/L at 2.5 g/L YE, pH 5.5 after 120 h. At lower YE (0.05 g/L), yield was 0.523 g/L after 96 h. $ZnSO_4$ addition enhanced productivity.	[24]
5.	A highly efficient identification of mutants generated by CRISPR/Cas9 using the nonfunctional - DsRed assisted selection in *Aspergillus oryzae*	China	CRISPR/Cas9 system using the autonomously replicable AMA1 plasmid and Cas9 under the gpdA promoter from *Aspergillus nidulans*. Inserting protospacer and PAM sequences into the nDsRed reporter gene for mutant identification.	CRISPR/Cas9 for gene editing, combined with nDsRed-assisted selection and AMA1-based plasmids for recurrent mutagenesis in genetic modification of *Aspergillus oryzae*	Successfully produced mutations in the kojic acid biosynthesis gene kojA. Transformants with nDsRed activity showed mutations in the kojA gene.	[25]
6.	Overexpression of a novel gene Aokap2 affects the growth and kojic acid production in *Aspergillus oryzae*	China	Construction of recombinant *A. oryzae* strains with Aokap2 overexpression. Growth, morphology, and kojic acid production were evaluated under controlled fermentation conditions.	Genetic engineering (gene overexpression), molecular biotechnology, fermentation analysis.	Aokap2-overexpressing strains showed altered growth patterns and significantly enhanced kojic acid yield compared to the wild type. Demonstrated that Aokap2 is an important regulator of KA biosynthesis.	[26]

			Transcriptional analysis performed to confirm gene expression changes.			
7.	Optimization Of Culture Conditions For Kojic Acid Production In Surface Fermentation By *Aspergillus Oryzae* Isolated From Wheat Grains	Egypt	Isolated 75 strains of 11 *Aspergillus* species from wheat seeds and selected A. oryzae 1034 as the most efficient kojic acid producer. Analyzed the effect of starch and glucose on kojic acid production. Used 0.5 g/L KH_2PO_4 for glucose media and 2.0 g/L KH_2PO_4 for starch media. Established an optimal temperature of 28ºC and pH of 4.5 for glucose media and 5.0 for starch media. Added Pb^{2+} to glucose media and Zn^{2+} to starch media to enhance kojic acid biosynthesis.	Surface microbial fermentation for kojic acid production using *Aspergillus oryzae*, with optimization of culture conditions including substrate concentration, temperature, pH, and heavy metals.	Optimal substrate produces glucose (60 g/L) and starch (80 g/L). Optimal phosphorus 0.5 g/L KH_2PO_4 (glucose) and 2.0 g/L KH_2PO_4 (starch). Maximum production of kojic acid at 28ºC for 11 days, pH 4.5 (glucose) and 5.0 (starch). Pb^{2+} increased biosynthesis to 79.3 g/L, Zn^{2+} to 68.8 g/L. Addition of amino acids decreased biosynthesis.	[30]
8.	Study and Effect of Agitation on Kojic Acid Production by Aspergillus oryzae in Liquid Fermentation	Mexico	Submerged fermentation in 1 L bioreactors with *A. oryzae* ATCC 10124. Tested three agitation/aeration strategies: static, tangential, and bubbling, under light vs dark conditions. Fermentation monitored for 0–168 h, analyzing pH, protein, biomass, reducing sugars, and KA concentration.	Bioprocess optimization (agitation, aeration, light conditions) in liquid fermentation.	Maximum KA yield: 7.86 ± 2.21 g/L under bubbling agitation with light exposure at 144 h. Aeration strongly influenced KA biosynthesis efficiency.	[27]
9.	Production of kojic acid by Aspergillus niger (PP330720) and Penicilium digitatum (PP892864) grown on guinea corn (Sorghum bicolor) sheaf	Nigeria	Submerged fermentation using agricultural waste (*Sorghum bicolor* sheaf) as carbon source. Two fungal isolates (*A. niger* PP330720 and *P. digitatum* PP892864) were cultured, and KA production was monitored over time. Quantification performed using spectrophotometry and TLC.	Agro-waste fermentation, microbial strain screening, biochemical quantification.	*A. niger* yielded higher KA compared to *P. digitatum*. Guinea corn sheaf proved to be an effective low-cost substrate for KA production.	[28]
10.	Functional role of a novel zinc finger protein, AoZFA, in growth and kojic acid synthesis in *Aspergillus oryzae*	China	Used CRISPR/Cas9 to generate deletion and overexpression mutants of *AozfA*; transcriptional activity assays; gene expression analysis (kojA, kojR); zinc supplementation experiments to test growth and metabolite production.	CRISPR/Cas9 gene editing, transcriptional activation assays, qPCR, phenotypic and growth analysis under zinc conditions.	Deletion of *AozfA* significantly increased kojic acid production, while overexpression reduced it. *AozfA* acts as a negative regulator by modulating *kojR*. Combined modification of *AozfA* and *kojR* enhanced kojic acid yield more than single-gene modifications.	[29]

Kojic Acid Manufacturing Process

The kojic acid production process begins with the isolation of fungal strains that have the ability to produce kojic acid as a secondary metabolite [20]. These strains, such as *Aspergillus oryzae* [21], *Aspergillus flavus* [13,14], *Aspergillus terreus* [22], and *Aspergillus nidulans* [1], commonly found on natural substrates such as moldy fruits [20], corn kernels [13,14], or wet wheat [23]. After isolation, the fungal strains are cultured on selective media, such as Potato Dextrose Agar (PDA), to ensure that only the target fungi grow [1,24]. PDA medium also helps prepare the fungi for the next stage of fermentation. Fungal cultures that have grown well on PDA are then transferred to fermentation media that have been optimized to support maximum kojic acid production. This fermentation medium consists of glucose (100 g/L), yeast extract (5 g/L), $KH_2 PO_4$ (1 g/L), $MgSO_4$ (0.3 g/L), and peptone (6 g/L), which were dissolved in a mixture of seawater and distilled water in a ratio of 1:1 and a salinity of 17 ppt. Under optimal conditions, fermentation is carried out at 28 ± 1 °C in a stationary state for 20 days, yielding a maximum production of up to 20 g/L of kojic acid. However, fermentation time can vary, with some studies suggesting an incubation time of 5-7 days [19,20] or up to 15-20 days, depending on the strain type and media conditions [15,24].

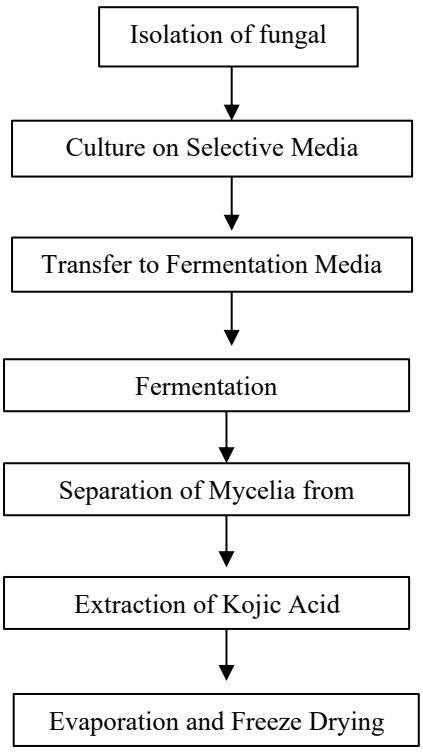

Figure 2. Kojic Acid Manufacturing Process

After the fermentation period is complete, the mushroom mycelia are separated from the liquid medium, as the mycelia do not contain the kojic acid produced. Next, kojic acid is extracted from the fermentation medium that has been separated from the mycelia. This extraction method usually involves the use of organic solvents such as butanol or ethyl acetate, which will bind to the kojic acid and separate it from other components in the medium [3,24]. After the organic solvent is added, the mixture is evaporated under vacuum conditions to obtain a crude extract of kojic acid. Alternatively, the fermentation medium can be frozen and lyophilized, which results in a crude extract powder after freeze-drying [24]. The final stage in this process is the purification of kojic acid to improve its purity. This purification is usually carried out by column chromatography methods or using ultraperformance liquid chromatography-mass spectrometry (UPLC-MS) technology, which allows the separation of components until pure kojic acid is obtained [3,24]. The kojic acid production process, including fermentation, extraction, and purification steps, is illustrated in Figure 2.

Biotechnology Techniques to Increase Kojic Acid Production Yields

Kojic acid is an organic compound that is widely recognized as a whitening agent in cosmetic products, and has potential applications in the pharmaceutical and food fields [11]. The natural production of kojic acid can be found in several types of fungi, particularly those from the genera *Aspergillus* and *Penicillium*. However, to meet the growing industrial demand, natural production methods are often deemed inefficient on a large scale. Therefore, various biotechnological techniques have been developed to significantly increase kojic acid production yields [25,26].

Biotechnology techniques, such as genetic cloning, heterologous expression, recombinant DNA, and most recently CRISPR-Cas9, have been demonstrated to enhance the efficiency and yield of kojic acid production. In the early stages of genetic engineering development, genetic cloning was a commonly used technique. This technique involves isolating and transferring a specific gene into a vector (typically a plasmid), which is then inserted into a host cell, such as a bacterium or fungus. In this way, the gene carrying the information to produce kojic acid can be copied and multiplied in large quantities. This method has been used to develop strains of microorganisms that can produce certain compounds more efficiently and consistently. For example, cloning the gene for kojic acid biosynthesis in the fungus *Aspergillus* allows for more controllable and sustainable production [1, 34, 35].

Heterologous expression techniques are used to produce proteins or compounds from species that do not naturally produce them. In the context of kojic acid production, this technique can be used to express genes encoding kojic acid biosynthesis in other microorganisms. Genes cloned from kojic acid-producing fungi are inserted into bacterial or yeast cells, and these cells can then be programmed to produce kojic acid in greater quantities and more efficiently. This method is often used to commercially scale up the production of bioactive compounds. This finding aligns with the research of Tamano et al. (2019), who successfully produced kojic acid heterologously in Aspergillus niger by expressing the kojA gene from *Aspergillus oryzae*. By identifying the gene inhibiting KA production, it was possible to

significantly increase KA production, showing the potential of A. niger as a more economical KA production platform [3][25]

Recombinant DNA refers to a technique that combines genetic material from different sources to produce new DNA not found in nature. In the context of kojic acid production, this technique allows the creation of microbial or fungal strains that can produce this compound efficiently [19]. By combining genes encoding kojic acid biosynthesis with recombinant vectors, we can modify the properties of these microorganisms to increase production and reduce costs. The recombination process was carried out by altering *A. oryzae* strains to express the kojR transcription factor gene that regulates kojic acid production, as well as the cellulase gene to facilitate the degradation of cellulose into glucose that can be used in kojic acid production. This recombination process resulted in a strain that can produce kojic acid directly from cellulose in the fermentation medium, which is an important step in developing a more cost-effective kojic acid production process [18].

The CRISPR-Cas9 method is a newer and more precise genetic editing technology. It enables researchers to precisely modify genes at the desired location on an organism's genome. CRISPR has brought about a revolution in genetic engineering due to its ability to modify genes with high precision and better efficiency compared to previous techniques. In the context of kojic production, several studies have shown an increase in kojic acid production through various biotechnological innovations. Feng et al. (2019) performed stepwise mutagenesis on the *Aspergillus oryzae* strain KA-11, using microwave, UV, LiCl-heat treatment, and atmospheric plasma techniques. This study successfully increased the yield to 96.5 g/L, representing a 292.3% increase over the initial strain. These results indicate that the combination of these mutagenesis techniques allows the selection of strains with better production characteristics, suggesting that the combination of mutagenesis techniques can significantly increase kojic acid production yields in various high-productivity *Aspergillus* strains [20].

Research by Ammar et al. (2017) highlighted the use of gamma radiation as an efficient method for mutagenesis to increase kojic acid production. By utilizing ionizing radiation from Cobalt-60 sources, spores of *Aspergillus flavus* HAk1 and *Aspergillus oryzae* HAk2 were exposed to various doses of gamma radiation. The results showed a 1.9 to 2.03 fold increase in kojic acid production compared to the parent strain. Gamma radiation has advantages in terms of time and cost efficiency. The technique can create random mutations in DNA without the need for complex or expensive equipment, making it an attractive method to use at an early stage in the development of improved strains. However, the random nature of the mutations requires strict selection of mutant strains to ensure production stability between batches [13,14].

In addition, UV mutagenesis techniques have also been used as a first step to increase yield. Shakibaie et al. (2018) demonstrated that the selection of Aspergillus terreus strains through UV exposure could increase production to 7.62 g/L, making the UV mutagenesis technique an effective alternative for improving kojic acid production programs. The UV mutagenesis technique offers a faster process and lower cost than CRISPR/Cas9, although the mutations are random, requiring a rigorous strain selection process to ensure the stability of the results [22].

Genetic engineering techniques to increase kojic acid production yield have been successfully applied to optimize the production of this active ingredient, which is essential in the cosmetic industry. Along with the advancement of biotechnology, CRISPR/Cas9-based genetic engineering techniques have been proven effective in improving the production efficiency of kojic acid [1,22]. After the basic strain is obtained through isolation and fermentation, mutagenesis is used to create mutations in the fungal DNA to increase the strain's capacity to produce kojic acid [21].

The use of this technology is highly relevant to meet the needs of industrial-scale production. CRISPR/Cas9 provides the long-term yield stability required to meet industry standards. CRISPR/Cas9 technology provides advantages in terms of genetic editing precision. With this technology, specific modifications can be made to genes associated with kojic acid production, such as the kojA gene promoter and kojR regulator. Manipulating these two genes can increase kojic acid production by up to 43%. In addition, CRISPR/Cas9 can identify kojR-binding motifs on the kojA promoter, which play an important role in the regulation of kojic acid biosynthesis [1]. The advantage of CRISPR/Cas9 lies in its ability to create strains with stable and consistent yields, which is crucial for meeting the high standards of large-scale production in the cosmetics industry. However, the use of CRISPR/Cas9 is more expensive and requires more sophisticated equipment and expertise, leading to a longer time for validation of the final result compared to random mutagenesis, such as gamma radiation [17,27].

Several studies have also demonstrated that the regulation of specific gene expression plays a crucial role in maintaining the stability of kojic acid production. Yamada et al. (2014) showed that increased expression of the kojR transcription factor gene in *Aspergillus oryzae* was able to increase productivity without significant changes in the fermentation medium [18]. Sano (2016) found that disrupting the nitrate transporter nrtA by adding sodium nitrate increased kojic acid production up to 3.7-fold compared to the control strain. This highlights the importance of manipulating specific genes to increase production stably and consistently on a large scale [21].

However, several challenges must be overcome in applying these techniques on an industrial scale. The primary obstacles are the risk of microbial contamination, high production costs, and the complexity of process control. Microbial contamination, for example, can reduce the quality and quantity of kojic acid production, requiring strict control and a sterile production environment [19,23]. CRISPR/Cas9 technology enables increased resistance to contamination in strains, but the high cost and sophisticated equipment required pose additional challenges that must be considered in industrial applications [27]. Additionally, the complex process control of this technology necessitates an automated

system to ensure optimal results and minimise the risk of errors in the genetic editing process [39].

Fermentation optimization has become one of the important strategies to increase kojic acid production, as shown in various studies. Azzahra et al. (2018) conducted an experiment to evaluate the effect of fermentation parameters such as pH and temperature on kojic acid production. The study found that setting the pH at 4.5 and the fermentation temperature at 35°C resulted in a 1.71 g/L increase in production. These results highlight the importance of setting optimal environmental conditions in fermentation to increase production efficiency [19].

Another study by Rasmey & Abdel-Kareem (2021) added a new dimension to fermentation optimization by using a glucose-starch combination substrate and supplementation of metal ions such as Pb^{2+} and Zn^{2+}. Their research showed that the addition of these ions acted as enzyme cofactors, accelerating the kojic acid biosynthesis reaction and thereby increasing the production yield to 79.3 g/L. This approach not only shows significant potential for improving production efficiency but also emphasizes the need for an in-depth understanding of the biochemical effects of fermentation media components [23].

The findings of these two studies confirm that careful regulation of fermentation parameters can significantly increase kojic acid production, especially on an industrial scale. Thus, the combination of fermentation optimization techniques and genetic engineering technology provides a great opportunity to increase kojic acid production yield efficiently and sustainably [19,20,23].

Safe Use of Genetically Engineered Kojic Acid

Kojic acid produced through genetic engineering, such as using gene cloning, heterologous expression techniques, and CRISPR/Cas9 techniques or mutagenesis, is generally considered safe for use provided that the production process meets food safety standards and applicable regulations [17]. The genetic engineering process aims to improve production efficiency without changing the basic chemical structure of kojic acid itself [18]. In Indonesia, genetically modified organisms (GMOs) must undergo a food safety assessment before being released. The Food and Drug Administration (BPOM) stipulates that every GMOs food must obtain food safety approval in accordance with Government Regulation No. 21/2005 on Biosafety of Genetically Engineered Products. This review process involves evaluating genetic information, assessing substantial equivalence, examining changes in nutritional value, assessing allergenicity, toxicity, and other relevant considerations. Only products that have passed this assessment are permitted for release. Therefore, genetically modified kojic acid that has gone through the evaluation process and meets the requirements and standards set by BPOM can be considered safe for use. The development of kojic acid through genetic engineering offers significant advances in production efficiency and product consistency. Random mutagenesis techniques, CRISPR/Cas9-based genetic engineering, or the use of optimized fermentation technologies can produce more productive fungal strains, increasing production yields several times compared to conventional methods [3]. In product development involving biotechnology, each stage must undergo a series of rigorous technical evaluations, including genetic stability tests, fermentation yield analysis, and product quality monitoring, to ensure that key components, such as kojic acid, are safe and effective for use [13,14]. Therefore, careful research needs to be conducted to optimize the production process and ensure that the products produced conform to high-quality standards [28].

From the perspective of regulators, such as BPOM in Indonesia or international food and drug regulatory bodies, including the FDA (Food and Drug Administration) and the EMA (European Medicines Agency), several steps must be taken to ensure the safety and quality of products containing genetically modified kojic acid. These regulators typically have stringent requirements, ranging from genetic safety tests on modified strains to monitoring potential microbial contamination risks, and proof that the product does not cause adverse side effects in users. National and international regulations require manufacturers to conduct clinical and pre-clinical trials, as well as continuous monitoring of products on the market [28]. In Japan, kojic acid, used as a skin whitening product, is regulated as a semi-drug. Semi-drugs are defined as "having a mild effect on the body but not intended for the diagnosis, prevention, or treatment of disease, nor to affect the structure or function of the body". In Indonesia, for example, BPOM stipulates that genetically modified products (GMOs), including those using active ingredients, must meet safety, quality, and effectiveness standards before they can be marketed. This aims to protect consumers from unknown potential health risks and ensure that products used in the market are medically and ethically acceptable [25].

From a consumer perspective, the safety and benefits of products containing genetically modified kojic acid are certainly a major concern. Consumers want products that are safe, effective and free from harmful side effects [28]. With genetic engineering, concerns exist that these products may have effects that are undetectable or not fully understood, particularly if there is insufficient evidence regarding their long-term impact. Therefore, transparency in the production process and strong scientific evidence on product safety are essential to build consumer trust [29]. If a product has passed tests from authorized regulatory bodies and shows positive results in safety and effectiveness testing, consumers will be more likely to trust the product. Safety in product use is a top priority for consumers, and clear and evidence-based information about the origin and production process of kojic acid is essential to ensure that the product meets their expectations [30,31].

Application of Kojic Acid in the Cosmetic Industry

Kojic acid has a wide range of applications in various fields, including agriculture, the food industry, chemistry, medicine, and, most notably, the cosmetic industry [32]. Currently, kojic acid is most widely utilized in skincare products in the cosmetic industry, specifically

to treat skin pigmentation problems. As a natural tyrosinase inhibitor, kojic acid works by inhibiting the enzyme tyrosinase, which is responsible for the formation of melanin, the pigment that gives skin its color. This ability makes kojic acid effective in treating hyperpigmentation problems, such as dark spots and acne scars, so it is often used in skin lightening creams and anti-aging products [33].

More than just a skin lightener, kojic acid and its derivatives also have great potential as anti-inflammatory ingredients, which is important for the pharmaceutical and cosmetic industries. Research conducted by Li et al. (2021) found that the fungus *Aspergillus* versicolor is capable of producing two kojic acid derivatives, known as kojicon A and B. These two derivatives are kojicon adducts. Both of these derivatives are adducts of kojic acid with a complex cyclic structure named cyclohexen-1,3-dione. Further research has demonstrated that these two compounds exhibit strong anti-inflammatory effects, both in laboratory testing (in vitro) and in vivo. These findings provide hope that kojic acid and its derivatives can be further developed as anti-inflammatory active ingredients in cosmetics and pharmaceutical products [5,27].

In addition, kojic acid also shows potential as a radiation protector and UV ray shield, making it a highly valuable ingredient in skincare products. Kojic acid has a high free radical scavenging ability, which serves to protect the skin from radiation damage, such as solar UV rays and other radiation [34,35]. Such potential makes it a promising radioprotective agent against radiation-induced damage. This protective effect can help prevent signs of premature aging and maintain healthy skin from damaging environmental factors. In addition, kojic acid also has anti-aging properties [8], anti-bacterial [4], anti-tyrosinase [36], and anti-fungal, which further adds to its beneficial value in cosmetics and skincare products [8].

Conclusion

Modern biotechnology has presented innovative solutions to significantly increase kojic acid production in the cosmetics industry. Techniques such as combined mutagenesis, gamma radiation, and CRISPR/Cas9-based genetic engineering have been shown to increase biosynthetic efficiency and produce high precision kojic acid in various *Aspergillus* strains. In addition, optimization of fermentation parameters such as pH regulation, temperature, and addition of supplements also plays an important role in increasing production yields and reducing operational costs. The right combination of substrates, such as glucose and starch, also contributes to more efficient production. Although promising, industrial-scale implementation still faces challenges, including contamination risks, high costs, and process complexity. However, with safety standards met, genetically modified kojic acid products are considered safe and have the potential to meet the growing demand for the market. Overall, the integration of modern biotechnology not only enhances the competitiveness of the cosmetics industry through more efficient and sustainable production but also creates opportunities for the development of innovative products with high quality and safety.

Author's Contribution

Most of the work in preparing this article was carried out by S. R. Herlaesa, including conceptualization, literature review, data analysis, interpretation, and manuscript writing. C. F. M. Muini and A. Khaerunisa contributed to the editing and alignment of the final content prior to submission. All authors approved the final version of the manuscript and are jointly responsible for the integrity of its content.

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