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Review

Factors affecting cannabidiol and tetrahydrocannabinol production in *Cannabis*: Internal mechanisms and environmental factors – A systematic review

[Factores que afectan la producción de cannabidiol y tetrahidrocannabinol en el *Cannabis*: Mecanismos internos y factores ambientales - Una revisión sistemática]

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Abstract

Context: The increasing demand for cannabidiol (CBD) and tetrahydrocannabinol (THC) in medical applications underscores the need for optimized *Cannabis* cultivation.

Aims: To explore the impact of environmental and genetic factors on cannabinoid production, focusing on CBD and THC, using systematic bibliometric analysis, principal component analysis (PCA), and regression modeling.

Methods: Data were collected from PubMed, ScienceDirect, and Scopus databases, resulting in 56 systematically reviewed studies. Information on temperature, humidity, altitude, photoperiod, and cultivation methods was also extracted. Bibliometric analysis was conducted using VOSviewer to identify research trends, whereas PCA and regression analyses were performed in RStudio to evaluate the relationships between environmental factors and cannabinoid profiles.

Results: The analysis highlighted that *Cannabis sativa* was the dominant species studied, with CBD being the most researched cannabinoid. PCA revealed positive correlations between CBD production and environmental factors such as temperature and humidity. Regression analysis supported these trends, with altitude showing a minimal direct influence. Cultivar differences had less impact on cannabinoid profiles than environmental variables.

Conclusions: Environmental factors play pivotal roles in cannabinoid production. These findings provide actionable insights for optimizing cultivation practices and advancing cannabinoid research.

Keywords: bibliometric analysis; cannabidiol; cannabinoid; *Cannabis sativa*; principal component analysis; tetrahydrocannabinol.

Resumen

Contexto: La creciente demanda de cannabidiol (CBD) y tetrahidrocannabinol (THC) en aplicaciones médicas subraya la necesidad de optimizar el cultivo de *Cannabis*.

Objetivos: Explorar el impacto de los factores ambientales y genéticos en la producción de cannabinoides, centrándose en el CBD y el THC, mediante análisis bibliométrico sistemático, análisis de componentes principales (PCA) y modelos de regresión.

Métodos: Se recopilaron datos de las bases de datos PubMed, ScienceDirect y Scopus, lo que resultó en 56 estudios revisados sistemáticamente. También se extrajo información sobre temperatura, humedad, altitud, fotoperiodo y métodos de cultivo. El análisis bibliométrico se realizó con VOSviewer para identificar tendencias de investigación, mientras que el PCA y los análisis de regresión se realizaron en RStudio para evaluar las relaciones entre los factores ambientales y los perfiles de cannabinoides.

Resultados: El análisis destacó que *Cannabis sativa* fue la especie dominante estudiada, siendo el CBD el cannabinoide más investigado. El PCA reveló correlaciones positivas entre la producción de CBD y factores ambientales como la temperatura y la humedad. El análisis de regresión confirmó estas tendencias, donde la altitud mostró una influencia directa mínima. Las diferencias entre cultivares tuvieron un menor impacto en los perfiles de cannabinoides que las variables ambientales.

Conclusiones: Los factores ambientales desempeñan un papel fundamental en la producción de cannabinoides. Estos hallazgos proporcionan información útil para optimizar las prácticas de cultivo y avanzar en la investigación sobre cannabinoides.

Palabras Clave: análisis bibliométrico; cannabidiol; cannabinoide; *Cannabis sativa*; análisis de componentes principales; tetrahidrocannabinol.

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Abbreviation: AAE1: Acyl-activating enzyme 1; CBD: Cannabidiol; CBDA: Cannabidiolic acid; CBDAS: Cannabidiolic acid synthase; CBG: Cannabigerol; CBGA: Cannabigerolic acid; GPP: Geranyl pyrophosphate; OAC: Olivetolic acid cyclase; PCA: Principal component analysis; PT: Prenyltransferase; THC: Tetrahydrocannabinol; THCA: Tetrahydrocannabinolic acid; THCAS: Tetrahydrocannabinolic acid synthase.

INTRODUCTION

The cultivation of *Cannabis* for medicinal and recreational purposes has garnered increasing attention in recent years (Wani et al., 2023). This is due to the growing recognition of its therapeutic potential and the legalization of *Cannabis* in various regions. Cannabidiol (CBD) and tetrahydrocannabinol (THC) are the most abundant cannabinoids found in *Cannabis*, with distinct applications (Citti et al., 2018). The global sales of pharmaceutical *Cannabis* are expected to reach US$1.37 billion by 2027, with CBD and THC becoming the significant compounds in the products (Grand View Research, 2023). This reflects the increasing market interest in CBD and THC for treatment.

While the demand for CBD and THC continues to surge, there is a critical need to understand the factors that influence its production. The production of CBD and THC in *Cannabis* plants is influenced by various genetic and environmental factors (Trancoso et al., 2022). The genetics of the plant determine its potential to produce certain cannabinoids. Based on the chemical composition, *Cannabis* is classified into chemotype I (drug-type, has mainly THC), II (intermediate-type, CBD and THC ratio equal to 1), III (fiber-type, has mostly CBD), IV [has mainly cannabigerol (CBG)] and V (all cannabinoids undetectable by gas chromatography analysis) (Aizpurua-Olaizola et al., 2016; Pacifico et al., 2008).

Environmental factors play a pivotal role in the cultivation of *Cannabis*, influencing not only the growth and health of the plants but also the potency and profile of the produced cannabinoids (Zheng et al., 2021). Thermal stress has been reported to reduce plant growth and trigger senescence in plants. Both high (heat stress) and low (cold stress) temperatures enhance the production of secondary metabolites (Gorelick and Bernstein, 2017). However, optimal temperatures can promote plant development, while extreme temperatures can cause stress or damage, affecting cannabinoid production (Park et al., 2022). Other factors, such as altitude, may affect *Cannabis* cultivation owing to changes in atmospheric pressure, temperature, and UV radiation (Giupponi et al., 2020; Trancoso et al., 2022). Environmental conditions such as humidity and lighting are required for the vegetative and developmental stages of *Cannabis*. In the vegetative growth phase, high light intensity is essential for optimal *Cannabis* development, whereas precise regulation of the photoperiod is vital for triggering the onset of flowering (Eichhorn et al., 2019).

While previous studies have explored cannabinoid biosynthesis, gaps remain in understanding the role of specific environmental variables such as temperature, humidity, and altitude. Furthermore, study methodologies and reporting inconsistencies hinder the ability to draw robust conclusions. This study addresses these challenges using bibliometric analysis, principal component analysis (PCA), and regression modeling to evaluate the relationships between environmental factors and cannabinoid production. The objectives were to identify key variables influencing CBD and THC synthesis and provide actionable insights for optimizing cultivation practices.

MATERIAL AND METHODS

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). In addition to the systematic review, a comprehensive bibliometric analysis was performed to examine research trends in the field. This analysis aimed to forecast future research directions concerning secondary metabolites, focusing on CBD and THC and the impact of different cultivars on their production.

Eligibility criteria

The inclusion of articles in this review was based on specific eligibility criteria. Each article provided detailed descriptions of CBD or THC profiles in *Cannabis* plants, with a particular focus on identifying chemotypes or cultivars. This allowed for an in-depth exploration of variations in cannabinoid content across different *Cannabis* strains. Only research articles were considered eligible, excluding book chapters, sections, review articles, or bibliographies. The articles were written in English to ensure the relevance and accuracy of the sources. Additionally, the keywords used in the articles had to align closely with the main topic of the review, focusing on cannabinoids, their profiling, and specific variations across *Cannabis* cultivars. The inclusion criteria were studies examining environmental variables (temperature, humidity, altitude, and photoperiod) and cannabinoid profiles (CBD and THC). Studies with incomplete data or a non-experimental design were excluded.

Information sources

The research articles for this study were gathered from several reputable and well-established academic sources to ensure the reliability and credibility of the data. These sources include ScienceDirect® (https://www.sciencedirect.com/), Scopus® (https://www.scopus.com/), and PubMed® (https://pubmed.ncbi.nlm.nih.gov/), which are widely recognized for their comprehensive and high-quality academic content. Data collection from these platforms was conducted in February 2024, allowing for the use of the most current and relevant studies.

Search strategy

A comprehensive and structured search strategy was employed to ensure the inclusion of relevant articles. The search process involved using specific keywords and Boolean operators in the search forms of the selected databases. The leading search query consisted of the terms "Cannabis" AND ("chemotype" OR "cultivar") AND "profiling" AND (("Cannabidiol" OR "CBD") OR ("tetrahydrocannabinol" OR "THC")). This combination of keywords aimed to capture articles that focused on the chemical profiling of CBD and THC and examine variations across different *Cannabis* cultivars. The data from these articles were collected in RIS format, facilitating easy export and further analysis. This search strategy was carefully designed to maximize the retrieval of relevant studies and minimize the inclusion of unrelated content, ensuring a targeted and precise dataset for the review.

Selection process

The data collected in the Zotero software underwent an additional screening filtration to ensure that only articles relevant to the research topic were included. This step involved assessing each article's alignment with the pre-established eligibility criteria. Articles that met these criteria were subsequently exported in .ris format, making them accessible for further bibliometric analysis. This systematic screening ensured that only high-quality studies were retained for the review.

Data collection process

Google Sheets and Zotero software efficiently collected data from reputable academic databases. As an online data processing tool, Google Sheets offers the advantage of real-time collaboration, enabling all authors to access and synthesize data simultaneously. This collaboration feature helped minimize the risk of bias throughout the review process. On the other hand, Zotero facilitated the compilation of articles with advanced features for checking duplicates, identifying article types, and providing detailed information such as author names, publication year, DOI, and more. These functionalities streamlined the review process, ensuring data organization and accuracy.

Data items

The data collected for this review included detailed information on several key factors related to *Cannabis* cultivation and cannabinoid production. These factors encompassed the cultivar, sample sources, cultivation method (outdoor or indoor), temperature (°C), humidity (%), altitude (m), and cannabinoid ratio. These variables were crucial for analyzing how different environmental conditions influenced the production of CBD and THC in *Cannabis* plants, providing insight into the factors that may shape cannabinoid profiles.

Study risk of bias assessment

Google Sheets, the same automated tool used for data collection, was also employed to study the risk of bias assessment. This approach enabled each author to independently assess studies based on the pre-established inclusion and exclusion criteria. Factors such as methodological rigor, data transparency, and consistency of findings were considered in the assessment. Studies that lacked sufficient methodological details, contained inconsistent data, or exhibited other forms of bias were excluded from the analysis to ensure the reliability and validity of the results. Using Google Sheets for this assessment ensured the evaluation process was transparent, reproducible, and consistent across all studies.

Effect measures

Bibliometric mapping was employed to visualize and interpret research trends in cannabinoid research. Keywords that appeared at least twice were included to identify dominant themes and relationships. Principal component analysis (PCA) was used to assess the impact of environmental and cultivation factors on cannabinoid production. This technique allows for the quantification and visualization of relationships between variables, highlighting key factors influencing CBD and THC production.

Synthesis methods

Data synthesis was performed through bibliometric mapping using VOSviewer and multivariate analysis using RStudio. Bibliometric analysis provided an overview of research trends and themes, whereas PCA offered more profound insights into the relationships between environmental variables and cannabinoid production. The integration of these methodologies provides a comprehensive under-

standing of the research landscape, highlighting the most significant factors influencing cannabinoid production in *Cannabis*.

Reporting bias assessment

To assess potential reporting biases, findings across multiple studies were compared to identify inconsistencies. The inclusion criteria were carefully designed to minimize bias, focusing on high-quality, original research articles. This process ensured that the review results reflected the most accurate and comprehensive picture of cannabinoid research, reducing the potential for bias in the final synthesis.

Certainty assessment

The certainty of the evidence was evaluated using established frameworks for systematic reviews, specifically the grading of recommendations assessment, development, and evaluation (GRADE) approach. This assessment considered the independent application of inclusion and exclusion criteria, the definition of bibliometric indicators, and the identification of potential methodological biases in the study design. Additionally, research limitations were acknowledged during the discussion phase, contributing to the critical evaluation of the evidence. Factors such as study design, sample size, consistency of findings, and methodological rigor were considered to ensure a high confidence level in the synthesized results. This approach provides a comprehensive understanding of the quality and robustness of the evidence generated by bibliometric analysis.

RESULTS

Study selection

In the literature screening process, articles were searched through PubMed, ScienceDirect, and Scopus databases with no time limitation on publication. Duplicated articles were removed to ensure data integrity. As a result, 56 articles were identified as eligible for bibliometric analysis (as shown in Fig. 1). Among those, 21 articles were eligible for PCA due to the completeness of their reported data. Some articles provided comprehensive information across all variables in the table, but most exhibited gaps, particularly in humidity, elevation, and lighting cycle.

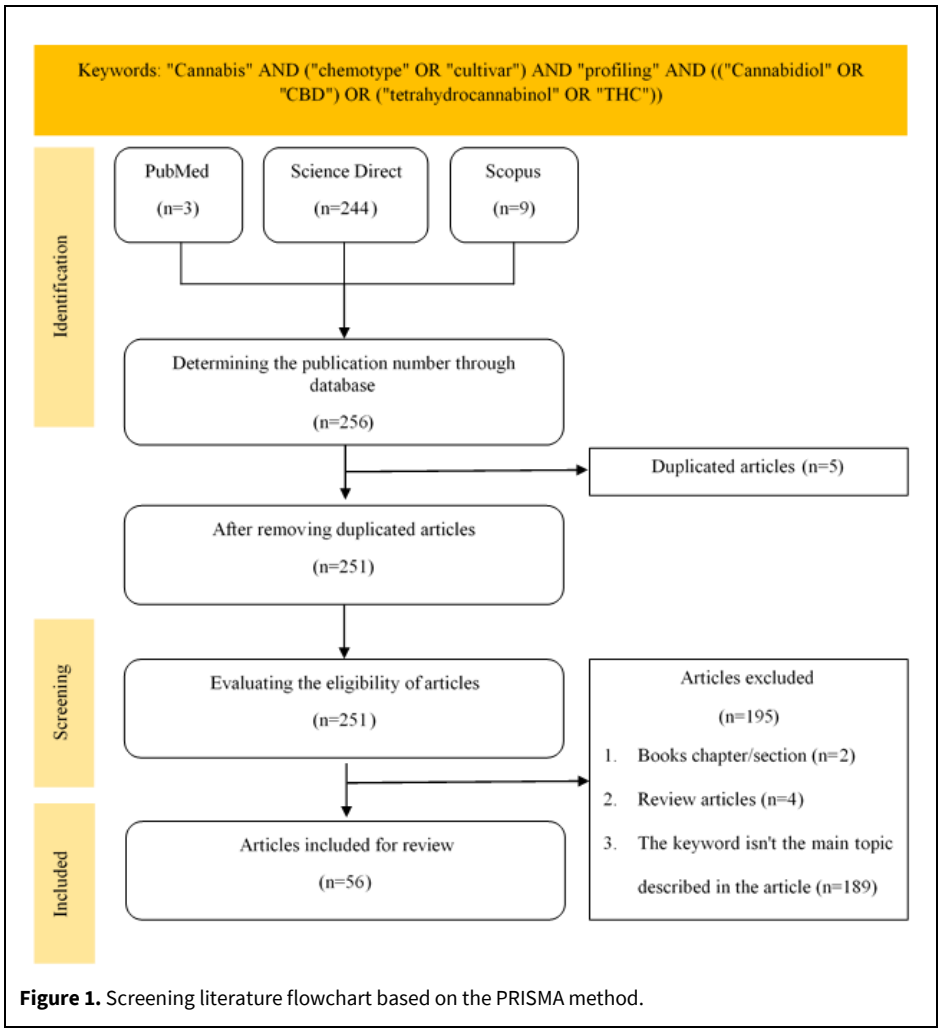

Figure 1. Screening literature flowchart based on the PRISMA method.

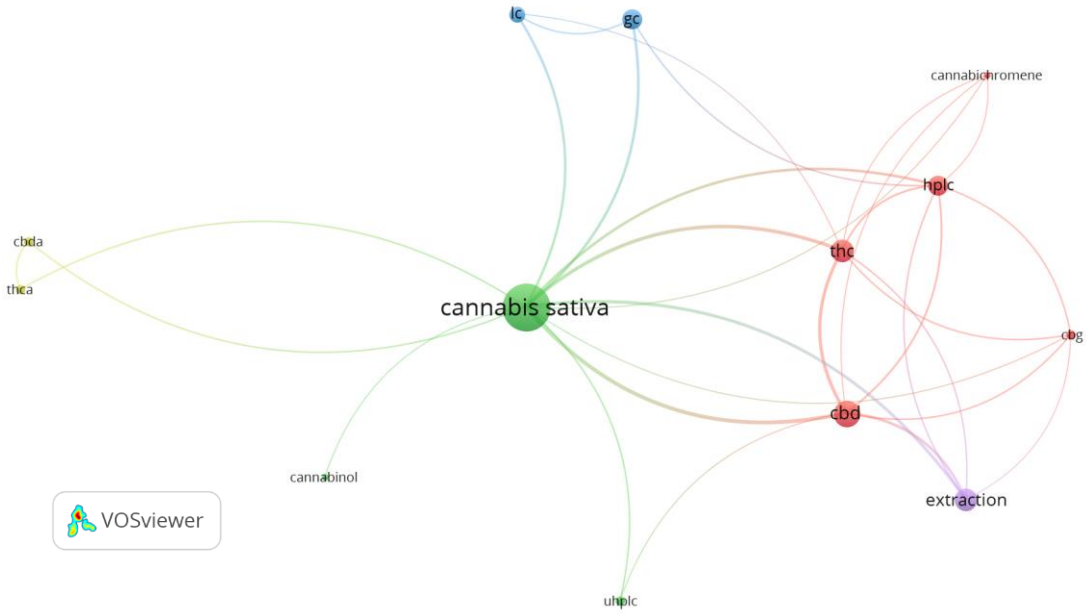

Figure 2. Co-occurrence analysis of the most frequent keywords.
Data was collected from PubMed, ScienceDirect, and Scopus, and the bibliometric web was generated using VOSviewer software.

Study characteristics

A total of 56 articles were reviewed, encompassing diverse *C. sativa* cultivars, cultivation settings, and environmental variables. These studies investigated experimental and real-world cultivation sites across regions with plants exposed to natural environmental conditions, including temperature variations between day (25-30°C) and night (15-22°C). The humidity levels ranged from 58-88%, reflecting varying climatic conditions. The altitudes of the cultivation sites varied significantly from lowland areas to highland regions.

Risk of bias in studies

Although a significant number of studies have explored the environmental and cultivar factors influencing cannabinoid production, there are gaps in reporting and variability across studies. For instance, many studies lacked information on specific environmental factors, such as precise humidity, elevation, or light cycles, which introduces uncertainty when comparing the results across studies. Potential biases may arise from inconsistencies in experimental conditions, such as geographic location, cultivation methods, or measurement techniques.

Results of individual studies

Bibliometric analysis

Network visualization analyzed co-citation links between journals, highlighting relationships and research trends. In visualization, closer lines represent stronger co-citation links, indicating greater relatedness between journals (Eck and Waltman, 2009; 2016). Larger nodes denote more frequently occurring keywords within the bibliographic network (Tsilika, 2023). As illustrated in Fig. 2, 13 items were categorized into five distinct clusters. The most significant clusters featured keywords such as *Cannabis sativa* (cluster 2) and CBD (cluster 1), reflecting the central focus of research in cannabinoid studies. Notably, no other species were identified during this analysis, reinforcing the dominance of *C. sativa* in the reviewed literature.

Internal factors

Cannabinoid pathway

In the cannabinoid pathway, as shown in Fig. 3, hexanoate is converted into hexanoyl Co-A through a reaction with acyl-activating enzyme 1 (AAE1). AAE1 forms hexanoyl Co-A at an optimum pH 9 and temperature 40°C. Additionally, this enzyme exhibits its highest activity with the assistance of Mg^{2+} ions as the cofactor. As a result of this conversion, hexanoyl CoA can be found in the highest concentration in the female flower (Stout et al., 2012). Hexanoyl CoA turns into 3,5,7-trioxododecanoyl-CoA, catalyzed by tetraketide synthase. Then, 3,5,7-trioxododecanoyl-CoA and olivetolic acid cyclase (OAC) synthase work together to produce olivetolic acid, which is essential for cannabinoid synthesis (Gagne et al., 2012). Olivetolic acid combines with geranyl pyrophosphate, synthesized by a geranyl pyrophosphate (GPP) syn-

thase complex, via aromatic prenyltransferase (PT) to form cannabigerolic acid (CBGA). In addition, the enzyme exhibits the most significant activity at 30°C and pH 7 (in Tris-HCl buffer). Furthermore, the enzyme reaction depends on magnesium ions (Mg^{2+}). This implies that Mg^{2+} is required as a cofactor or as part of the reaction condition for optimal enzyme activity (Fellermeier and Zenk, 1998). Tetrahydrocannabinolic acid synthase (THCAS) and cannabidiolic acid synthase (CBDAS) then catalyze CBGA into delta-9-tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), the major cannabinoids in *Cannabis* (Sirikantaramas et al., 2005; Taura et al., 2007). Factors such as heat or high temperature can lead to the decarboxylation of THCA (tetrahydrocannabinolic acid) and CBDA (cannabidiolic acid) into THC (tetrahydrocannabinol) and CBD (cannabidiol), respectively (Clarke and Merlin, 2013).

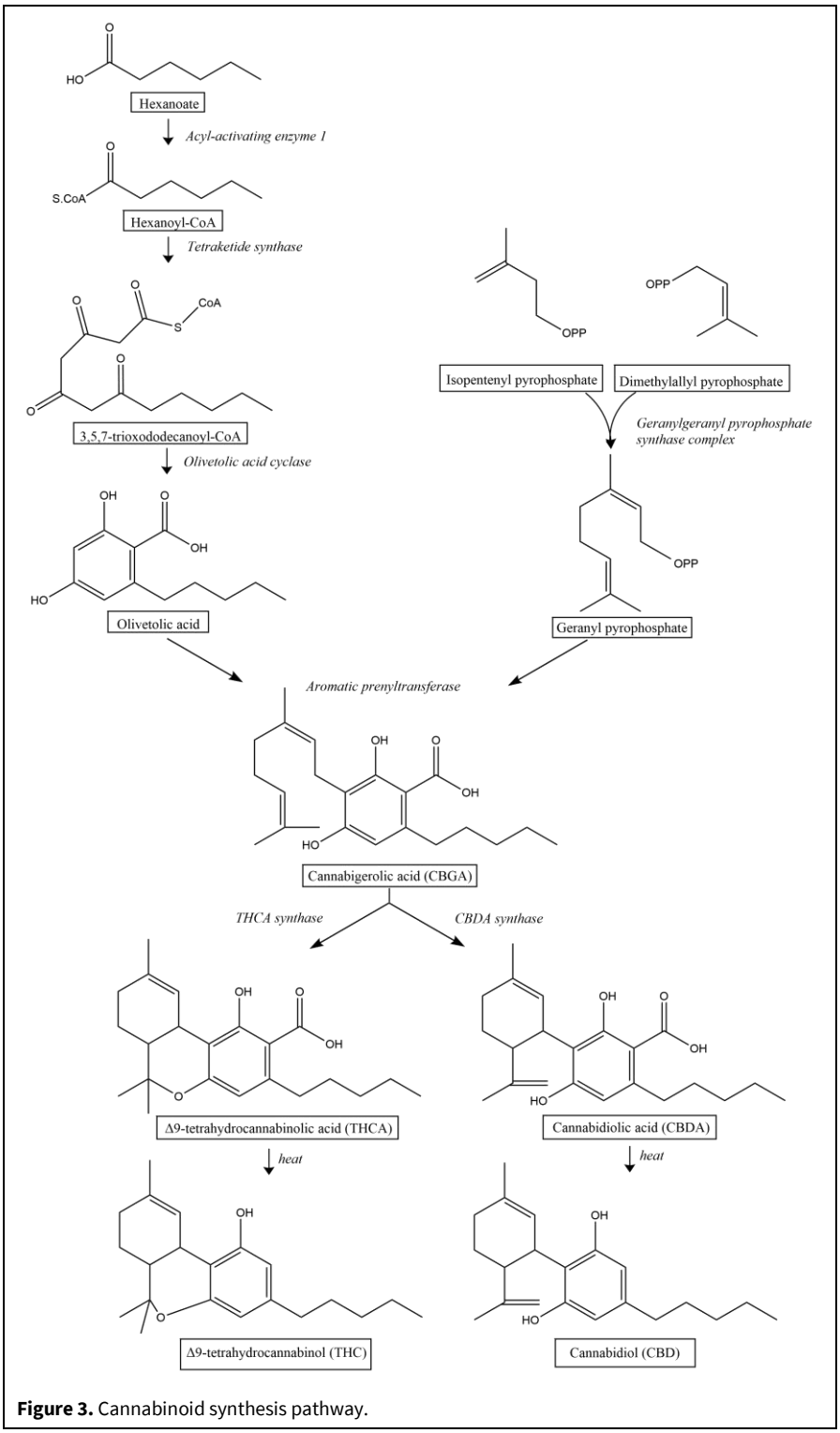

Figure 3. Cannabinoid synthesis pathway.

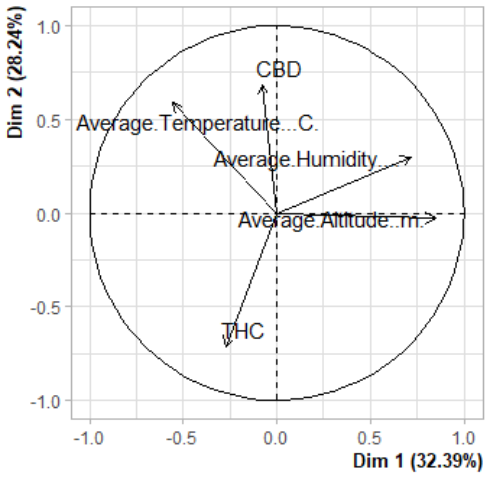

Figure 4. Principal component analysis (PCA) of external factors influencing cannabinoid production.

The PCA biplot illustrates the relationships among various variables, including THC, CBD, average temperature (°C), average humidity (%), and average altitude (m). The first two principal components (Dim 1 and Dim 2) account for 32.39% and 28.24% of the total variance, respectively. Vectors indicate the direction and strength of the correlation between each variable and the principal components.

Cultivar

Different cultivars of C. *sativa* have been developed and selected over time because of their unique chemical compositions, with some explicitly bred for higher CBD content and lower THC levels (Grassi and McPartland, 2017; Hazekamp and Fischedick, 2012). Cultivars of *C. sativa*, specifically Finola, Ferimon, Helena, Monoica, Tiborszallasi and Carmagnola, consistently demonstrate a higher CBD/THC ratio (Chasiotis et al., 2022; Drinić et al., 2021; Glivar et al., 2020; Gunjević et al., 2021; Marzorati et al., 2020; Palmieri et al., 2023). Another genetic factor influencing cannabinoid production is the sexual expression of the *C. sativa* flower. Female flowers tended to have more cannabinoids than male flowers. This is because flowers are more specialized in producing secondary metabolites. In contrast, male flowers have transcriptomes that are more specialized for pollen formation (Busta et al., 2022). Meanwhile, a study by Tipparat et al. (2012) showed that male plants reach inflorescence at an earlier stage of their development and tend to have higher THC and CBD contents than female plants. Cannabinoid content is also influenced by the growth stage of plants (older plants in the vegetative stage tend to show higher cannabinoid content) (Tipparat et al., 2012).

External factors

Principal component analysis (PCA) emphasizes the crucial role of environmental factors such as temperature, humidity, and altitude in influencing cannabinoid production, as shown in Fig. 4. The eigenvalues represent the variance captured by each principal component, with higher eigenvalues signifying greater contributions to the overall variance. Component 1 has the highest eigenvalue (1.619) and accounts for approximately 32.39% of the total variance, followed by component 2, which has an eigenvalue of 1.412, explaining about 28.24%. The PCA biplot illustrates correlations between the environmental variables and cannabinoid profiles, providing valuable insights into the complex interactions affecting CBD and THC synthesis.

Humidity

The humidity levels in the dataset varied from 40% to 88%, with optimal CBD production occurring under moderate to high humidity (65-78%). PCA results reveal a positive correlation between increased humidity (quadrant I) and CBD production. However, the impact of moisture on THC production remains uncertain, suggesting interactions with other environmental variables. This complexity underscores the importance of effective humidity management, including ventilation, air circulation, and dehumidification, to sustain optimal growth conditions.

Temperature

The dataset shows that daytime temperatures ranged from 21 to 32°C, while nighttime temperatures varied between 15 and 25°C across *Cannabis* cultivation sites. Most cultivars thrived in moderate temperature ranges of 24 to 26°C during the day and 15 to 16°C at night, suggesting these conditions are optimal for growth. The PCA results (quadrant II) further highlight the link between moderate temperatures and increased CBD production. However, the relationship between temperature and THC production remains unclear and is likely influenced by cultivar-specific interactions.

Altitude

The dataset revealed that altitude varied significantly, ranging from 2 m to 2652 m above sea level. Most cultivars were grown at mid-altitudes (77 m–1126 m), where environmental conditions seem to

support balanced cannabinoid production. Notably, the highest altitude (2652 m) exhibited a unique profile characterized by higher CBD:THC ratios, suggesting an adaptive response to extreme environmental factors. While the PCA results (quadrant IV) indicate that altitude has a minimal impact on cannabinoid production, its association with variables such as UV radiation highlights its broader significance in shaping cannabinoid profiles.

UV radiation

Although UV radiation was not explicitly analyzed in the PCA, its association with higher altitudes (quadrant IV) suggests that it may promote THC synthesis, as increased UV exposure often stimulates the production of secondary metabolites.

Photoperiod

The photoperiod was not directly represented in the PCA results but remained a critical factor influencing growth and cannabinoid production. Its variability likely interacts with other environmental parameters, contributing to the observed differences in cannabinoid profiles.

Outdoor vs. indoor cultivation

Outdoor cultivation was predominant, particularly for CBD-dominant cultivars, such as Carmagnola and Ferimon, associated with higher humidity and mid-altitudes. Indoor cultivation provided controlled environments favoring THC-dominant cultivars, such as Tachllta Till and Theresa, thriving at 22-25°C and lower humidity levels (40-57%). Although outdoor and indoor cultivation methods were not directly represented in the PCA, field-grown cultivars such as Pilar, Aida, and Juani exhibited slightly higher CBD and THC levels than greenhouse-grown samples. However, exceptions such as Theresa showed enhanced cannabinoid levels under greenhouse conditions. These findings suggest that environmental factors, including UV radiation, light intensity, and temperature variability, influence outdoor cultivation, whereas greenhouse conditions optimize specific variables for individual cultivars (Delgado-Povedano et al., 2020).

Synthesis results

Based on the data in Table 1, the regression analysis revealed that environmental factors impact THC and CBD levels. For CBD, temperature (DIM 1) had a weak positive effect, explaining 4.46% of the variance (R^2 0.0446) with a slight positive slope (0.0162). This indicates that an increase in temperature results in a slight rise in CBD levels. Humidity (DIM 2) had an almost negligible effect on CBD, explaining only 0.22% of the variance (R^2 0.0022) with a slight positive slope (0.0195). Altitude (DIM 3) shows a very weak negative impact on CBD, explaining 0.06% of the variance (R^2 0.0006) with a slightly negative slope (-0.3492), indicating that higher altitudes slightly decrease CBD levels. For THC, temperature (DIM 1) also had a weak negative effect, explaining 2.63% of the variance (R^2 0.0263) with a slightly negative slope (-0.0106), suggesting that higher temperatures slightly decrease THC levels. Humidity (DIM 2) had a weak negative relationship with THC, explaining 4.76% of the variance (R^2 0.0476) with a negative slope (-0.0763), indicating that higher humidity slightly decreased THC levels. Altitude (DIM 3) has a more significant negative impact on THC, explaining 2.05% of the variance (R^2 0.0205) with a more significant negative slope (-1.6624), suggesting that higher altitudes significantly decrease THC levels.

Table 1. Results of regression analysis of environmental factors toward cannabinoids.

Metric	Value toward THC	Value toward CBD
R-square DIM 1	0.0263	0.0446
R-square DIM 2	0.0476	0.0022
R-square DIM 3	0.0205	0.0006
Slope DIM 1	-0.0106	0.0162
Slope DIM 2	-0.0763	0.0195
Slope DIM 3	-1.6624	-0.3492

Reporting biases

Numerous studies have revealed inconsistent documentation of environmental variables, particularly photoperiod and humidity. These biases highlight the necessity for standardized reporting protocols in *Cannabis* research.

Certainty of evidence

The evidence was particularly strong for temperature and humidity as key factors influencing CBD production. However, due to limited data, the certainty of altitude and other variables, such as photoperiod, was moderate.

DISCUSSION

General interpretation of results in the context of other evidence

Cultivar

Recent findings suggest that the chemical composition of *C. sativa* may not be significantly influenced by the cultivar type. The study conducted by Welling et al. (2016) revealed that the chemical composition of

C. sativa is unaffected by the cultivar type. Research has demonstrated varying chemotypes among different cultivars, such as Kompolti (Chemotypes I, II, and III), Futura 77 (Chemotypes II and III), Fedrina 74 (Chemotypes II and III), and Pan 3 (Chemotypes I, II, and III) (Welling et al., 2016). However, the present study did not clarify the factors contributing to these chemotype variations.

External factors

Humidity

Cannabis requires high humidity (approximately 75%) during the juvenile stage (germination or rooting). The humidity should be reduced to 55-60% during the vegetative and flowering stages. Adjusting humidity and watering practices based on growth stage, plant size, container size, temperature, and other factors ensures optimal plant health and development (Asiimwe et al., 2022; Chandra et al., 2013; 2017; Punja et al., 2023).

Temperature

The effect of temperature on the CBD: THC ratio varied depending on the specific cultivar. Tachllta Till and Argvana Heart cultivars exhibit a decrease in their CBD: THC ratios as the temperature increases (McGarvey et al., 2020). In contrast, the PP cultivar showed a slight decrease in the CBD: THC ratio when compared to 25°C and 26°C. However, HMK maintained the same ratio at both temperatures (Tipparat et al., 2012). These phenomena are related to the decarboxylation of THCA and CBDA into THC and CBD, indicating the relationship between environmental conditions and cannabinoid expression in *Cannabis* plants. As temperature rises, various physiological processes within the plant, including cannabinoid synthesis pathways, may be affected. Higher temperatures may trigger alterations in enzymatic activity or gene expression related to cannabinoid production, leading to a shift in the balance between CBD and THC accumulation (Tahir et al., 2021). However, no studies have compared the most stable or optimal temperature for THCA and CBDA enzyme activity.

Altitude

Several studies have shown that altitude may play a crucial role in influencing the cannabinoid composition of *C. sativa*. For instance, samples grown in the Western Himalayan regions at an altitude of 2652 m exhibit higher concentrations of cannabinoids than those cultivated in tropical areas (Rashid et al., 2021). Another study conducted by Tipparat et al. (2012) also compared the cannabinoid content of *Cannabis* plants cultivated at two distinct locations: Queen Sirikit Botanic Garden (QSBG) in Chiang Mai City and Ban Rom Klao Arboretum (BRKA) in Pitsalunok, both situated in Northern Thailand. In this study, *Cannabis* plants cultivated at QSBG, with higher elevation and cooler temperatures, exhibited higher THC and CBD contents than those grown at BRKA (Tipparat et al., 2012). A recent study examined female and male flowers from similar geographical origins in Nebraska, suggesting similar cannabinoid profiles. Plants with similar geographical origins tend to produce identical cannabinoid profiles (Busta et al., 2022). This proved that cannabinoid production could be attributed to variations in geographical factors such as altitude and temperature.

UV radiation

Regarding altitude, the results could be associated with ultraviolet (UV) radiation. At higher altitudes, the concentrations of ozone, aerosols, air molecules, and atmospheric clouds tend to decrease. This leads to higher levels of UV radiation (Dvorkin and Steinberger, 1999). UV exposure plays a significant role in stimulating cannabinoid production in the *Cannabis* trichomes (Brousseau et al., 2021). Evidence of the role of UV exposure in cannabinoid production was assessed by Lydon (1987). An increase in the UV-B dose affected the Δ^9-THC level in the leaf and floral tissues of greenhouse-grown drug-type *C. sativa*, but it did not affect the fiber type of *C. sativa* (Lydon et al., 1987). This finding suggests that cannabinoid production can be attributed to UV exposure and its genetic role. Another evidence of UV exposure and genetic relation shows that treatments with higher UV exposure in the breaking wave (BW) cultivar increased the content of Δ^9-THC. However, it decreased Δ^9-THC and CBD in low tide (LT) cultivars. The increase in Δ^9-THC was likely due to an adaptive response mechanism to UV stress. Additionally, UV radiation suppressed the morphology and physiology of *Cannabis* in both BW and LT cultivars, which is correlated with increased UV exposure (Rodriguez-Morrison et al., 2021).

Photoperiod

Understanding the photoperiod requirements of *C. sativa* is essential for optimizing its growth and cannabinoid production. This species requires long-day photoperiods (16.0-18.0 hours per day) to promote vegetative growth. When it is in the transitions of the flowering stage, it requires approximately 12 h of light exposure and 12 h of dark period (Chandra et al., 2015; Dang et al., 2021; Moher et al., 2021). However, Peterswald et al. (2023) reported that the photoperiod elicits varied responses to cannabinoid pro-

duction among different *Cannabis* strains. In other words, not all strains yield optimal results when exposed to light for 12 hours (12/12-hour photoperiod) (Peterswald et al., 2023). In terms of light intensity, in a study examining the chemical composition of *C. sativa* under varying lighting conditions, samples grown under LED tubes with a combined power of 320 watts (R5) exhibited higher cannabinoid concentrations than those cultivated under Metal-Halide 400 watts lighting (R1) (McGarvey et al., 2020). This finding suggests that external factors, such as photoperiod, light source, and intensity, could significantly affect cannabinoid production in *C. sativa*, consistent with previous research conducted in different environmental settings.

Outdoor vs. indoor cultivation

Further evidence supporting the influence of external factors on cannabinoid composition is provided by Delgado-Povedano's study (2020), which compared the cannabinoid levels of cultivars (Pilar, Theresa, Aida, and Juani) grown in both greenhouse and field conditions. Pilar, Aida, and Juani exhibited slightly higher CBD and THC levels when cultivated in the field, whereas Theresa exhibited higher CBD and THC levels when grown in a greenhouse. These results may be due to the influence of different cultivar types (Delgado-Povedano et al., 2020). This finding suggests that environmental factors, such as UV radiation, light source, and light intensity, can significantly impact cannabinoid production in C. *sativa*, consistent with previous research conducted in different environmental settings.

Limitations of the evidence

This review provides valuable insights into the factors that influence cannabinoid production. However, this study had several limitations that warrant consideration. Variability in reporting across studies, particularly for environmental variables such as humidity, elevation, and light cycles, led to gaps in the dataset. These inconsistencies may have influenced the depth of analysis but were addressed through robust methodologies, including PCA and regression modeling, which effectively identified significant trends despite data variability. Differences in experimental conditions, including cultivation methods, geographic settings, and measurement techniques, further contributed to the variability in the findings. These issues underscore the need for standardized protocols in future studies to improve data comparability and ensure reliable conclusions.

Limitations of the review process

The review process was methodologically rigorous, but certain constraints were unavoidable. The inclusion criteria prioritized studies with complete datasets and experimental designs, and potentially relevant studies with partial data were excluded. This selective approach ensured data quality but may have introduced a degree of selection bias. The analysis focused on specific environmental variables, such as temperature, humidity, and altitude, to maintain clarity and precision. While this narrow scope may not capture all factors influencing cannabinoid production, it allows for targeted and meaningful insights into key determinants. PCA has been used to visualize trends and relationships among variables, but its linear nature may not fully capture complex nonlinear interactions. The combination of PCA and regression modeling mitigated these limitations by enhancing the robustness of the findings.

Implications for practice, policy, and future research

The findings of this review have important implications for *Cannabis* cultivation, policymaking, and future research. Environmental factors such as temperature and humidity were identified as key determinants of cannabinoid production, offering actionable insights for optimizing cultivation practices. Policymakers can leverage these findings to establish guidelines to promote sustainable and efficient *Cannabis* production tailored to medical and commercial objectives. Future research should integrate genetic and environmental data to develop predictive models of cannabinoid synthesis. Standardizing methodologies for measuring and reporting ecological variables will improve the reliability and comparability of the findings across studies. Practical applications include optimizing environmental conditions to enhance cannabinoid yields, improving quality, and meeting the growing demands for medical *Cannabis*. This review highlights the current understanding of ecological influences on cannabinoid production and areas for further exploration, providing a foundation for advancing research and practice in *Cannabis* cultivation.

CONCLUSION

Understanding the environmental influences is essential for optimizing medical *Cannabis* cultivation practices. Bibliometric analysis highlights C. *sativa* as the predominant species in medical *Cannabis* research, with CBD emerging as the most frequently studied cannabinoid. Co-citation analysis revealed five major thematic clusters, emphasizing the critical role of environmental and genetic factors in cannabinoid production. PCA and regression analyses provided valuable insights into the complex relationships between

environmental variables and cannabinoid expression. Humidity and temperature were key factors that positively influenced CBD production. At the same time, altitude demonstrated a minimal direct impact on PCA, which remains relevant due to its indirect effects, such as increased UV exposure. These findings suggest that although cultivar differences have a limited effect on CBD production, environmental conditions play a pivotal role in shaping cannabinoid profiles. By integrating these insights, growers can optimize cultivation methods to maximize THC and CBD yields, focusing on controlling critical environmental variables. Simultaneously, bibliometric findings offer guidance for future research to address gaps in understanding the genetic-environmental interplay, further advancing the science of cannabinoid production. Taken together, these findings have significant implications for improving the quality, efficacy, and commercial viability of medical *Cannabis*.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Nabila CIB	Ramona Y	Wirasuta IMAG	Karsono J
Concepts or ideas	x	x	x	x
Design	x		x	x
Definition of intellectual content		x		x
Literature search	x		x	
Experimental studies		x		
Data acquisition	x		x	
Data analysis	x	x	x	
Statistical analysis	x			
Manuscript preparation	x		x	
Manuscript editing	x	x	x	x
Manuscript review	x	x	x	x

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