



BIBLIOMETRIC ANALYSIS OF POPPY ALKALOIDS AND MORPHINE BIOSYNTHESIS

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Abstract: This bibliometric analysis examines the scientific literature development in poppy alkaloids and morphine biosynthesis from 1980 to 2024. Using data from 845 Web of Science publications, we conducted comprehensive analyses including annual scientific production, international collaboration networks, keyword analysis, citation patterns, and thematic mapping. Our findings reveal steady growth in scientific output since the 1980s, peaking at 45 publications in 2016. The USA, Canada, UK, Germany, and Australia emerge as the most productive and influential countries in international collaboration networks. Citation analysis identifies Facchini (1996), Morishige (2000), Liscombe (2007), and Hagel (2010) as the field's most influential reference points. Thematic mapping identifies "opium poppy," "molecular-cloning," and "expression" as motor themes driving the field, while "biosynthesis," "alkaloids," and "morphine" constitute core themes. Word cloud analysis shows "Papaver somniferum" as the most frequently used term (frequency: 76), representing 8% of the total research focus according to treemap analysis. This study provides a comprehensive mapping of the scientific structure and developmental dynamics in poppy alkaloids and morphine biosynthesis research, offering valuable insights for identifying research gaps and predicting future directions in this interdisciplinary field.

Keywords: Poppy, Alkaloids, Bibliometric

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1. Introduction

Human activities, industrial development, urban sprawl, intensive agriculture and deforestation threaten the genetic diversity of plant species. This poses a major challenge to world agriculture and food security, as well as a critical loss of medicinal value (Çeliktaş et al., 2022). Plants have the potential to produce a large number of metabolites used in the treatment of various diseases and hence in the production of medicines, and many have been used as medicines since the beginning of life. Among these plants is *Papaver somniferum* L. (poppy), which produces phytochemicals with numerous pharmacological effects (Portakal and Tan, 2024). Poppy (*Papaver somniferum* L.) belongs to the order *Rhoadales*, family *Papaveraceae* and genus *Papaver*. Türkiye is considered very rich in *Papaver* species. "Flora of Türkiye" states that there are a total of 39 *Papaver* species, 19 annual and 20 perennial. Of these, 10 species, 2 subspecies and 4 varieties are endemic to Türkiye (Davis et al., 1988; Kapoor, 1997). Poppy, which is among the cultivated and medicinal plants, is of great importance in our country in terms of the alkaloids it contains. The benzyloisoquinoline alkaloids (BIA) produced by the poppy plant are the most important medicinal properties of this plant. Herbal medicines are obtained from the roots, stems, bark, leaves, flowers,

seeds or the whole plant (Ameri et al., 2015). Opium is obtained as a result of solidification of the liquid leaked by scratching the ripe capsule of the poppy plant (Özgen et al., 2017). The latex obtained is thoroughly dried and opium powder is prepared. Opium contains up to 25% alkaloids by weight (Masihuddin et al., 2018). Poppy plant contains various groups of alkaloids such as tebain, codeine, noscapine, papaverine and morphine which are important for the medical sector. Apart from these, capsules containing more than 30 different alkaloids are used in the production of raw materials of semi-synthetic drugs with high material value (Şahin, 2023). It also exhibits analgesic, antidiarrheal, narcotic and antitussive properties. The German researcher Sertürner's isolation of morphine from opium in 1804 was revolutionary and the scientific study of opium alkaloids increased over the years, but interest in opium has continued to the present day. It is monographed in numerous pharmacopoeias. Since Sertürner, more than 40 alkaloids have been extracted from opium. Scientific studies have proven that the activity of opium is due to its alkaloids. Five main alkaloids, namely morphine, codeine, tebain, noscapine and papaverine, are most widely used (Baser and Arslan, 2014).

Numerical analysis and statistical analysis of scientific studies can be defined as Bibliometrics. Bibliometric methods apply a quantitative approach to the



identification, evaluation and interpretation of previously published research. Bibliometric analysis is one of the analysis methods used by researchers to interpret and evaluate research areas, countries, citation rates of publications or journal numbers. In bibliometric methods, researchers first explore the literature and show the researcher's work by revealing the most influential studies (Freire and Nicol, 2019; Donthu et al., 2021). At the same time, this analysis is to evaluate the historical development, current status and future trends of a particular research area with mathematical and statistical methods, as well as to obtain the findings of the researchers and the collective bibliographic data produced by other researchers working in this field and to express the results through citation or writing (Yavuz, 2023). In addition, it determines the amount of academic publications in a specific time period and also reveals the extent to which a study influences subsequent research. The goal of bibliometric methods is to obtain the findings of researchers and bibliographic data produced by other scientists operating in this field and to present the findings through reference or text. In addition to this, bibliometric methodology is attracting increasing attention in the scientific field and has come to the forefront as a field of study shaped by the rapid advancement of computer technology and internet usage. Bibliometric methodology is a fundamental method for evaluating scientific studies and is based on general librarianship and information science (Persson et al., 2009; Merigó and Yang, 2017; Derviş, 2019; Han et al., 2020). Bibliometrics is the quantitative study of certain characteristics of publications such as author, subject, publication information, and cited sources. In bibliometric analysis, quantitative and statistical approaches are used to characterize publication trends in a particular field or literature (Abdi et al., 2018). All statistical evaluations were performed using R software with the "bibliometrix" package (R Core Team, 2020). In a study, a total of 1643 documents containing the search query "Papaver somniferum" in the title, abstract and/or keywords for the period 1910-2022 were accessed from the Scopus database. Although the first document was published in 1910, the number of articles did not exceed 10 publications per year until 1970. Until the 1990s, the number of publications remained relatively stable at around 10-20 articles per year (Diaz-Bárcena and Giraldo, 2023). The data were bibliographically generated from the WoS system in plain text format. The aim of this study is to analyze the scientific publications in the field of poppy alkaloids and morphine biosynthesis indexed in the Web of Science database between 1980 and 2024 using bibliometric analysis methods. Our research aims to identify the temporal evolution of scientific production in the field, international collaboration networks, conceptual structure, as well as the most important publications of the selected time period. This analysis will contribute to assessing the current state of the field, identifying research gaps and

predicting future research directions. It will also provide researchers working in the field of poppy alkaloids and morphine biosynthesis with a holistic perspective on the scientific structure and developmental processes of the field.

2. Materials and Methods

This study was conducted to determine the bibliometric analysis of scientific publications in the field of poppy alkaloids and morphine biosynthesis indexed in the Web of Science database. Within the scope of the study, articles published between 1980 and 2024 were analyzed. The keywords "poppy alkaloids", "morphine biosynthesis", "benzylisoquinoline alkaloids", "Papaver somniferum", "opium poppy", "codeine biosynthesis", "thebaine biosynthesis" and "noscapine biosynthesis" were used in the data collection process. These keywords were selected from the terms frequently used in the publications of leading researchers in the field in order to comprehensively search for studies in the field of poppy alkaloids and morphine biosynthesis. As a result of the search, a total of 845 scientific publications were identified and these publications constituted the data set for bibliometric analysis. VOSviewer (version 1.6.18) and Bibliometrix R-package (version 3.1.4) software were used for bibliometric analysis. VOSviewer is a particularly useful tool for visualizing and mapping bibliometric networks (van Eck and Waltman, 2010). The Bibliometrix R-package is an open source software designed for comprehensive bibliometric analysis (Aria and Cuccurullo, 2017). In the data analysis process, raw data were first cleaned and standardized. Then, by applying the bibliometric analysis methods mentioned above, the scientific structure and development of the field of poppy alkaloids and morphine biosynthesis were comprehensively mapped. The main bibliometric indicators used in the analysis are: number of publications, number of citations, h-index, co-authorship links, keywords and citation networks. These indicators were used to assess the productivity, impact, collaboration and conceptual structure of the field.

3. Results

3.1. Annual Scientific Production (1980-2024)

When the temporal development of scientific production in the field of poppy alkaloids and morphine biosynthesis is analyzed, a clear upward trend is observed between 1980 and 2024. Scientific studies, which started with an average of 2-3 articles per year in the early 1980s, reached 5-6 articles in the mid-1990s. With the first significant increase in 1995, the annual number of articles increased to 13 articles, but fluctuations were observed in the following years. In the early 2000s, annual production was around 8-10 articles, with a gradual increase to 13-14 articles between 2002 and 2006. After reaching 20 articles in 2006, there was a decline between 2008 and 2010. After 2010, a rapid

increase in scientific production was observed, reaching the highest levels in the field with 25 articles in 2012, 32 articles in 2014 and 45 articles in 2016. Between 2016 and 2022, annual scientific production fluctuated between 27-40 articles, reaching a second peak of 40

articles in 2022. After declining to 27 articles in 2023, scientific production dropped sharply to 7 articles in 2024. This last decline can be explained by the fact that the data collection process was not yet complete (Figure 1).

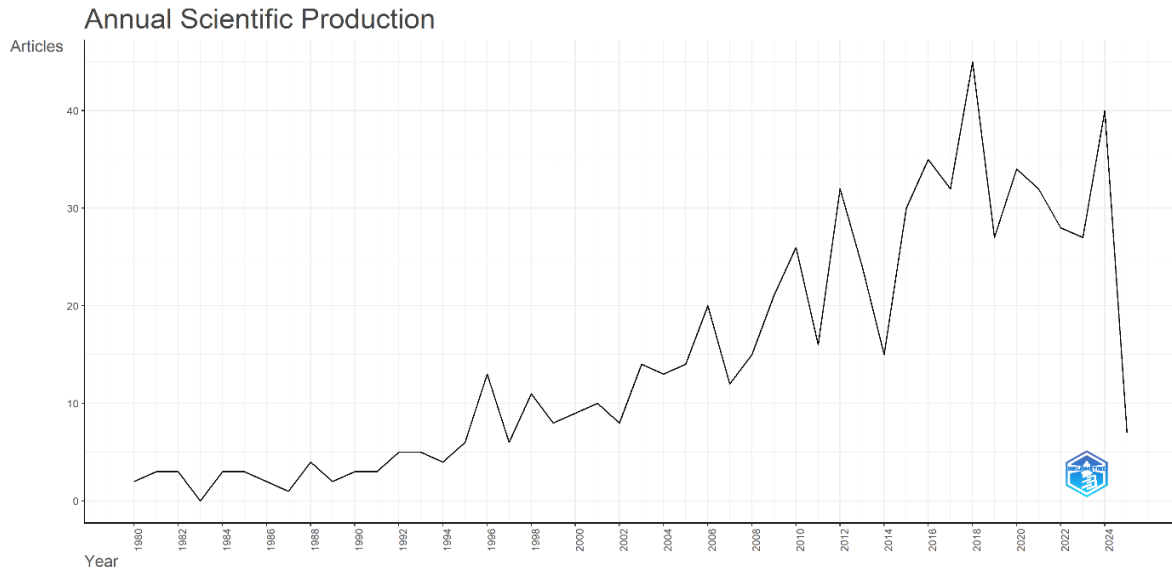


Figure 1. Annual scientific production (1980-2024).

3.2. Country Collaboration Map

The international collaboration network analysis revealed the existence of a significant international research network in the field of poppy alkaloids and morphine biosynthesis (Figure 2). The geographical collaboration map shows that there are dense connections between North America, Europe, Asia and Australia. The United States of America (USA) and Canada stand out as the countries with the highest intensity of scientific production and collaboration in the field. The United States has particularly strong collaborative links with Europe (United Kingdom, Germany, France), Asia (China, India, Japan) and Australia. The thickness of the connection lines on the

map reflects the intensity of cooperation, and it was observed that the connections between the US-Australia, the US-United Kingdom and the US-China represent the most intense cooperation networks. The intensity of countries' scientific production is shown in shades of color on the map, with darker shades of blue representing higher scientific production. Accordingly, the United States, Canada, the United Kingdom, Germany, China, India and Australia are the most productive countries in the field. Some countries in the Middle East and Asia (Iran, Türkiye, Japan, South Korea) show moderate scientific production, while Latin American and African countries show limited participation in the field.

Country Collaboration Map

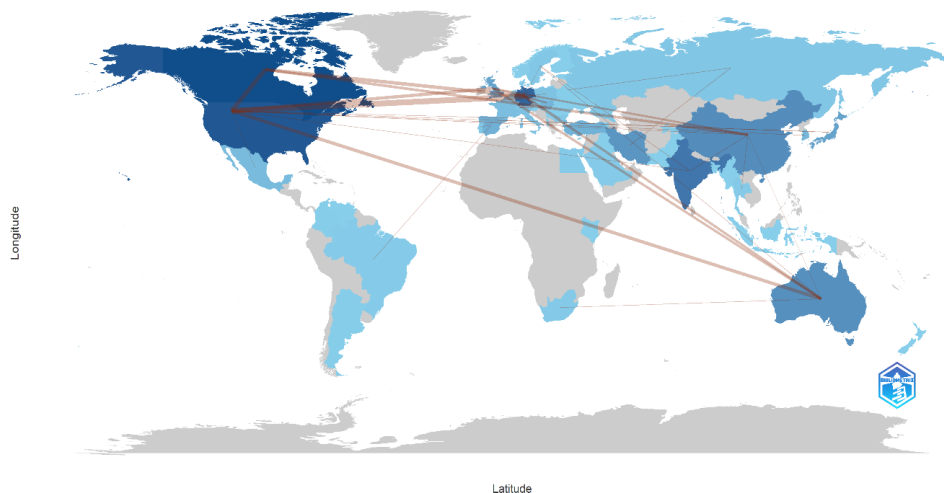


Figure 2. Country collaboration map.

3.3. The Keyword Network Analysis

The keyword network analysis (Figure 3) visualizes the main conceptual structure and research foci in the field of poppy alkaloids and morphine biosynthesis. The network map clearly shows the interrelationships and clustering trends of key terms in the field. The results of the analysis reveal the existence of five main conceptual clusters in the field. The centrally located terms “molecular-cloning” and “opium poppy” have the highest centrality values of the network and represent the main focal points of research in the field. The purple cluster formed around these two terms covers molecular biology and gene cloning studies. Within this cluster, the terms “enzyme”, “benzylisoquinoline alkaloid biosynthesis”, “norcoclaurine synthase”, “codeinone reductase” and “protein” show high link density. This cluster represents research focused on the molecular characterization of enzymes involved in the biosynthesis of poppy alkaloids.

The second important cluster is the group around the term “biosynthesis”, shown in blue. Within this cluster, the terms “pathway”, “cells”, “cultures”, “poppy” and “plant” exhibit high link density. The third cluster, shown in orange, is the group centered around the term “alkaloids”. The terms “identification”, “growth” and “mass-spectrometry” stand out in this cluster. The fourth cluster, shown in green, is the group centered around the term “morphine”. Within this cluster, the terms “thebaine”, “liquid-chromatography” and “separation” show clear connections. The fifth cluster is a small group shown in red and includes the terms “codeine” and “urine”. When the links between the terms are analyzed, it is seen that the relationship between the terms “molecular-cloning” and “biosynthesis” constitutes the strongest link, followed by the link between “opium poppy” and “alkaloids” (Figure 3).

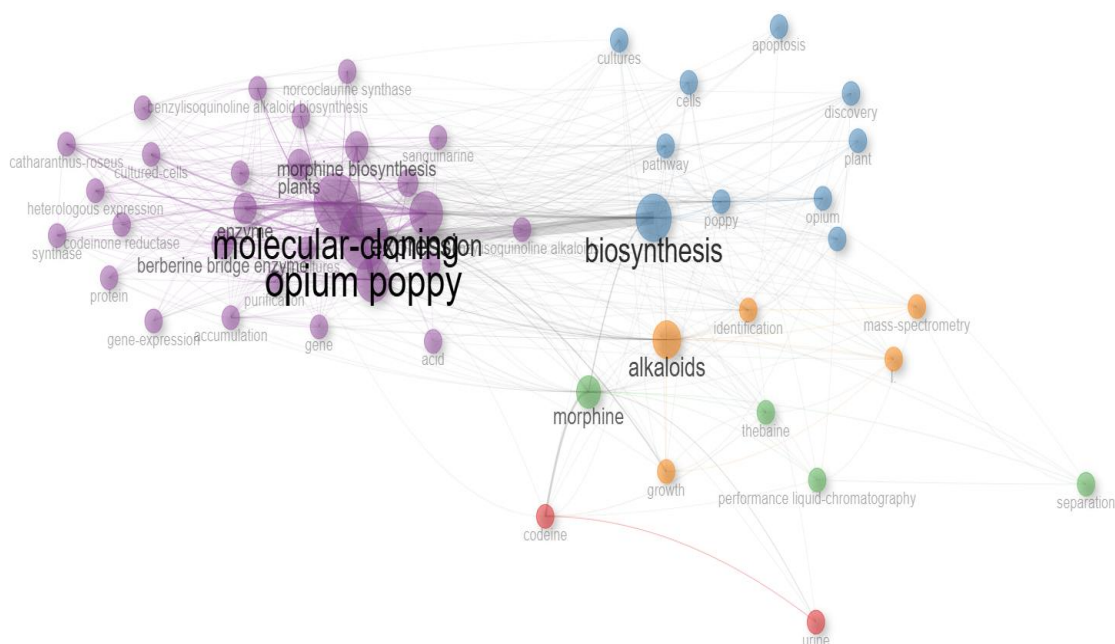


Figure 3. The keyword network analysis.

3.4. Citation Analysis And Author-Subject Relationship (1980-2024)

Citation analysis and author-subject relationship visualizes researchers and their fields of study in the field of poppy alkaloids and morphine biosynthesis. This analysis shows the source articles on the left, authors in the middle and research topics on the right. The thickness of the connecting lines represents the strength of the relationships. The results of the citation analysis reveal that the prominent researchers in the field are Facchini PJ, Hagel JM, Kutchan TM and Liscombe DK. Facchini PJ stands out as the researcher with the highest citation impact and is particularly notable for his work on “opium poppy”, “benzylisoquinoline alkaloids” and “biosynthesis”. Facchini’s papers published in 1996, 2001, 2003 and 2014 are among the most influential in the field. Hagel JM was ranked as the second researcher

and made significant contributions especially in the fields of “metabolic engineering”, “secondary metabolism” and “morphine”. Kutchan TM is the third ranked researcher and has conducted research on “biosynthesis” and “benzylisoquinoline alkaloids”. Liscombe DK’s article published in the Journal of Biological Chemistry in 2007 stands out as the most influential work in the field. This study deals with the molecular characterization of the enzyme “norcoclaurine synthase” and was carried out in collaboration with Facchini PJ. As can be seen in the diagram, the Liscombe-Facchini collaboration stands out in terms of the number of joint publications. Other important researchers include Sato F, Chen X and Shukla S. These researchers have made significant contributions on “alkaloids”, “opium” and “thebaine”, respectively. As can be seen in the diagram, Sato F’s work shows particularly strong links with “alkaloids” and

“papaveraceae”, Chen X's work with “opium” and “codeine”, and Shukla S's work with “thebaine” and “morphine”. When the research topics are analyzed, it is seen that the terms “benzylisoquinoline alkaloids” (number of links: 28), “opium poppy” (number of links:

25), “biosynthesis” (number of links: 24) and “morphine” (number of links: 22) have the highest link density. This indicates that research in the field is mainly focused on the biosynthesis of benzylisoquinoline alkaloids, poppy plant physiology and morphine metabolism (Figure 4).

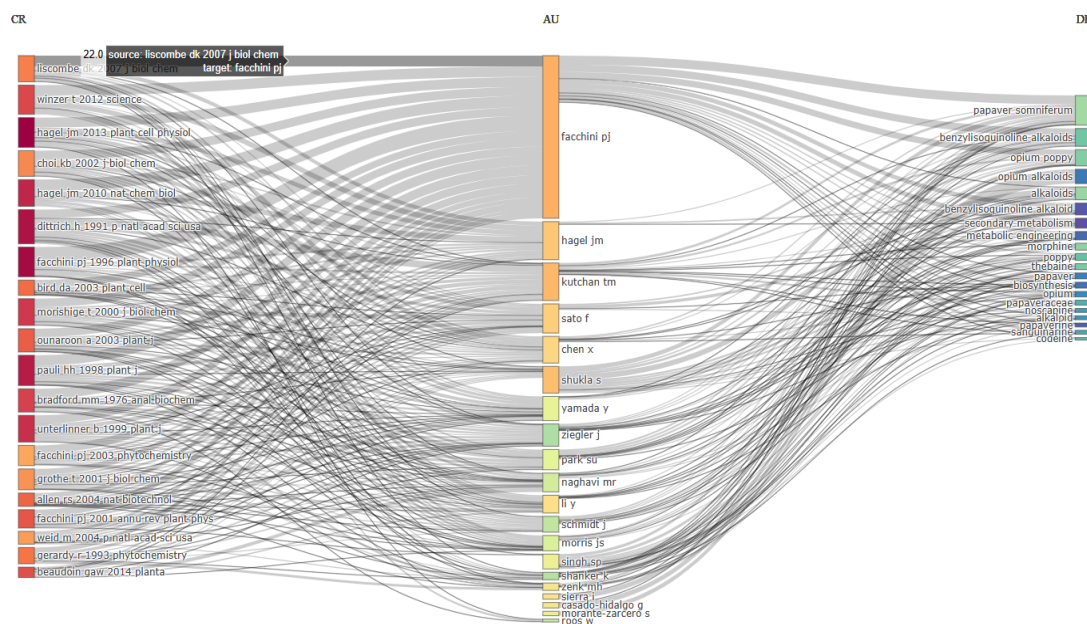


Figure 4. Citation analysis and author-subject relationship (1980-2024).

3.5. Word Cloud Analysis

The word cloud analysis in Figure 5 visualizes the most frequently used terms and key concepts in the field of poppy alkaloids and morphine biosynthesis. In the word cloud, the size of the words is proportional to the frequency of use and the color coding represents different thematic categories. In the word cloud analysis, the term “papaver somniferum” has the highest frequency of use and is the main focus of research in the field. The term “opium poppy” also exhibits high frequency of use. The term “Alkaloids” has the second highest frequency of use and refers to the general class of secondary metabolites found in the poppy plant. The term “Benzylisoquinoline alkaloids” also shows high frequency of use and represents the specific subclass of alkaloids to which poppy alkaloids such as morphine, codeine and tebain belong. The term “morphine” has the third highest frequency of use, representing the most

important pharmacological component of the poppy plant and the main target of research in the field. The terms “thebaine”, “codeine” and “noscapine” (frequency value: 420) also show high frequency of use and represent other important alkaloids of the poppy plant. The term “biosynthesis” had the fourth highest frequency of use. The terms “alkaloid biosynthesis” and “morphine biosynthesis” also show high frequency of use and represent research focusing on specific biosynthetic processes. The term “Papaveraceae” refers to the plant family to which the poppy plant belongs and represents taxonomic studies in the field. The terms “papaver” and “papaverine” also exhibit high frequency of use and represent other species and components of the poppy genus. The terms “secondary metabolism” and “secondary metabolites” also show significant frequency of use and represent research examining the role of alkaloids in plant metabolism.



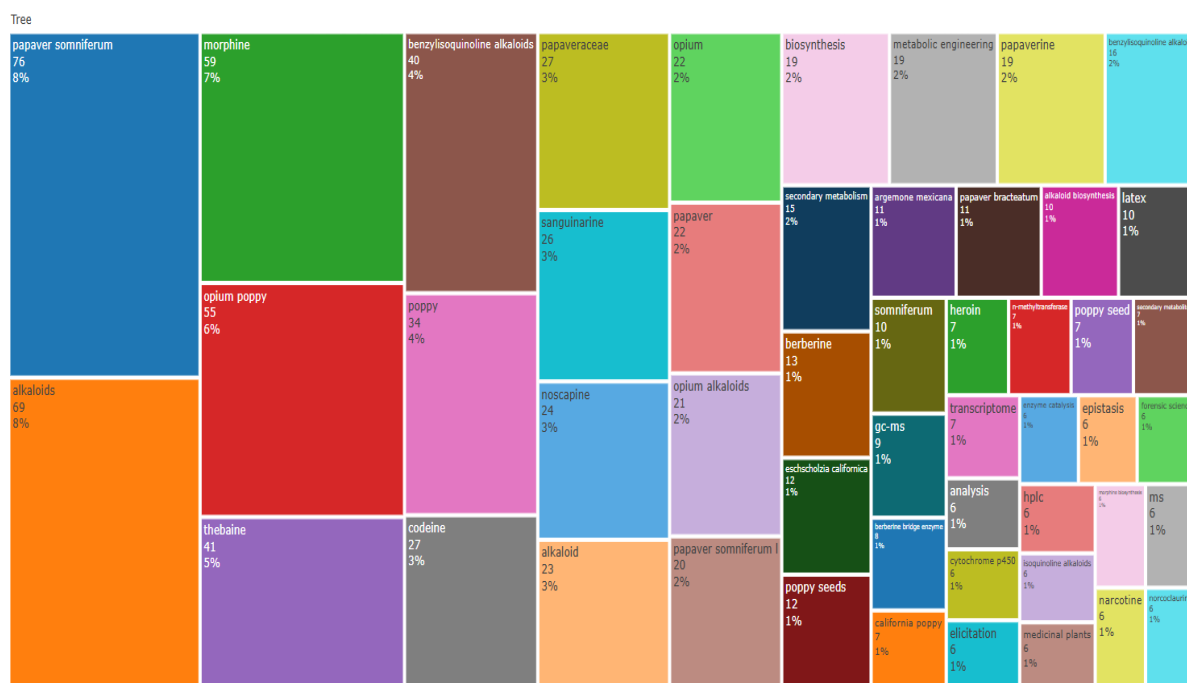


Figure 6. Treemap analysis.

3.7. The Conceptual Structure Map

The Conceptual Structure Map (Figure 7), created by Multidimensional Coherence Analysis (MCA), visualizes the distribution of key concepts in the field of poppy alkaloids and morphine biosynthesis in two-dimensional space and the relationships between them. This analysis reveals the conceptual structure and research clusters in the field. In the map, dots represent individual terms and colored areas represent conceptual clusters. The factorial map analysis shows that research in the field is divided into six main conceptual clusters. The first dimension (x-axis) explains 56.3% of the total variance and the second dimension (y-axis) explains 17.9%. Together, these two dimensions represent 74.2% of the conceptual structure in the field. The red cluster in the upper right of the map represents molecular biology and enzymology studies. This cluster includes terms such as “molecular-cloning”, “benzylisoquinoline alkaloid biosynthesis”, “synthase”, “enzyme”, “berberine bridge enzyme”, “heterologous expression”, “adenosyl-l-methionine” and “norcoclaurine synthase”. The blue cluster in the bottom right of the map represents plant physiology and biosynthesis studies.

This cluster includes terms such as “biosynthesis”, “benzylisoquinoline alkaloids”, “opium poppy”, “pathway”, “gene-expression”, “protein”, “cells”, “plants”, “sanguinarine”, “accumulation” and “cultures”. The pink cluster in the bottom left of the map represents the study of plant growth and development.

This cluster contains the terms “growth”, “plant” and “l.”. The light blue cluster in the centre left of the map contains the terms “alkaloids”, “identification”, “mass spectrometry”, “discovery” and “hashish”. The yellow cluster in the upper left region of the map contains the terms “morphine”, “thebaine”, “separation” and “performance liquid-chromatography”. The green cluster at the top of the map represents clinical and pharmacological studies. The terms “codeine” and “urine” are included in this cluster. The conceptual structure map reveals the multidimensional and interdisciplinary character of the field of poppy alkaloids and morphine biosynthesis and visualises the role and relationships of molecular biology, plant physiology, analytical chemistry and clinical research approaches in the field.

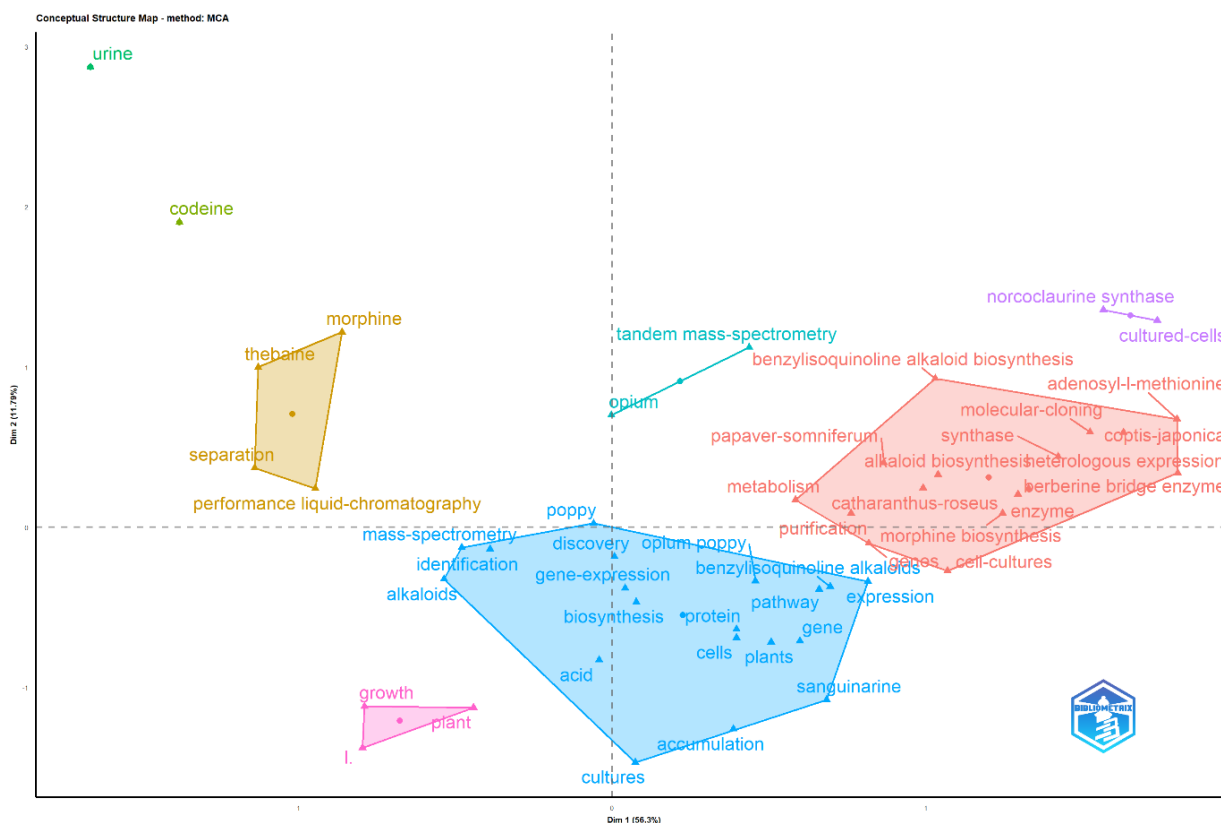


Figure 7. Multidimensional correspondence analysis (MCA).

3.8. The Thematic Map analysis

The Thematic Map analysis (Figure 8) visualises the distribution of research themes in the field of poppy alkaloids and morphine biosynthesis according to their centrality (x-axis) and density (y-axis). In the map, the circles represent the themes and the size of the circles represents the visibility of the themes in the literature. The thematic map shows that the research themes in the field are divided into four main categories: Core Themes (bottom right quadrant): These themes, which have high centrality and low density values, constitute the conceptual basis of the field. This category includes the themes of "biosynthesis", "alkaloids", "identification", "morphine", "thebaine" and "separation". These themes represent the main research areas for the biosynthesis, identification and characterisation of poppy alkaloids. In particular, the "biosynthesis" theme stands out as one of the most central themes in the field and covers studies aimed at elucidating alkaloid biosynthesis pathways. The themes "morphine" and "thebaine" represent research

focussing on specific alkaloids. Motor Themes (top right quadrant): With high centrality and high intensity values, these themes represent the driving forces driving the development of the field. This category includes the themes "opium poppy", "molecular-cloning" and "expression". Niche Themes (top left quadrant): This category includes the themes "codeine", "urine", "oxidative stress", "death", "resistance", "validation", "combining ability" and "f-2 generations". Emerging or Declining Themes (bottom left quadrant): These themes, which have low centrality and low intensity values, represent research areas that are still developing or losing their importance in the field. This category includes the themes "analogues", "biological evaluation", "apoptosis", "binding" and "in-vitro". The thematic map analysis reveals the strategic research structure of the field of poppy alkaloids and morphine biosynthesis and visualises the research dynamics and potential future development areas in the field through the identification of core, engine, niche and emerging/declining themes.

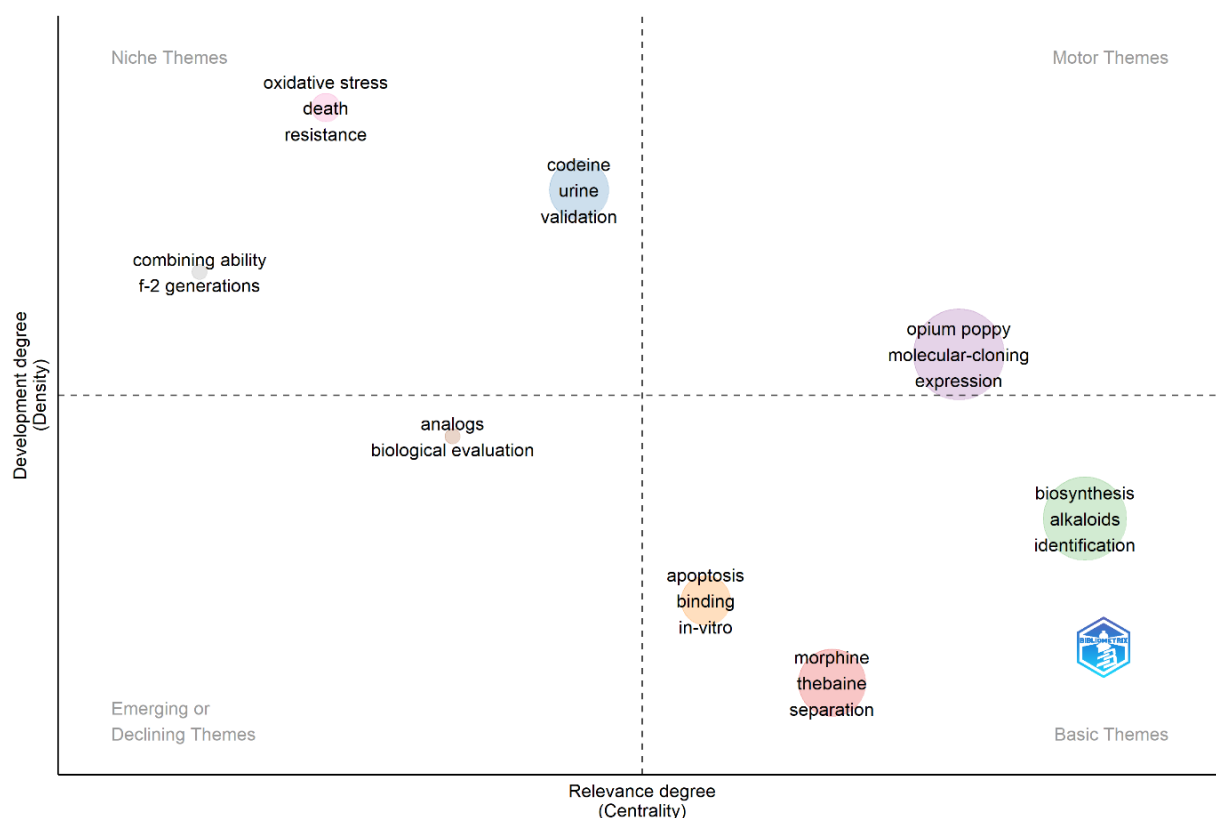


Figure 8. Thematic map analysis.

4. Conclusion

The bibliometric analysis conducted in this study provides a comprehensive assessment of the scientific literature in the field of poppy alkaloids and morphine biosynthesis. The analysis of publications between 1980 and 2024 reveals international collaboration networks, citation analysis, author-subject relationships, and the most frequently used keywords. The study shows that scientific output in the field of poppy alkaloids has increased since the 1980s and reached high levels especially between 2000 and 2016. When evaluating the international collaboration network analysis, it is determined that the United States of America, Canada, the United Kingdom, Germany, Australia, China, and Japan are among the countries that produce the most scientific publications in the field of poppy alkaloids. Keyword network analysis revealed the existence of five main conceptual clusters, with the terms "molecular-cloning" and "opium poppy" being the most central. Citation network analysis shows that studies published by Facchini PJ (1996), Morishige T (2000), Liscombe DK (2007), and Hagel JM (2010) are the most influential reference sources in the field. In the word cloud analysis, the term "papaver somniferum" has the highest frequency of use and constitutes the main focus of research in the field. The conceptual structure analysis shows that the field is divided into four main research clusters: (1) molecular biology and enzymology, (2) plant physiology and metabolism, (3) biosynthetic pathway analysis, and (4) analytical methods. The strong links

between these clusters reflect the interdisciplinary integrated nature of the field. Thematic analysis shows that "opium poppy," "molecular-cloning," and "expression" are the motor themes of the field, while "biosynthesis," "alkaloids," and "morphine" constitute the core themes. The themes "codeine," "oxidative stress," and "resistance" represent niche research areas, while the themes "analogues" and "biological evaluation" reflect emerging or declining research areas. In conclusion, the bibliometric analysis reveals that the field of poppy alkaloids and morphine biosynthesis is an interdisciplinary and global research area. The future development of the field will be shaped by the advancement of engineering approaches and the expansion of biology applications. These developments will provide important opportunities for the sustainable production of poppy alkaloids, the discovery of new bioactive compounds, and the expansion of pharmaceutical applications.

Author Contributions

The percentages of the author' contributions are presented below. The author reviewed and approved the final version of the manuscript.

	T.B.
C	100
D	100
S	100
DCP	100
DAI	100
L	100
W	100
CR	100
SR	100
PM	100
FA	100

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The author declared that there is no conflict of interest.

Ethical Consideration

Since no studies involving humans or animals were conducted, ethical committee approval was not required for this study.

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