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Antimicrobial Potential of Secondary Metabolites: A Scientometric Review*

Potencial antimicrobiano de los metabolitos secundarios: una revisión cienciométrica

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Abstract

There is growing concern in public health regarding antibiotic resistance. This highlights the need to control pathogens using alternatives to conventional drugs. In this context, numerous studies have found that secondary metabolites extracted from plants, fungi, and bacteria have the capacity to inhibit certain microorganisms, often pathogens. The objective of this review is to explore the antimicrobial potential of secondary metabolites for their possible applications in the health, agricultural, and agro-industrial sectors. To achieve this, a scientometric analysis was conducted using the Tree of Science algorithm, with a bibliographic search performed in the two main databases, WoS and Scopus, covering the period from 2003 to 2024. Additionally, an analysis of scientific production by country, journal, and author working on this topic was carried out. The results identified three main groups, distinguished by the origin of the metabolites: plants, fungi, and bacteria. In conclusion, secondary metabolites, regardless of their origin, show significant potential for use in healthcare as pathogen control agents and in agriculture as replacements for chemical pesticides.

Keywords: Antimicrobial activity, secondary metabolites, bioactive, scientometry, antibiotic resistance.

Resumen

Existe una creciente preocupación en salud pública por la resistencia a los antibióticos, lo que pone de relieve la necesidad de controlar los patógenos mediante el uso de alternativas a los fármacos

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convencionales. En este contexto, numerosos estudios han encontrado que los metabolitos secundarios extraídos de plantas, hongos y bacterias tienen la capacidad de inhibir ciertos microorganismos, a menudo patógenos. El objetivo de esta revisión es explorar el potencial antimicrobiano de los metabolitos secundarios para sus posibles aplicaciones en los sectores de la salud, la agricultura y la agroindustria. Para ello, se realizó un análisis cienciométrico mediante el algoritmo Tree of Science, con una búsqueda bibliográfica realizada en las dos principales bases de datos, WoS y Scopus, que abarca el periodo de 2003 a 2024. Adicionalmente, se realizó un análisis de la producción científica por país, revista y autor que trabaja en este tema. Los resultados identificaron tres grupos principales, diferenciados por el origen de los metabolitos: plantas, hongos y bacterias. En conclusión, los metabolitos secundarios, independientemente de su origen, muestran un potencial significativo para su uso en la salud como agentes de control de patógenos y en la agricultura como sustitutos de los pesticidas químicos.

Palabras clave: Actividad antimicrobiana, metabolitos secundarios, bioactivos, cienciometría, resistencia a antibióticos.

1. Introduction

Antibiotic resistance has become a global public health issue, driven by the excessive and uncontrolled use of antibiotic drugs. This has led to the emergence of multidrug-resistant pathogenic bacteria [1], [2]. In this context, antibiotic resistance is responsible for 700,000 deaths per year, and data analysts predict this figure could rise to 10 million by 2050 [3]. Similarly, by 2050, agricultural production losses are estimated to reach $100 billion, along with 300 million cases of premature plant deaths [4]. Given the above, the search for natural antimicrobials is crucial as a potential solution to the growing resistance problem and to reduce the use of chemicals in agriculture [5]. Previous research suggests that there are compounds produced by living organisms with antimicrobial properties, known as secondary metabolites (SM) [6].

SMs are compounds or substances resulting from metabolic processes occurring at the cellular level in any living organism. These compounds are usually associated with advantages rather than essential biological processes. Such substances enable organisms to defend themselves against natural predators or pathogenic organisms. In the case of plants, they also produce aromatic compounds that attract pollinators [7].SM derived from plants and microorganisms are notable for their structural and functional versatility, resulting in a wide diversity of compounds. Key examples include flavonoids, polyphenols, and anthocyanins, with specific types varying across species [8]. Given their diversity and biological activity, continued research into the antimicrobial properties of plant- and microorganism-derived SM is essential.

In addition, SM are potentially used in agricultural biocontrol and the food industry as pesticide alternatives and natural food preservatives, respectively [9]. These metabolites not only inhibit bacteria but also show efficacy against pathogenic fungi and viruses [10], [11]. Thus, SM present a sustainable option for addressing antimicrobial challenges across multiple sectors.

In this context, numerous review articles have reported on the antimicrobial activity of secondary metabolites (SM) derived from plants, bacteria, and fungi. For instance, Keswani et al. [12] evaluated the antimicrobial potential of SMs for protecting plants against pests and pathogens, as well as promoting plant growth. Similarly, Conrado et al. [13] determined that SMs extracted from fungi exhibit antimicrobial properties. In addition, Allemailem [14] investigated the inhibitory capacity of natural extracts against pathogenic fungi that primarily affect plants. Consequently, Keita et al. [15] emphasized the need for continued research into SMs due to the growing issue of antibiotic resistance.

Given these antimicrobial properties, researchers have also sought to understand the mechanisms of action behind these metabolites' inhibitory effects. It has been described that SMs disrupt the integrity of the cell wall of the targeted organism, interfere with the pathogen's metabolic pathways, and inhibit its enzymatic activity. Moreover, SMs exhibit considerable variability in their chemical structures, depending on the species of origin. This diversity provides a distinct advantage in terms of antimicrobial potency [16].

Additionally, studies have explored the combined use of SMs with antibiotics, yielding promising results. This approach has been shown to enhance effectiveness while requiring lower doses of antibiotics, thereby potentially slowing the development of antibiotic resistance in pathogens. However, researchers recommend further evaluation of fully replacing antibiotics with natural alternatives [17].

In conclusion, SMs present a promising alternative to conventional antibiotics. Moreover, their application can be extended to various fields, including agriculture and agroindustry. Therefore, it is essential to continue conducting scientometric analyses on this topic to identify key points and research directions that could serve as a foundation for future studies.

This review provides a comprehensive overview of the current scientific landscape regarding SMs and their properties, based on recent research while considering the foundational work that established each line of inquiry. These insights were developed using scientometric tools, offering clarity on the state of research in this domain.

2. Methodology

This review focused on the antimicrobial activity of SM produced by plants and microorganisms. For this purpose, a bibliographic search was conducted in the WoS and Scopus databases, which encompass a large number of scientific journals and offer verified, high-quality content, making them the most comprehensive and widely used resources [18]. Other authors have also utilized the ToS tool with the Scopus and WoS databases to perform scientometric analysis on topics of interest. For instance, Gómez-Restrepo et al. [19] used the ToS tool to analyze methods applied in the literature for the financial evaluation of photovoltaic energy projects. Likewise, Moreno-Vargas et al. [20] analyzed literature on wastewater treatment using photocatalysis with the ToS methodology, concluding that photocatalysis is a promising alternative for water remediation. Additionally, Manjarres et al. [21] conducted a bibliometric and systematic review using ToS on articles investigating emotional skills, emphasizing their importance in social contexts. The search parameters and detailed results for each database are presented in Table I.

Table I. Search parameters used in WoS and Scopus.

Parameter	**Web of Science**	**Scopus**
Range	2003-2024	
Date	October 30, 2024	
Document Type	Paper	
Words	TITLE ("antimicrobial activity" OR "antibacterial activity" OR "antifungal activity" OR "antiviral activity") AND TITLE ("metabolites" OR "secondary metabolites" OR "natural products" OR "bioactive compounds" OR "plant metabolites" OR "microbial metabolites")	
Results	248	637
Total (Wos+Scopus)		797

Once the search results from each database were obtained, the ToS software was used for data analysis, as it is a tool that allows for the mapping of bibliographic data, highlighting the areas of study developed around a specific topic [22]. Additionally, it classifies information based on its historical and current relevance. This process produced a hierarchical tree, where the roots represent the primary findings and methodologies related to antimicrobial activity. Following this, the trunk comprises the initial studies exploring the antimicrobial activity of various metabolites and their potential in health and agriculture. Finally, three branches were identified, representing recent research that investigates practical applications of SM. ToS has been widely used in academic research [23], [24], [25], [26], [27].

Consequently, Gephi 10.1 software was employed to create a network that facilitated the visualization of the collected literature, allowing for connections between the themes of the articles in each branch. Similarly, a word cloud was generated with the keywords from the articles in each branch, where the size of each word corresponds to its frequency.

Figure 1 presents the flowchart summarizing the methodology used to obtain bibliographic information and manage the resulting data.

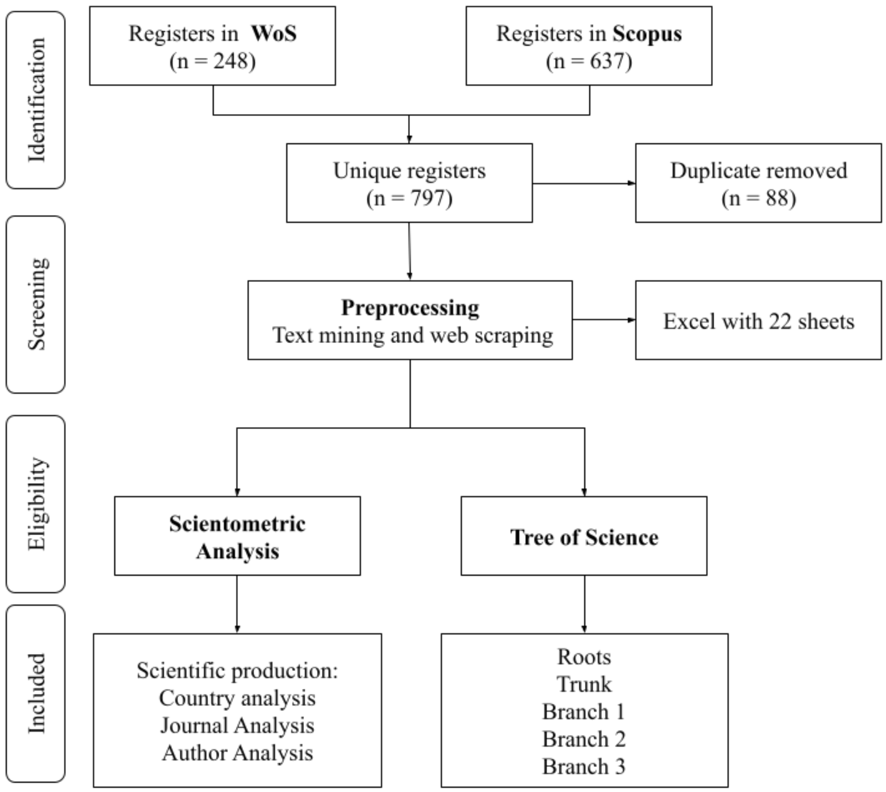

Figure 1. Flow diagram

3. Results

Scientific production

Figure 2 illustrates the scientific production from 2003 to 2024 related to the antimicrobial activity and SM of plants, fungi, and bacteria. The figure provides a detailed breakdown of academic output in WoS (yellow bars) and Scopus (green bars), as well as the total unique publications combining both databases (red line). Additionally, it presents the total citations received (WoS + Scopus) represented by the purple line. The figure demonstrates sustained growth over time in this area of research. Notably, Scopus consistently shows higher production than WoS in most years (except for 2003). However, incorporating WoS data is crucial for this analysis, as the total production (red line) has consistently exceeded Scopus's output, indicating that both databases are necessary for a comprehensive analysis. The total growth in production during this period (as represented by the purple line) was 15.6%, highlighting a mature and continually expanding field of knowledge. The following sections describe the three periods identified in the figure in greater detail.

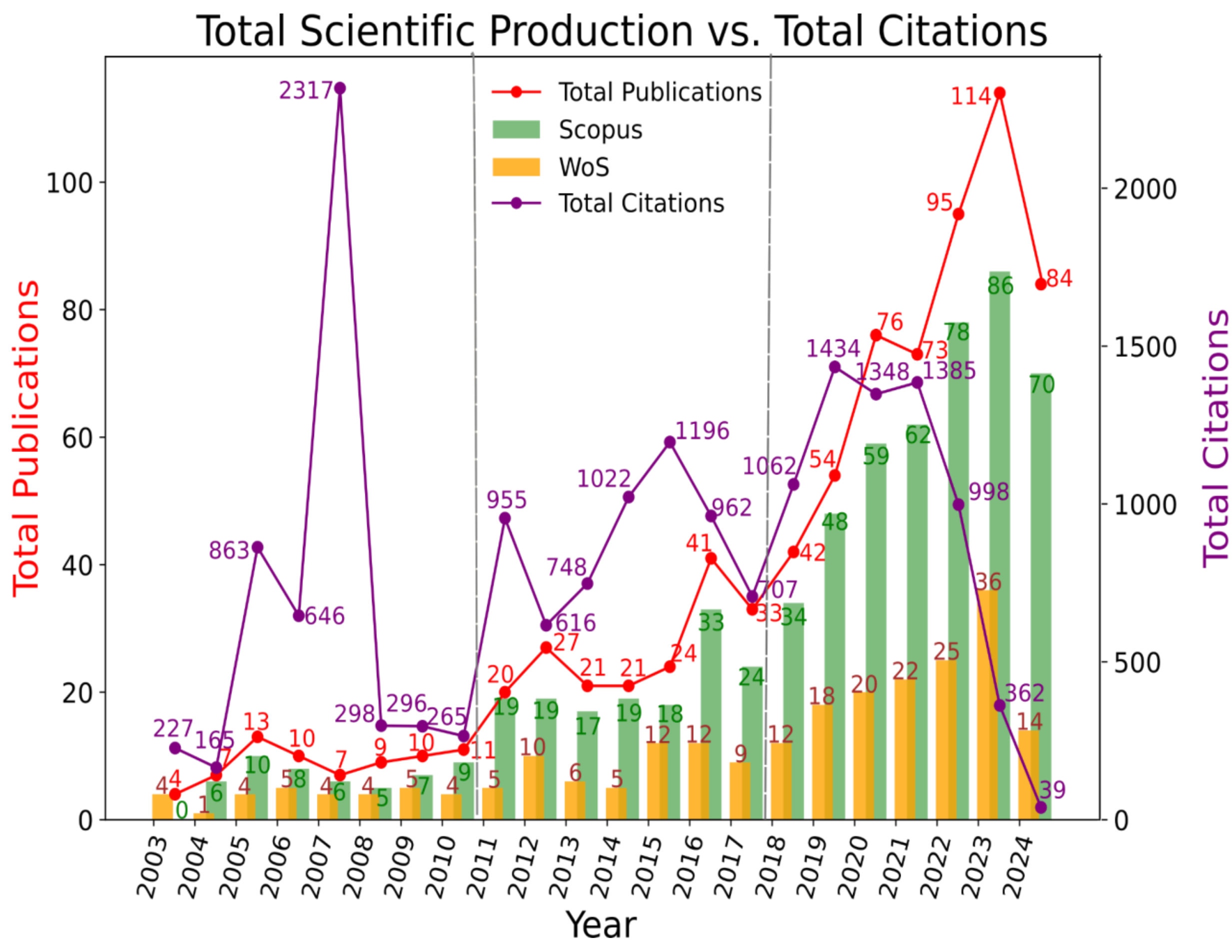

Figure 2. Trends in Total Scientific Production and Citations (2003–2024)

Period 1 – Initial Growth (2003–2010)

This period is characterized by an initial growth of 15.55% and a peak in citations received. The highest citation peak was driven by research comparing various methods for identifying antimicrobial activity in natural compounds [28]. Similarly, in 2005, a significant milestone was achieved with the work of Kumar et al. [29], which highlighted the high efficacy of SM extracted from a bacterial strain against phytopathogenic fungi. This opened new research avenues on the use of these antimicrobials as biocontrol agents in agriculture. Furthermore, in 2006, another citation peak occurred with the study by Volk and Furkert [30], which evaluated the algicidal, antibacterial, and antifungal activities of metabolites produced by cyanobacteria.

Period 2 – Stability (2011–2017)

During this period, growth slowed to 8.7%, a lower rate compared to the previous phase. However, researchers maintained a strong interest in the topic. Three main citation peaks were observed in 2014, 2015, and 2016, driven by the studies [31], [31], [32], respectively. These articles focused on evaluating SM from various sources against pathogenic microorganisms. The figure illustrates the significance of these studies, reflected in the high number of citations they received.

Period 3 – Accelerated Growth (2018–2023)

Between 2018 and 2023, research in this field grew by 22.10%, indicating its increasing scientific relevance. This growth is attributed to the potential applications of SM, which span diverse areas such as healthcare, agriculture, and agro-industry. The most significant citation peak occurred in 2019, led by the research of Perczak et al. [33], which evaluated the antifungal activity of essential oils against Fusarium species. Additional peaks were recorded in 2020 and 2021 during the SARS-CoV-2 pandemic, driven by studies that explored natural metabolites to inhibit the replication of the virus upon cell contact [34].

Country analysis

The academic output of countries reflects their efforts to foster innovation within industries. Table II presents three key variables to analyze the academic productivity of countries. The first variable is production, measured by the number of articles published by each country. The second is impact, assessed through the total number of citations received by all articles from a given country. The third is quality, evaluated based on the quartiles of Scimago rankings. In this context, China emerges as the leader in academic production with 115 articles, accounting for 14.13% of the total. It also leads in impact, with its articles receiving 1,878 citations, representing 12.39% of the total. Furthermore, the majority of its articles (58) are published in the highest quartile (Q1), underscoring the quality of its research output.

Table II. Country Contributions to Secondary Metabolite Research: Production, Citation, and Quartile Distribution

Country	Production		Citation		Q1	Q2	Q3	Q4
	Count	percentage	Count	percentage				
China	115	14.13 %	1878	12.39 %	58	18	23	3
India	95	11.67 %	1345	8.87 %	8	28	29	14
Brazil	46	5.65 %	1454	9.59 %	12	12	9	4
USA	40	4.91 %	1292	8.52 %	26	7	2	1
Egypt	39	4.79 %	532	3.51 %	12	6	8	4
Indonesia	33	4.05 %	170	1.12 %	2	10	17	4
Malaysia	27	3.32 %	293	1.93 %	2	8	7	4
Thailand	21	2.58 %	481	3.17 %	6	6	1	3
Germany	20	2.46 %	654	4.31 %	10	4	2	0
Irán	20	2.46 %	420	2.77 %	4	4	7	2

China has recently conducted studies on Camellia fascicularis, a plant with significant medicinal and nutritional value, to analyze the potential of its metabolites. Although research on its bioactive properties is still limited, the study successfully isolated and analyzed fifteen compounds using various techniques, such as spectral analysis and nuclear magnetic resonance (NMR), supported by literature reviews. The compounds were evaluated for their antimicrobial and antioxidant activities, with some showing minimum inhibitory concentrations against Pseudomonas aeruginosa, while others effectively inhibited Escherichia coli and Staphylococcus aureus [35].

Figure 3 illustrates the scientific collaboration among countries, highlighting the number of communities by size as well as the nodes and links over time. Three major communities stand out: the first led by China, the second by the USA and Germany, and the third by the United Kingdom. Some of China's research has involved collaboration with Malaysia and India. For example, a study focused on the development of purified SM from Bacillus subtilis to combat two pathogenic fungi, Fusarium oxysporum and Rhizoctonia solani.

These metabolites were purified from extracellular extracts of B. subtilis, including volatile organic compounds and membrane proteins. The treatments significantly inhibited the growth of these pathogens, demonstrating the great potential of these compounds as biocontrol agents.

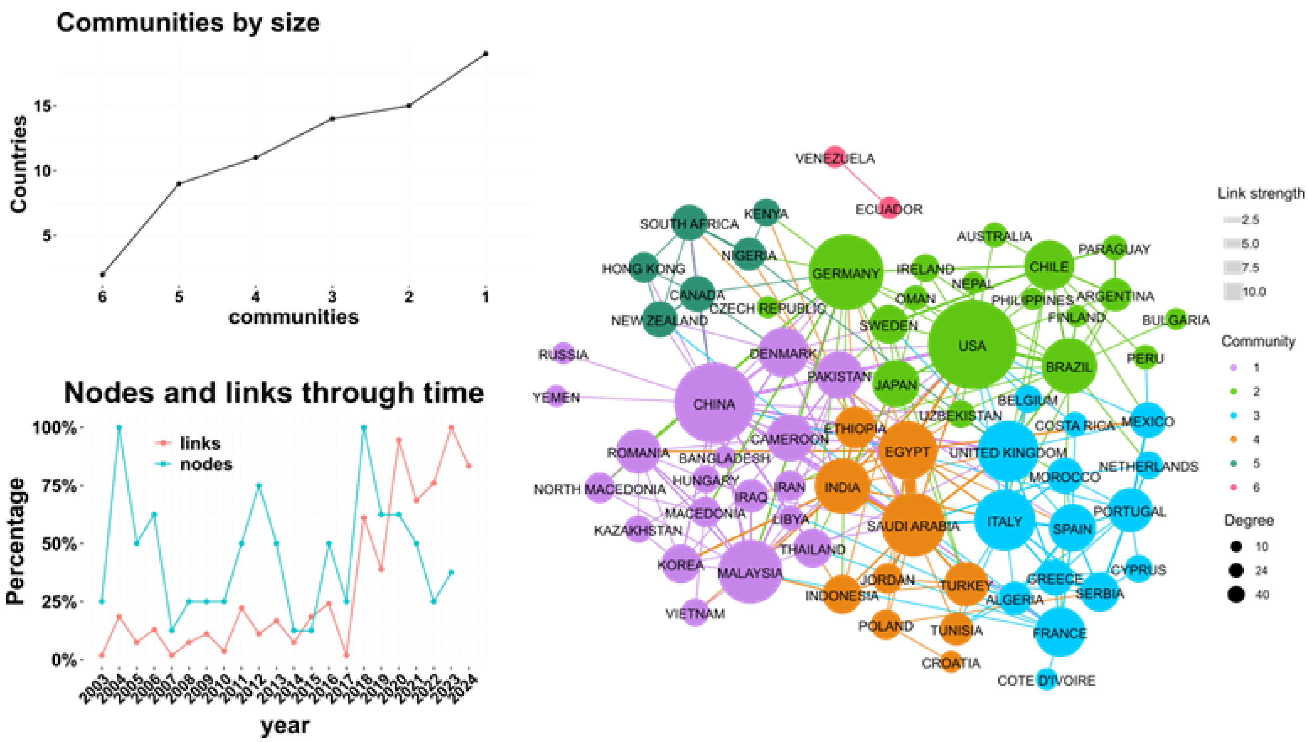

Figure 3. Global Collaboration Network by Country in Secondary Metabolite Research

Although Colombia does not have significant visibility on the map, it has also contributed to this field of research. For instance, one study focused on exploring the antiviral activity of an indole-type compound derived from natural products to combat dengue—a viral disease prevalent worldwide. The primary objective of the study was to understand the interaction between this compound and the NS5 protein of the dengue virus. Through in vitro tests, the researchers aimed to determine whether the compound exhibits antiviral activity against dengue, especially given the lack of a definitive treatment targeting the virus [36].

Journal Analysis

Table III presents a list of journals with the highest academic output on the topic. It is notable that the majority of the journals are ranked in the highest quartile (Q1), with five journals in this category. Only two journals are ranked in Q3, while three are in Q2. The journal with the highest number of publications on the subject is Natural Product Research, followed by Molecules and Frontiers in Microbiology. Additionally, the table includes the H-index for each journal, which serves as an indicator of the journal's quality. The journal with the highest H-index is the Journal of Agricultural and Food Chemistry (345), meaning that all its published articles have been cited at least 345 times, reflecting its strong academic influence.

Table III. Top Journals in Secondary Metabolite Research: Publication Metrics and Impact

Journals	N.°	%	Country	Impact Factor	Quartile	H. index
Natural Product Research	30	0.04	United Kingdom	0.41	Q2	71
Molecules	23	0.03	Switzerland	0.744	Q1	227
Frontiers In Microbiology	21	0.03	Switzerland	1.065	Q1	233
Chemistry Of Natural Compounds	20	0.03	United States	0.287	Q3	47
Journal Of Agricultural And Food Chemistry	14	0.02	United States	1.114	Q1	345
Plants	10	0.01	Switzerland	0.795	Q1	92
Journal Of Applied Microbiology	9	0.01	United Kingdom	0.764	Q2	185
Natural Product Communications	9	0.01	United States	0.298	Q3	63
Journal Of Natural Products	8	0.01	United States	0.802	Q1	161
Applied Sciences	7	0.01	Switzerland	0.51	Q2	130

Figure 4 illustrates a citation network among journals, thematically grouping them based on their research focus. Group 1 is led by the journal Molecules, with its thematic focus centered on the development or identification of renewable biological resources derived from food or food waste. This group also emphasizes the utilization of SM from endophytic strains, which contribute to the production of biocontrol agents for both the food and agricultural industries.

Additionally, Molecules has its strongest connection with Food Chemistry, a journal that has published studies on the antimicrobial activity of plant extracts, many of which are rich in SM [37].

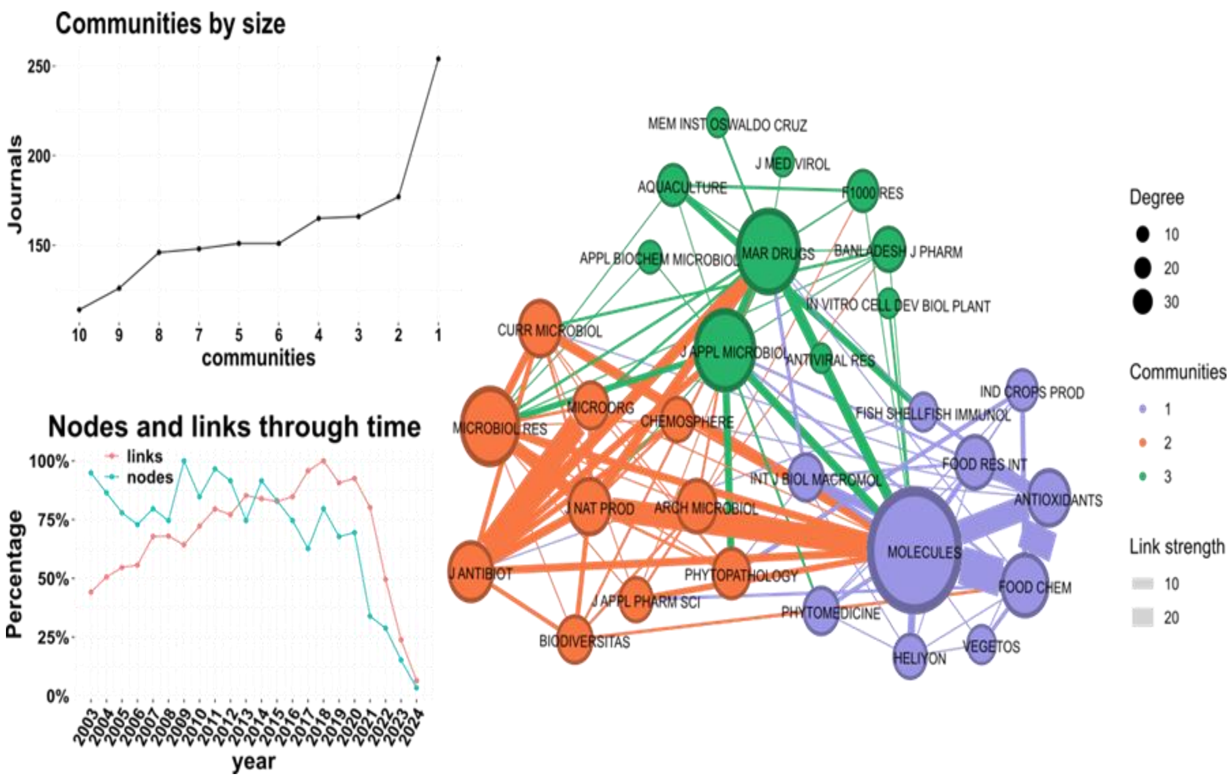

Figure 4. Citation Network of Journals: Communities and Interconnections in Antimicrobial Secondary Metabolite Research

The second group is led by the Journal of Applied Microbiology, which has its strongest connection with the journal Marine Drugs. Their shared focus includes studies on the antimicrobial properties of natural products [38] and extracts from marine fungi habitats [39].

Similarly, the third group is led by Microbiological Research, which maintains a strong link with the Journal of Antibiotics. Their most recent investigations include the antimicrobial activity of extracts from species of the genus Pantoea against multidrug-resistant strains [40]. Additionally, research has explored the antiviral properties of metabolites from Talaromyces sp. [41].

Author Analysis

Table IV lists the 11 most prolific authors in the field. Professor Zhang Y, from the College of Chemistry, leads with 14 publications. Notably, this aligns with previous findings and underscores China's prominent role in this area of research. For instance, 9 out of the 11 most productive authors are based in China.

Table IV. Top 11 Most Prolific Authors in Secondary Metabolite Research and Their Affiliations

Authors	**Total Publications**	**Affiliation**
Zhang Y	14	College of Chemistry and Life Science, Zhejiang Normal University, Jinhua 321004, People's Republic of China.
Li Y	11	Institute of Chinese Herbal Medicines, Hubei Academy of Agricultural Sciences, Enshi 445000, China
Li J	9	Key Laboratory of Microbial Resources Collection and Preservation, Ministry of Agriculture and Rural Affairs, Institute of Agricultural Resources and Regional Planning, Chinese Academy of Agricultural Sciences, Beijing 100081, China.
Liu Y	9	College of Forestry and Landscape Architecture, South China Agricultural University, Guangzhou, China
Wang X	9	Department of Medicinal Chemistry, University of Mississippi, University, Mississippi 38677, USA.
Xu L	8	School of Life Sciences, Huizhou University, 516007, Huizhou, P. R. China
Li Z	7	College of Agronomy, Sichuan Agricultural University , Wenjiang District, Chengdu 611130 , P.R. China.
Chen X	6	Key Laboratory of Microbial Diversity in Southwest China, Ministry of Education, College of Life Science, Yunnan University, Kunming 650091, China
Chen Y	6	Key Laboratory of Microbial Diversity in Southwest China, Ministry of Education, College of Life Science, Yunnan University, Kunming 650091, China
Li L	6	The Metabolomics Innovation Centre and Department of Chemistry, University of Alberta, Edmonton, AB T6N1H1, Canada
Yang X	6	Functional Molecules Analysis and Biotransformation Key Laboratory of Universities in Yunnan Province, Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry Education and Yunnan Province, School of Chemical Science and Technology, Yunnan University, 2nd Cuihu North Road, Kunming, 650091, P. R.China.

The scientific collaboration network illustrates the formation of distinct academic communities. Figure 5 was constructed using the ego networks of the principal authors (Table 4). For instance, Zhang Y has collaborated with Li S, Jiang D, Kong L, Zhang P, and Xu J [42]. Their study investigated the antifungal potential of metabolites derived from Streptomyces canus associated with termites. Two metabolites, resistomycin and tetracenomycin D, were isolated and their structures were analyzed using spectroscopy. The results showed that resistomycin possesses strong inhibitory effects on the mycelial growth of *Valsa mali* and *Magnaporthe grisea*. Additionally, germination and in vivo spore tests demonstrated excellent results, highlighting resistomycin as a promising candidate for development into an effective fungicide.

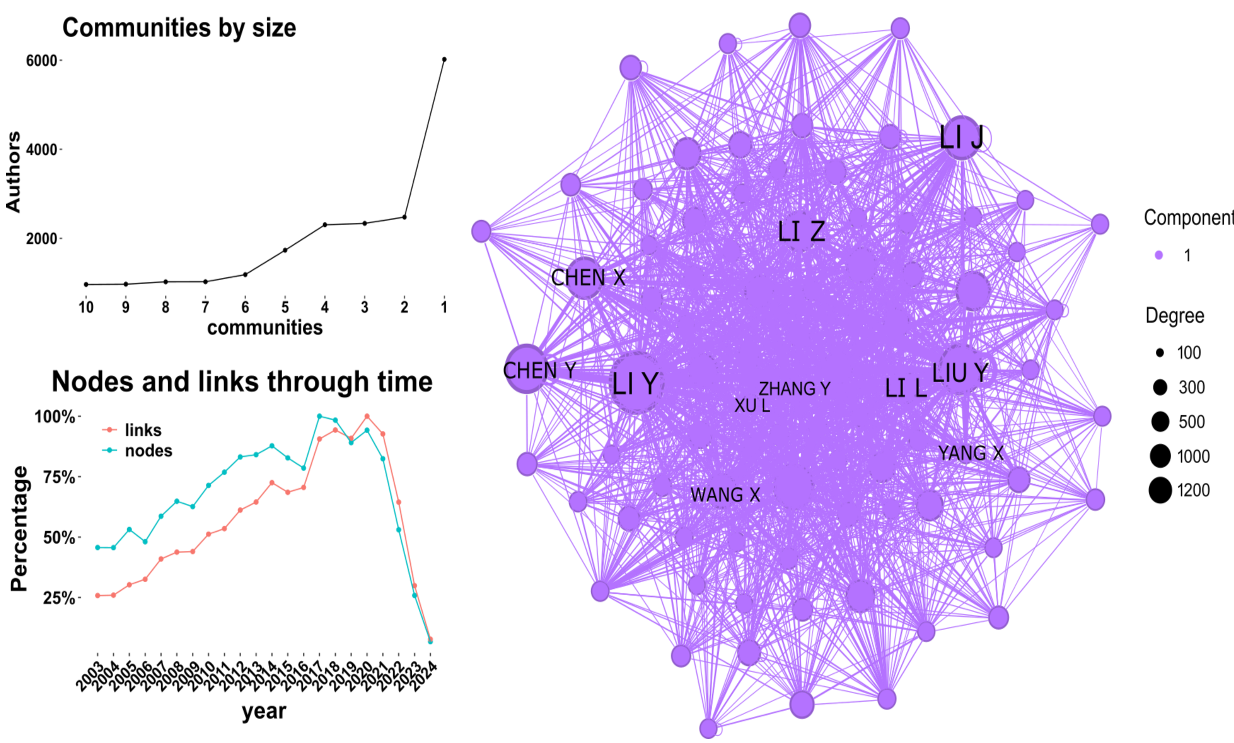

Figure 5. Scientific Collaboration Network in Secondary Metabolite Research: Key Authors and Communities

Tree of Science

Root

In the roots, four articles were identified that established the foundation for the study of antimicrobial activity of SM. One of the first advancements in antimicrobial research was described by Bauer et al. [43], who developed a method for measuring bacterial susceptibility to different antibiotics using antibiotic-impregnated paper disks. This method remains widely used today due to its reproducibility and precision. Additionally, Eloff [44] introduced the microplate method to determine the minimum inhibitory concentration (MIC) of an antibiotic or secondary metabolite that inhibits the growth of the target microorganism, optimizing testing efficiency and allowing a greater number of samples to be processed simultaneously. These methods laid the foundation for evaluating the antimicrobial potential of various compounds.

Given this foundation, plants produce SM that have demonstrated inhibitory effects against certain microorganisms. The methods for extracting these metabolites depend on their origin and the antagonistic activity assessment, which varies with the target microorganism [45]. Various in vitro methods are used to assess antimicrobial activity, the most common being diffusion methods with disks impregnated with the compound or extract and broth dilution methods to determine MIC. Additionally, other methods like time-kill assays, which assess microorganism viability over time while exposed to the antimicrobial, and the ATP bioluminescence assay, which uses ATP as an indicator of microbial viability [46][46], are also employed. This range of methods allows for tailored approaches to measure the antimicrobial potential of plant-derived SM.

Furthermore, there is concern about the antibiotic resistance that certain pathogenic bacteria have developed, which opens up a field for investigating new antimicrobials for these bacteria. For instance, Jawad [47] investigated the inhibitory potential of SM produced by Aspergillus terreus against five bacterial pathogens, showing the strongest results against the pathogen Streptococcus pneumoniae, with lesser effects against the other pathogens; it also showed inhibitory effects against the fungus itself. In light of these findings, it is crucial to continue exploring these antimicrobial compounds for their potential in pathogen inhibition.

Trunk

The trunk of the tree was formed by three articles that consolidated knowledge in the subject. The antimicrobial and antioxidant potential of SM from plants, bacteria, and fungi has driven research efforts to counter bacterial resistance to antibiotics. These metabolites also have potential in agriculture as sustainable alternatives to chemical pesticides. Several authors have reported significant findings in this area, showing promising results for pathogen control.

In this context, Yahia et al. [48] reported the potential of Aspergillus sp. DHE 4 as an antimicrobial agent, showing notable effectiveness primarily against the pathogenic bacterium Staphylococcus aureus (ATCC6538-P) and the yeast Candida albicans (ATCC 10231). Similarly, Zhen-Cheng et al. [49] documented two Trichoderma fungal strains that produced SM with antifungal activity against pathogenic fungi from the genera Fusarium, Aspergillus, Penicillium, Colletotrichum, Neofusicoccum, and Phytophthora, highlighting their potential as biological control agents. Likewise, Stracquadanio et al. [50] explored the antioxidant and antimicrobial potential of extracts from two strains of the genus Ziziphus Mill, finding inhibition against Staphylococcus aureus (ATCC25923), Salmonella typhimurium (NRLB4420), and Escherichia coli (ATCC35218). In summary, SM produced by plants, fungi, and bacteria show significant potential to inhibit pathogen growth, underscoring the need for continued research in this area.

Figure 6 presents the data network generated using Gephi 10.1, linking the database results from WoS and Scopus on the antimicrobial activity of metabolites. Additionally, a word cloud of keywords from each article is included.

Figure 6. Network and Word Cloud.

Branch 1 - Antimicrobial Potential of Bacterial Secondary Metabolites

Over time, research has been conducted to delve into the use and production of secondary metabolites as antimicrobial agents. In the following study, Kun Zhang et al. [36] evaluated the antimicrobial capacity of metabolites produced by the marine actinobacterium Streptomyces sediminicola sp. strain "SCSIO 75703T" against bacterial strains such as Bacillus thuringiensis, Staphylococcus aureus, Bacillus subtilis, Acinetobacter baumannii, and Escherichia coli. The study highlighted the potential of these strains to produce secondary metabolites that inhibit the growth of some of the studied species

Similarly, Rewan Abdelazis et al. [51] emphasized the importance of SM produced by the actinobacterium Streptomyces coeruleorubidus. These metabolites were tested for antibacterial activity against Streptococcus agalactiae, both in vitro and in vivo, a pathogen that infects marine species like tilapia. The metabolites showed significant antimicrobial properties, helping mitigate the negative impacts on these marine species. Additionally, Pouryousef et al. [52] assessed the antimicrobial activity of Streptomyces spp. isolates from Qom Lake sediments against Pseudomonas aeruginosa using the disc diffusion method.

Among seven isolates with antimicrobial activity, one strain, SCC15, demonstrated particularly strong activity against clinical strains of Pseudomonas aeruginosa.

On the other hand, F. A. Ripa et al. [53] extracted metabolites from a Streptomyces sp. strain (VITGV38) isolated from tomato plants. These metabolites, extracted with ethyl acetate, were tested against urinary tract pathogens such as Proteus mirabilis, Enterococcus faecalis, Klebsiella pneumoniae, and Escherichia coli, showing strong antibacterial activity and indicating their potential for antibiotic development. Likewise, Inas Abou El-Enain et al. [54] investigated SM produced by actinomycetes from animal manure. Among the 22 isolates tested, diisooctyl phthalate emerged as a promising metabolite, exhibiting broad-spectrum inhibitory activity against pathogenic bacteria and fungi.

In another study [55], SM from Aspergillus terreus isolated from soil were analyzed for their biological potential. Fermentation cultures yielded purified metabolites with strong antimicrobial activity against human pathogens. Similarly, another investigation [56] assessed the antibacterial capabilities of bioactive compounds from fungi such as Alternaria sp., Cladosporium sp., Ulocladium sp., Chaetomium sp., A. niger, E. nidulans, and Fusarium sp. against, P. aeruginosa. While most showed varying inhibitory capacities, metabolites from Ulocladium sp., Alternaria sp., Cladosporium sp., and E. nidulans did not exhibit activity against P. aeruginosa.

Another research explored natural compounds isolated from Prismatomeris filamentosa, such as Filament A and anthraquinone derivatives, which showed mild antimicrobial activity against bacteria like B. subtilis, B. cereus, S. aureus, E. coli, P. aeruginosa, and S. sonnei [57]. The aim of another study [58] was to isolate metabolites from Streptomyces triticidaridicis strain NEAU-H2T. These metabolites, characterized using nuclear magnetic resonance and mass spectrometry, exhibited antifungal potential, showing 63% similarity to the natamycin gene cluster. Lastly, research profiled metabolites from Chamaecytisus albus, which acted as antifungal agents [37]. These were tested against soil-derived phytopathogens such as B. cinerea, F. oxysporum, and S. sclerotiorum using chromatography and spectrometry. The results revealed biocontrol activity, highlighting their potential use in creating sustainable fungicides.

Branch 2 - Plant-Derived Secondary Metabolites: Exploring Antimicrobial Potential and Applications in Drug Development

Plants play a pivotal role in the evolution of science and its applications. Ari Sri Windyaswari et al. [59] demonstrated that metabolites with potent antimicrobial activities could be isolated from the wall of Potosí. The first isolated compound, stigmasterol, exhibited notable activity against the fungal and bacterial pathogens Aspergillus niger and Aeromonas hydrophila.

Following this line of research, Marcelle Ngangoue et al. [60] analyzed the antibacterial activity of anonamol B and other SM extracted from the stem bark of Anonidium mannii. These compounds, isolated using routine chromatography techniques, were evaluated against Escherichia coli, Enterobacter aerogenes, Klebsiella pneumoniae, Providencia stuartii, and Pseudomonas aeruginosa. The results revealed inhibitory concentrations ranging from weak to moderate, showcasing their potential.

Another study examined the in vitro antibacterial efficacy of SM isolated from the roots of Cyphostemma adenocaule, a therapeutic plant traditionally used to treat various conditions [61]. The metabolites, extracted using silica gel column chromatography, were tested through agar diffusion assays. The findings underscore C. adenocaule as a valuable source of antimicrobial metabolites, with promising implications for pharmaceutical applications.

Salha M. Aljubiri et al. [62] investigated the cytotoxic and antibacterial activities of the total extract, fractions, and isolated SM from Euphorbia schimperiana. The study highlighted significant cytotoxic effects against cancer cells and notable antibacterial activity, suggesting that structural analyses of these metabolites through diverse techniques are effective for evaluating both cytotoxic and antimicrobial potential of organic compounds.

Another study explored the SM and antimicrobial activity of extracts from Hypericum perforatum (St. John's Wort) [63]. Plant samples were macerated using n-hexane, ethyl acetate, and methanol, and tested against clinical gram-positive bacterial isolates. The extracts demonstrated strong antibacterial activity, indicating their potential as agents against gram-positive bacteria.

The article by Al-Mijalli et al. [64] evaluated the antibacterial activity of Euphorbia balsamifera. Extracts from this plant exhibited substantial activity against several pathogens, including Listeria monocytogenes Scott A, Staphylococcus aureus, Bacillus cereus, Enterococcus faecalis, Salmonella enterica serotype Enteritidis, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli. Similarly, research by Salazar et al. [65] demonstrated the high pharmacological potential of Plukenetia huayllabambana, identifying its components as promising anti-infective bioactives.

Another investigation focused on the bioactive compound profile and antimicrobial activity of Pogostemon benghalensis, an aromatic shrub [66]. Ethyl acetate extracts showed significant antimicrobial activity at a concentration of 80 µg/mL, particularly against Klebsiella aerogenes and Enterococcus faecalis, highlighting its therapeutic value.

Moreover, a study examined the antibacterial properties of leaf and flower extracts from Woodfordia fruticosa [67]. While the observed antibacterial activity was moderate, the findings support the potential of these extracts for the development of antibacterial drugs.

Finally, innovative research developed three deep neural network (DNN) methods to predict the antibacterial activity of plant-derived metabolites [68]. The first model employed metabolite fingerprints as features, the second assessed similarities between them, and the third enhanced the classification results of the previous models. These computational approaches hold promise for advancing metabolite-based drug discovery.

These studies collectively showcase the diverse and significant contributions of plant-derived SM to antimicrobial research, emphasizing their potential for pharmaceutical innovation and sustainable pathogen control.

Branch 3 - Antimicrobial Potential of Secondary Metabolites: Insights into Plant-Derived Alternatives for Sustainable Pathogen Control

Another significant research avenue focuses on the use of SM extracted from plants. An initial study investigated 15 isolates of Bacillus spp [69]. derived from wheat plants to combat the phytopathogens Fusarium graminearum and Macrophomina phaseolina. Results revealed that 7 out of 15 isolates effectively inhibited one or both pathogens.

Additionally, Pan Liu et al. [70] explored the antifungal and probiotic activities of Weissella cibaria against three spoilage-causing fungal pathogens: Aspergillus fumigatus, Penicillium expansum, and P. oxalicum. The authors postulated that W. cibaria diminishes fungal growth by disrupting hyphal decoration and damaging the mycelium structure, based on promising experimental outcomes.

Shan Huang et al. [71] proposed an alternative for developing organic fungicides by investigating the biological and antifungal potential of the fungus Trichaptum laricinum against the pathogen Colletotrichum anthisci. The study demonstrated an inhibition range of 50% with minimum inhibitory concentrations (MIC) of 256 µg/mL. Notably, three isolates showed excellent inhibitory activity against this pathogen in avocado fruit, presenting a viable candidate for eco-friendly solutions in agriculture.

Similarly, Shereen A. Soliman et al. [72] evaluated the antifungal activities of Bacillus amyloliquefaciens and B. velezensis using a dual-culture technique. The isolates exhibited significant antifungal activity, highlighting their potential as alternatives to chemical pesticides for managing key plant diseases.

Jyotsna Chakrawarti et al. [73] examined the antimicrobial activities of SM produced by endolichenic fungi from the genus Parmotrema. From 73 isolates, five were identified as having notable antimicrobial activity, with one displaying a unique metabolite expression pattern, making it a promising source of antibacterial compounds.

Another study analyzed the antibacterial and antifungal activities of indole alkaloid derivatives produced by Bacillus velezensis and Bacillus thuringiensis against a variety of bacteria and phytopathogenic fungi [74]. While most isolates showed moderate activity, a subset exhibited strong inhibitory effects against the tested fungal pathogens.

A related investigation isolated a strain of Pseudomonas aeruginosa B18 from sugarcane roots for its biocontrol potential [75]. This strain demonstrated multiple activities that could enhance sugarcane's resistance to smut, a disease that significantly reduces yield and quality, positioning P. aeruginosa B18 as a promising sustainable biofertilizer for sugarcane cultivation.

Finally, a study examined the diversity, antibacterial activity, and metabolites of fungi isolated from the bark of Syzygium zeylanicum [76]. Using the Kirby-Bauer method, isolates were screened against Escherichia coli, Salmonella typhi, Staphylococcus aureus, and Bacillus subtilis. The fungi with the highest antibacterial activity were further analyzed to identify their bioactive compounds.

Moreover, another investigation [77] analyzed antifeedant and antifungal activities of metabolites derived from the co-culture of Aspergillus tubingensis with red ginseng. The identified compounds—asperterubine, panaxitriol, aspterric acid, monomeric carviolin, and asperazine—showed selective inhibition against phytopathogens such as A. tubingensis, Nigrospora oryzae, and Phoma herbarum. The co-culture extract exhibited enhanced antifungal and antifeedant properties, emphasizing its potential in sustainable pathogen control.

These studies collectively highlight the diverse and promising applications of SM derived from plants, fungi, and bacteria as sustainable alternatives to chemical pesticides and biocontrol agents.

Conclusions

This study presents a scientometric review of the antimicrobial activity of SM, utilizing the ToS algorithm based on a search conducted in Scopus and WoS. The findings indicate that this topic has been studied for many years, initially focusing on identifying foundational methods to effectively evaluate the antimicrobial activity of various compounds, particularly those derived from plants, bacteria, and fungi. These foundational studies paved the way for further research into the antimicrobial potential of SM, with a growing emphasis on addressing antimicrobial resistance, a pressing global concern. Additionally, three major research trends were identified.

The first trend highlights the antimicrobial activity and secondary metabolite production of various bacterial species. These bacteria demonstrate significant biological potential, which can be leveraged across diverse fields such as medicine, agro-industry, and agriculture.

The second trend focuses on the investigation and review of SM derived from plants and their antimicrobial activity. These metabolites present a promising alternative due to their accessibility, facilitating more affordable research opportunities and enabling significant advancements.

The third trend centers on the inhibitory and antimicrobial capacities of fungi against various pathogens. The primary goal of this research is to develop sustainable alternatives to chemical products or pesticides, positioning fungi as biocontrol agents for sectors such as agriculture and food production.

As with any research, certain limitations were identified. The analysis was confined to studies published from 2003 onwards and included only English-language articles. However, ToS mitigates this bias by integrating references, thereby enabling the identification of older articles. Moreover, the search yielded few articles in languages other than English. Nevertheless, these limitations are not expected to significantly impact the final results.

Future research should explore specific applications of SM with antimicrobial properties using scientometric tools. Additionally, further investigation is recommended into the applicability of these metabolites in other disciplines, such as biotechnology and pharmacology.

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