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Research Article
Zerumbone: Comprehensive Examination of the Scientific Literature

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Abstract

Background and Objective: Zerumbone is a monosesquiterpene volatile organic compound isolated from the *Zingiber zerumbet* Smith plant and has versatile biological activities. Since 1960, plenty of research has been conducted on this compound's phytochemistry, pharmacology and other aspects. This bibliometric study quantifies impact, identifies trends, maps collaborations in zerumbone research and reveals its scientific landscape and themes. **Materials and Methods:** The bibliographic data for this study, focusing on zerumbone research, was retrieved from the Scopus database using PRISMA Guidelines and the MeSH database of terms. The analysis of the data was carried out utilizing VOSviewer and R-based Bibliometrix applications. Various features and parameters, such as publication trends, author productivity, co-citation patterns, thematic clusters and emerging topics, were examined to provide a comprehensive understanding of the scientific landscape and themes in zerumbone research. **Results:** Zerumbone research has expanded significantly since 1960, particularly in recent decades. Murakami, A. from Japan emerged as the most productive and influential scholar, while Kitayama, T. assumed prominence in journals associated with zerumbone research. Malaysia showed prolific engagement in this field. Major thematic clusters included apoptosis, docking, NF-κB, angiogenesis, Alzheimer's disease and antioxidant activity. The analysis identified a turning point in 2016 and highlighted trending topics such as cisplatin combination, antimicrobial activity, molecular docking, colorectal cancer and oxidative stress. **Conclusion:** The findings provided a comprehensive overview that guides future research, collaborations and decision-making to advance scientific understanding of zerumbone.

Key words: Zerumbone, *Zingiber zerumbet*, bibliometric study, VOSviewer, R-based bibliometrix

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Zerumbone, a bioactive compound derived from the *Zingiber zerumbet* Smith plant[1], is a sesquiterpenoid and cyclic ketone with (1E,4E,8E)-alpha-humulene structure, featuring an oxo group at the carbon atom connected to two double bonds[2]. The compound is abundant in the essential oil of *Z. zerumbet* and can be extracted through steam distillation[1]. Notably, zerumbone offers a range of health benefits and medicinal properties[3]. It exhibits potent anti-inflammatory effects and demonstrates antioxidant activity[4]. The anti-inflammatory properties stem from its ability to hinder the production of pro-inflammatory molecules, including cytokines and prostaglandins. It impedes NF-κB activation, thereby reducing the expression of inflammatory genes and inhibits COX-2 activity[5,6]. Moreover, it modulates various inflammatory signaling pathways such as MAPK and JAK/STAT, making it a promising candidate for the management of chronic inflammatory conditions[7]. Additionally, zerumbone showcases antimicrobial activity against bacteria, fungi and viruses[8,9]. Despite its diverse pharmacological properties, further research is necessary to elucidate its mechanisms of action and potential applications in human health.

Zerumbone has been shows promise against cancer in research. It inhibits cancer cell growth, induces apoptosis and prevents tumors. Zerumbone targets numerous signaling pathways involved in cancer formation and progression to fight cancer[1,8,10]. Zerumbone suppresses cancer cell proliferation and reduces pro-inflammatory mediators via inhibiting NF-κB[5]. It also modulates cancer cell growth and survival molecular targets. It downregulates Bcl-2 and Bcl-xl and upregulates Bax and caspases[1]. Cancer cells undergo programmed cell death due to this pro and anti-apoptotic protein imbalance. Anti-angiogenic qualities of zerumbone prevent the creation of new blood vessels that feed malignancies. Zerumbone limits tumor growth by cutting off its blood supply[11,12]. Additionally, zerumbone exhibits selective antitumor action. Selectivity is essential for reducing cancer treatment adverse effects[13,14]. Many research have examined the effects of zerumbone on breast, lung, prostate, colon and liver cancer[1,7,15-19]. In these experiments, zerumbone has consistently inhibited cancer cell proliferation, induced apoptosis and suppressed tumor formation. Despite its unknown processes, zerumbone's capacity to target several cancer development pathways and selectivity for cancer cells make it an attractive choice for cancer treatment and research. More preclinical and clinical research is needed to determine its efficacy, safety and cancer treatment potential.

Bibliometric research provides quantitative insights and metrics to evaluate research impact, identify trends and collaboration networks and inform decision-making in various fields[20]. A bibliometric study on zerumbone research illuminates its scientific landscape. A study like this can reveal zerumbone research's growth trajectory, key research areas and emerging trends. The study maps collaborative networks and connections between researchers and institutions to identify potential research collaborations and understand global zerumbone scientific engagement. Citation analysis helps identify leading researchers and institutions in the field, assess the impact of zerumbone research and identify research gaps and opportunities for further study[21]. A bibliometric study on zerumbone research provides a comprehensive overview that guides future research, collaborations and decision-making to advance scientific understanding. The current study was designed to bibliometrically study zerumbone research.

MATERIALS AND METHODS

Database selection and search terms: Scopus was chosen as the database for this bibliometric study due to its comprehensive coverage of scientific literature across various disciplines, including medicine, life sciences and social sciences[22]. Scopus provides a wide range of publications and citation data, making it suitable for analyzing the impact of research on zerumbone. The search term used for this study was "Zerumbone". To ensure thoroughness, synonyms and related terms were checked in the MeSH (Medical Subject Headings) database[23] to include all relevant articles related to the compound.

Inclusion criteria: The selection of data and study design followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[24]. The inclusion criteria for articles included being written in English, original studies, being in the final stage of publication (not preprints) and having no time limits. Review articles, conference papers, conference reviews and book chapters were excluded. Data extraction was performed using CSV (Comma-Separated Values) and BibTeX formats, allowing for efficient collection and organization of relevant information from the selected articles. Figure 1 explains the PRISMA steps employed in this study.

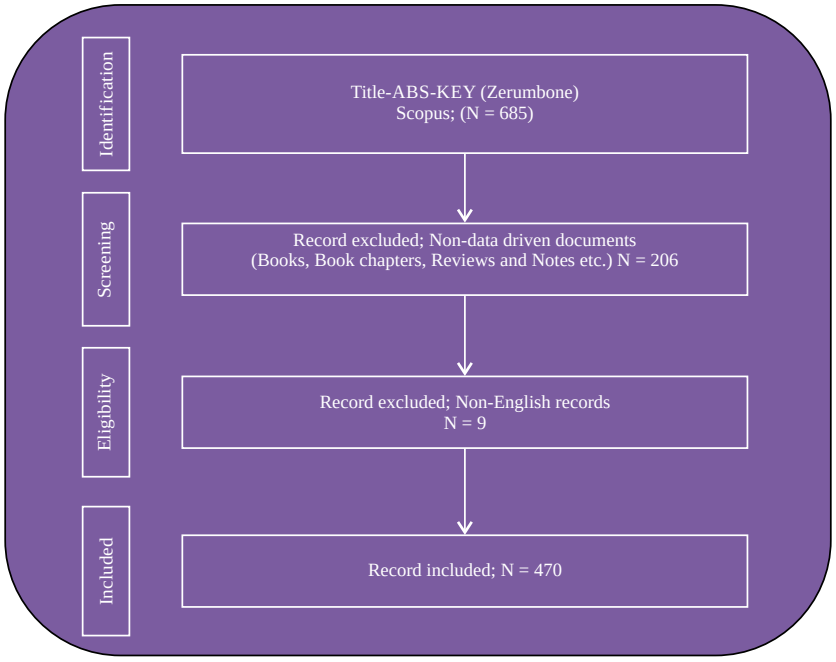

Fig. 1: Selection of data and study design followed the guidelines outlined in the preferred reporting items for systematic reviews and meta-analyses (PRISMA)

Data analysis: The data analysis for this bibliometric study was conducted using two software tools: Bibliometrix and VOSviewer[25,26]. Bibliometrix is a package in R (4.6.1) software that provides a set of functions for bibliometric analysis, including citation analysis, co-authorship analysis and keyword analysis. VOSviewer (1.6.20), on the other hand, is a software tool for constructing and visualizing bibliometric networks, such as co-authorship networks and co-citation networks. The parameters used for data analysis include citation counts, publication trends over time, co-citation networks, co-authorship patterns, keyword frequencies and network visualizations, among others. These parameters help provide insights into the impact, collaboration networks and research trends related to zerumbone.

RESULTS

Annual growth: The time span for the analysis of zerumbone research covers the period from 1960 to 2024 (Fig. 2). This extensive timeframe allows for a comprehensive evaluation of the development and evolution of research on zerumbone over several decades, encompassing both early studies and the most recent advancements in the field. Including such a broad timespan enables a deeper understanding of the historical context, trends and progress in exploring the properties, applications and potential benefits of zerumbone. The distribution of zerumbone research publications varies across different years. In 2023 there were 24 publications, accounting for 5.11% of the total. The year 2022 saw 28 publications, making up 5.96% of the total. The most publications occurred in 2021 and 2020, with 36 publications each, representing 7.66% of the total in both years. In 2019, there were 31 publications (6.60%), while in 2018, there were 35 publications (7.45%). The distribution shows fluctuations in the number of publications over time, with a recent increase in interest and research in zerumbone, particularly in the last decade.

Key contributors: In the field of zerumbone research, key contributors with a significant number of publications include Murakami, A. (24 publications), Abdul, A.B. (21 publications) and Kitayama, T. (20 publications). Other notable contributors include Ohigashi, H., Rasedee, A., Sawada, S., Radhakrishnan, K.V. and Abdelwahab, S.I. Most of the authors contributing to zerumbone research are from Asia, reflecting a strong presence of researchers from this region. About 1,904 authors contributed to zerumbone research, including 5 single-authored documents, advancing understanding of its properties and applications. Among the prominent affiliations in this research area are Universiti Putra Malaysia (66 publications), Kyoto University (29 publications), Kindai University (27 publications), Universiti Malaya (22 publications)

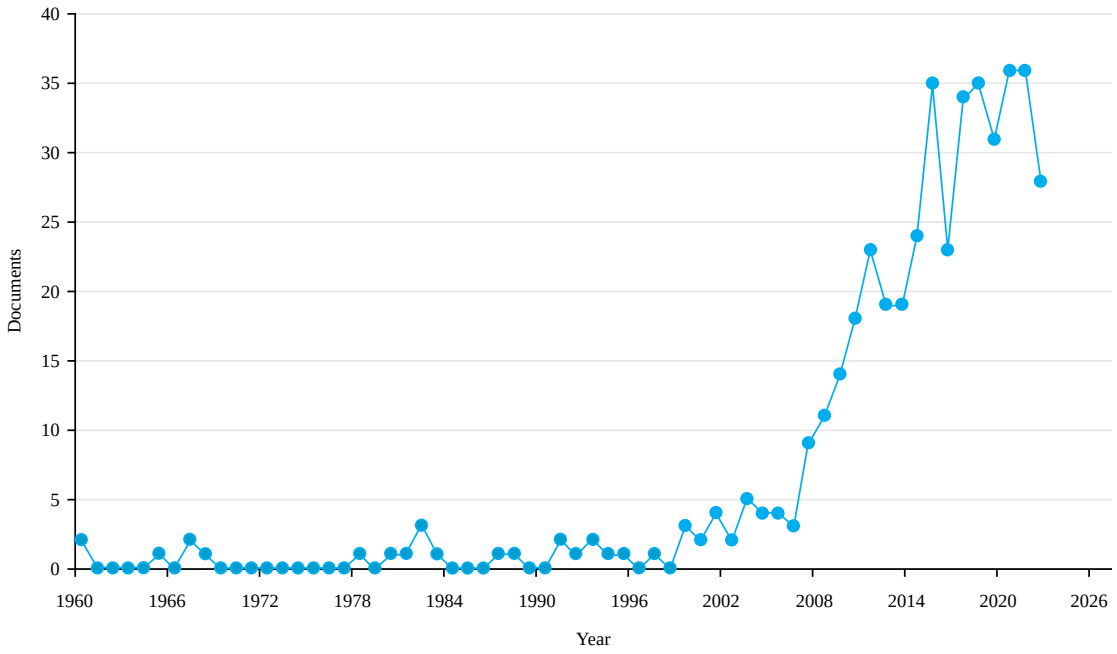

Fig. 2: Annual production

and Universiti Kebangsaan Malaysia (20 publications). The countries with a substantial presence in zerumbone research include Malaysia (110 publications), India (81 publications), Japan (70 publications), China (48 publications) and the United States (43 publications). This regional concentration highlights the importance and interest in studying zerumbone's potential benefits within Asian research communities. The analysis of zerumbone research includes a total of 275 different sources (journals). Some noteworthy source titles in this field are the Journal of Essential Oil Research, Molecules, Evidence-Based Complementary and Alternative Medicine, Natural Product Research and Tetrahedron. It is important to note that this information is based on the provided data and may not encompass the complete landscape of zerumbone research. The sources in zerumbone research are distributed across various subject areas. The majority of the research falls under the categories of biochemistry, genetics and molecular biology, accounting for 23.91% of the sources. Pharmacology, toxicology and pharmaceutics contribute 18.12%, while chemistry constitutes 14.63%. Additionally, medicine and agricultural and biological sciences each represent around 14 and 9% of the sources, respectively. Immunology and microbiology contribute 5.35%, followed by chemical engineering at 4.37%. The remaining subjects, such as environmental science, multidisciplinary studies, nursing and materials science, each contribute less than 2% of the sources. The distribution reflects the multidisciplinary nature of zerumbone research, with a strong emphasis on biochemistry, genetics and molecular biology, as well as pharmacology and chemistry.

Sankey diagram: The previous section provided absolute numbers, but there must be a way to know the relationship between the key contributors such as authors, country and journal. Figure 3 shows how these elements can be represented in a Sankey diagram. A Sankey diagram is a visual representation that can depict the relationship between multiple elements, using the width of lines and the size and color of rectangles. The size of each rectangle can be proportional to the number of publications contributed by that author. The diagram provides a holistic view of the distribution of authors from different countries, their contributions to specific journals and the overall landscape of zerumbone research. Figure 3 highlighted the dynamic nature of zerumbone research by showing changes in the ranking of countries. The top ten most published journals played a significant role in altering the ranking of key contributors. Additionally, Japan surpassed Malaysia as the country with the highest number of publications. These findings emphasized the evolving landscape of zerumbone research and the active involvement of different countries and journals in advancing the field.

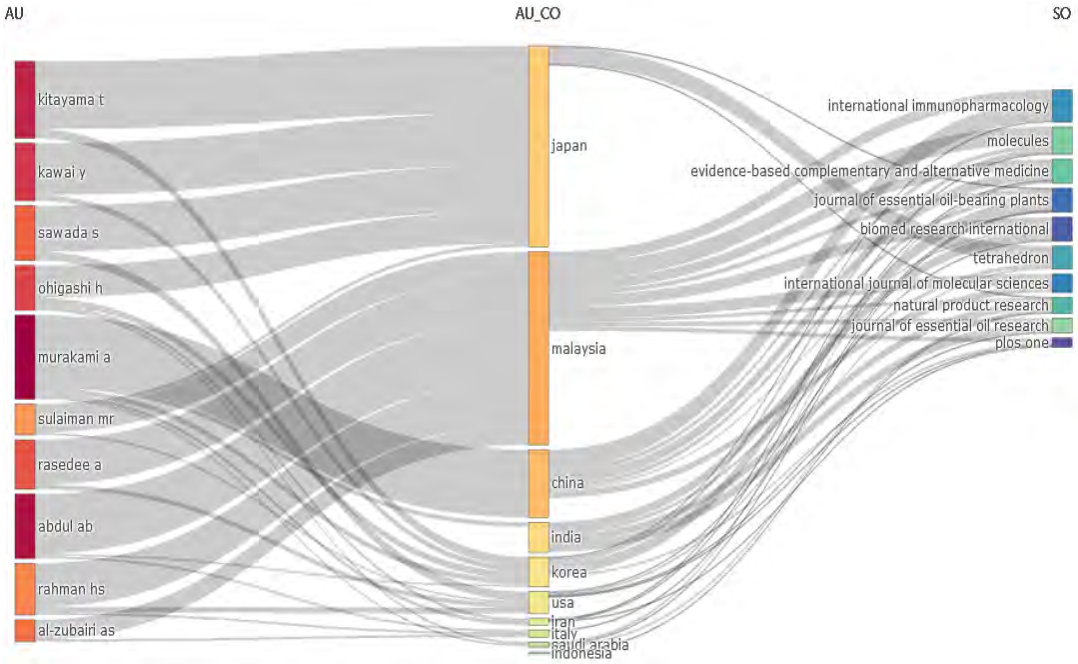

Fig. 3: Sankey diagram

Citation and co-citation analysis

Top-cited documents: The top-cited documents (Table 1) in zerumbone research provide valuable insights into the most influential studies in the field. Topping the list is a paper published in 2002 in Carcinogenesis, which highlights the significant impact of zerumbone in suppressing free radical generation, pro-inflammatory protein production and cancer cell proliferation. Following closely is a study published in Oncogene in 2005, demonstrating how zerumbone inhibits NF-κB and IκBα kinase activation, leading to the suppression of antiapoptotic and metastatic gene expression. Another notable paper published in Cancer Research in 2009 emphasizes the role of zerumbone in enhancing TRAIL-induced apoptosis in colon cancer cells through the induction of death receptors and reactive oxygen species. The list also includes studies exploring cytotoxic components, tumor suppression effects and the activation of drug metabolizing enzymes by zerumbone. These top-cited documents reflect the diverse aspects of zerumbone research and highlight its potential as a valuable compound in cancer treatment and prevention.

Most-cited countries: Mapping of top-cited countries was performed using VOSviewer. With five as a minimum number of documents per country, of the 49 actively involved in zerumbone research and 22 meet the thresholds. Figure 4 is the density visualization of the most-cited countries. In this representation, the intensity of the yellow color indicates the relative density of citations for each country. The circle's circumference represents the citation count, with wider circles indicating higher citation counts. This visualization allows for a quick comparison of the citation densities among the countries in Fig. 4. Figure 4 presented the citation counts for the top-cited countries in zerumbone research. Japan emerges as the most-cited country with 3346 citations, followed closely by Malaysia with 2918 citations. The United States ranks third with 2100 citations. Other countries such as Italy, Thailand, India, South Korea, Taiwan and China also have notable citation counts. These numbers indicate the global interest and collaboration surrounding zerumbone research. While citation counts alone do not determine research quality, they demonstrate the contributions and impact of researchers from these countries in advancing the field of zerumbone.

Authors' local impact: Table 2 presents the local impact of several authors based on different citation metrics. Each author is associated with an element and their h-index, g-index, m-index, total citations (TC), number of publications (NP) and the year of starting publication (PY_start) are provided. Murakami, A. has an h-index of 20, indicating that they have published at least 20 papers that have received 20 or more citations each. Abdul, A.B. has the highest m-index of 0.938, suggesting a relatively high citation rate per paper compared to other authors. In terms of total citations,

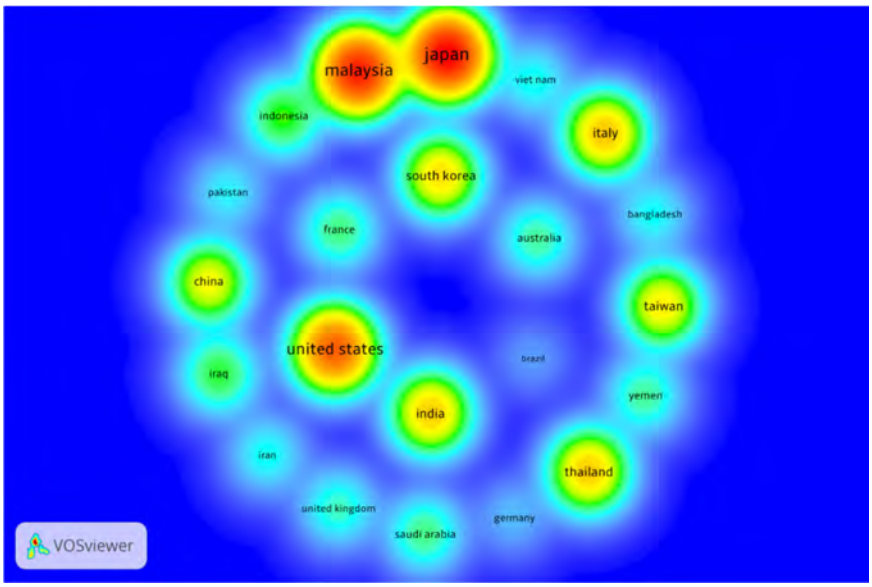

Fig. 4: Density visualization of the most-cited countries

Table 1: Top-cited documents in zerumbone research

Rank	Title	Journal	Year	Citations	Citation average
1	Zerumbone, a Southeast Asian ginger sesquiterpene, markedly suppresses free radical generation, pro-inflammatory protein production and cancer cell proliferation accompanied by apoptosis: The α,β-unsaturated carbonyl group is a prerequisite	Carcinogenesis	2002	307	13.95
2	Zerumbone abolishes NF-κB and IκBα kinase activation leading to suppression of antiapoptotic and metastatic gene expression, upregulation of apoptosis and downregulation of invasion	Oncogene	2005	182	9.58
3	Zerumbone enhances TRAIL-induced apoptosis through the induction of death receptors in human colon cancer cells: Evidence for an essential role of reactive oxygen species	Cancer Research	2009	162	10.80
4	Cytotoxic components of *Zingiber zerumbet*, *Curcuma zedoaria* and *Curcuma domestica*	Phytochemistry	1980	161	3.66
5	Zerumbone, a sesquiterpene in subtropical ginger, suppresses skin tumor initiation and promotion stages in ICR mice	International Journal of Cancer	2004	153	7.65
6	Zerumbone, a tropical ginger sesquiterpene, activates phase II drug metabolizing enzymes	FEBS Letters	2004	152	7.60
7	Zerumbone, a tropical ginger sesquiterpene, inhibits colon and lung carcinogenesis in mice	International Journal of Cancer	2009	146	9.73
8	Identification of zerumbone in *Zingiber zerumbet* Smith as a potent inhibitor of 12-o-tetradecanoylphorbol-13-acetate-induced epstein-barr virus activation	Bioscience, Biotechnology and Biochemistry	1999	130	5.20
9	Novel and known constituents from Buddleja species and their activity against leukocyte eicosanoid generation	Journal of Natural Products	1999	129	5.16
10	Zerumbone induced apoptosis in liver cancer cells via modulation of Bax/Bcl-2 ratio	Cancer Cell International	2007	129	7.59
11	Zerumbone-loaded nanostructured lipid carriers: Preparation, characterization and antileukemic effect	International Journal of Nanomedicine	2013	127	11.55
12	*In vitro* ultramorphological assessment of apoptosis induced by Zerumbone on (HeLa)	Journal of Biomedicine and Biotechnology	2009	123	8.20
13	Zerumbone down-regulates chemokine receptor CXCR4 expression leading to inhibition of CXCL12-induced invasion of breast and pancreatic tumor cells	Cancer Research	2008	123	7.69
14	Antimicrobial activity and essential oils of *Curcuma aeruginosa*, *Curcuma mangga* and *Zingiber cassumunar* from Malaysia	Asian Pacific Journal of Tropical Medicine	2012	120	10.00
15	Effects of selected food factors with chemopreventive properties on combined lipopolysaccharide and interferon-γ-induced IκB degradation in RAW264.7 macrophage	Cancer Letters	2003	119	5.67

Table 2: Authors' local impact

Author	h-Index	g-Index	m-Index	TC	NP	PY_Start
Murakami, A.	20	24	0.8	2066	24	1999
Abdul, A.B.	15	21	0.938	942	21	2008
Kitayama, T.	12	20	0.48	491	20	1999
Ohigashi, H.	12	12	0.48	1346	12	1999
Rahman, H.S.	11	11	1.00	375	11	2013
Rasedee, A.	11	12	0.846	462	12	2011
Abdelwahab, S.I.	10	10	0.625	510	10	2008
Sawada, S.	10	12	0.40	418	12	1999
Kawai, Y.	9	12	0.36	334	12	1999
Perimal, E.K.	9	10	0.60	336	10	2009

TC: Total citations, NP: Number of publications and PY_Start: Year of starting publication

Ohigashi, H., leads with 1346 citations, followed by Murakami, A. with 2066 citations. The number of publications varies among the authors, ranging from 10 to 24. The starting years of publication for these authors range from 1999 to 2013, indicating the duration of their research careers. These metrics provide insights into the local impact of each author, reflecting their citation performance, productivity and longevity in the field. It helps evaluate the contributions and influence of individual researchers within their respective research areas.

Co-citation analysis: The co-citation analysis is a valuable method used in bibliometrics and research evaluation to examine the relationships between scholarly works based on their shared citations. It involves analyzing the co-occurrence of citations between two or more documents, authors or topics to identify patterns and connections within a research field. It is a powerful tool for understanding the intellectual structure, influence and dynamics of a research field. It helps researchers gain insights into the relationships between scholarly works, identify influential authors and papers and track emerging trends in a discipline. Figure 5 depicted the co-citation analysis of the authors. One hundred citations were set as the minimum number of citations of an author. Of the 40929 authors, 27 meet the threshold. For each of the 27 authors, the total strength of the co-citation links with other authors was obtained using VOSviewer. The authors with the greatest total link strength were selected. The number of authors was 27. The total link strength (TLS) of the whole map is 75425, with 351 links between these countries. Three clusters were extracted (blue, red and green). The co-citation analysis of authors reveals the strength of connections between researchers based on their shared citations in the field of zerumbone research. The author with the highest link strength is Murakami, A., TLS of 19906. Following closely is Ohigashi, H., with a TLS of 14897. Koshimizu, K., Kitayama, T., Tanaka, T. and Sawada, S., have noteworthy TLS of 8890, 8666, 7532 and 6916, respectively. These TLSs indicate the frequency and extent to which other researchers co-cite these authors' works. Their co-citation patterns highlight their collective impact and influence on the discourse surrounding zerumbone research.

Keywords frequency: The keyword frequency analysis in bibliometric analysis is valuable for understanding the research landscape and identifying key themes in a field. By examining the frequency of keywords, researchers can map the intellectual structure of a field, track the evolution of research over time and evaluate the impact and dissemination of research. In the provided keyword frequency distribution, "Zerumbone" emerges as the most frequent keyword with 243 occurrences, followed by "*Zingiber zerumbet*" with 58 occurrences, "apoptosis" with 32 occurrences and "Zingiberaceae" with 20 occurrences. Other notable keywords include "essential oil" (17 occurrences), "NF-κB" (16 occurrences) and "inflammation" (11 occurrences). The frequencies of these keywords indicate their relevance and prominence in the literature. Additionally, keywords like "oxidative stress" (10 occurrences), "antimicrobial" (9 occurrences), "breast cancer" (9 occurrences) and "natural products" (8 occurrences) highlight important areas of research. Keyword frequency analysis provides insights into research focus and trends. It helps researchers make informed decisions and contribute to advancing knowledge in their respective fields.

Thematic map: Table 3 and Fig. 6 provide information about different clusters identified in a thematic map of zerumbone's research, along with their parameters and components. Each cluster is characterized by its Callon Centrality (relevance) and Callon Density (development) scores, which measure the cluster's importance and density of connections. The "Keywords" column lists the terms associated with each cluster, providing a glimpse into the thematic focus of the

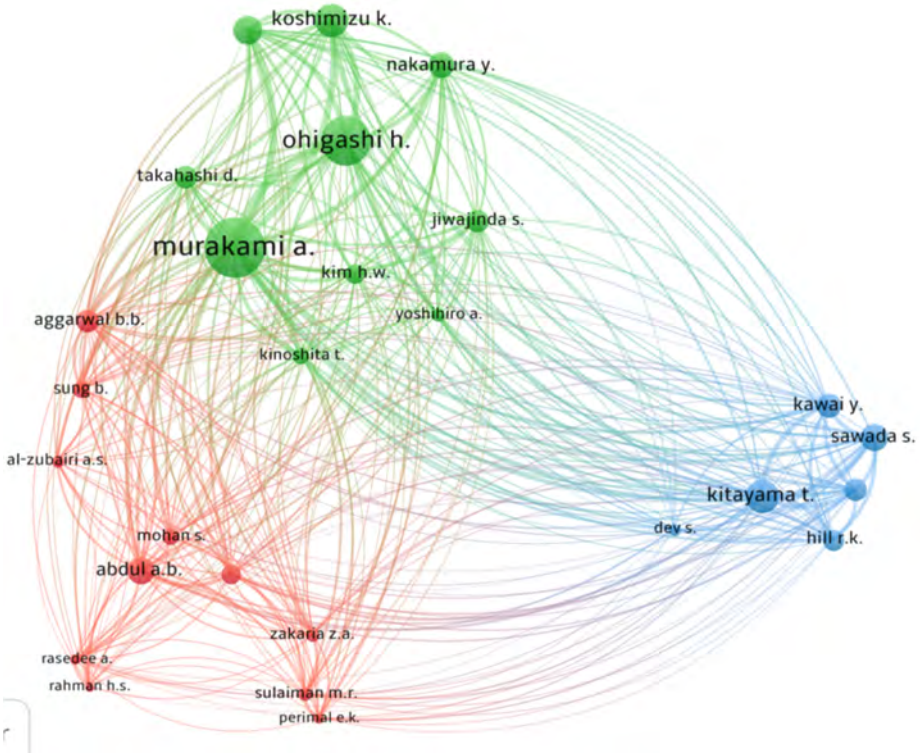

Fig. 5: Co-citation analysis of the authors

One hundred citations were set as the minimum number of citations of an author. Of the 40929 authors, 27 meet the threshold. For each of the 27 authors, the total strength of the co-citation links with other authors was obtained using VOSviewer

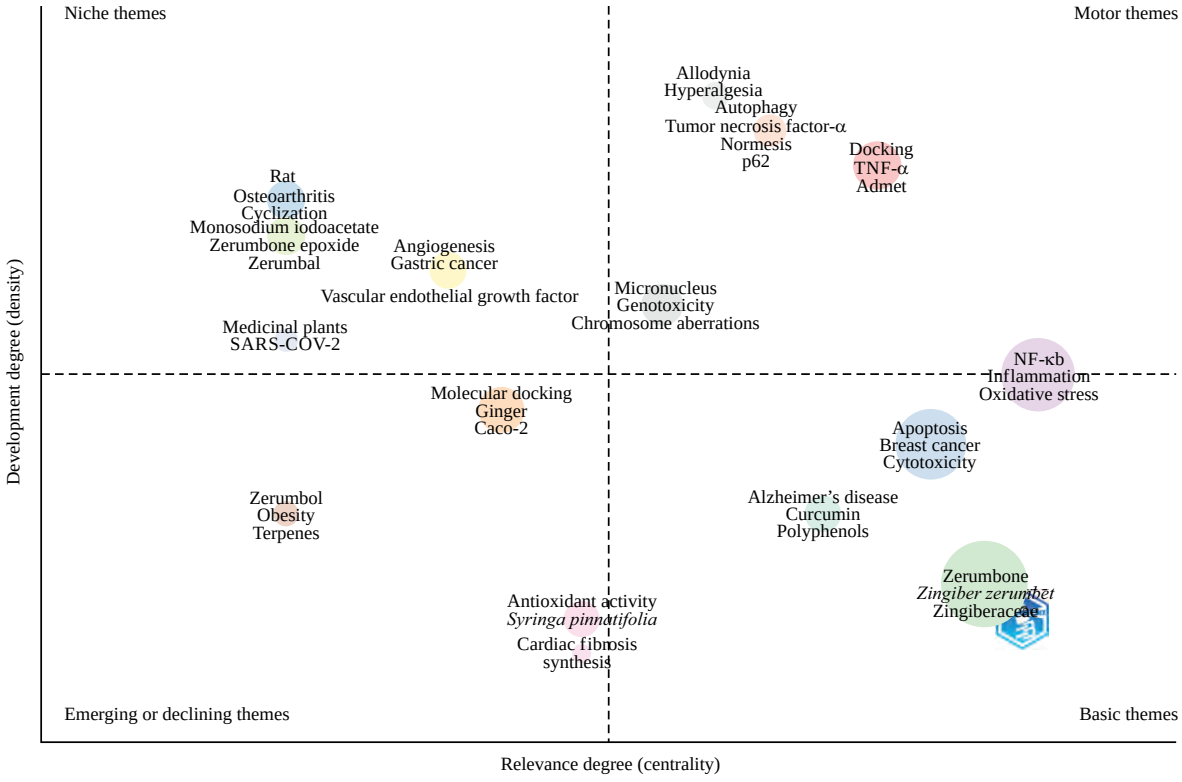

Fig. 6: Thematic map

Table 3: Clusters of the thematic map and their parameters and components

Cluster	Callon centrality	Callon density	Terms of the clusters	Classification
Docking	0.83	80.56	Docking, TNF-α, ADMET, atherosclerosis, caspase-3, cervical cancer, chaperonin, DFT, HPLC, humulene, md simulation, NMR	Motor
Apoptosis	1.21	52.85	Apoptosis, breast cancer, cytotoxicity, anti-cancer, cisplatin, combination therapy, cell cycle arrest, cell proliferation, immunomodulation, p53, stat3, acute lung injury, cell cycle, cell migration, leukemia, proliferation, reactive oxygen species, zerumbone-loaded nanostructured lipid carrier, Bcl-2, cancer cells, caspase, cervical intraepithelial neoplasia, cytokine, heat shock protein, HO-1, HSP27, innate immunity, mitochondrial pathway, nanostructured lipid carrier, NRF2, tubulin and tunel assay	
Zerumbone	1.96	47.78	Zerumbone, *Zingiber zerumbet*, Zingiberaceae, essential oil, essential oil composition, antimicrobial, *Zingiber zerumbet* Smith, cytotoxic, sesquiterpenes, antibacterial activity, β-caryophyllene, antimicrobial activity, GC/MS, ROS, antifungal, antiproliferative activity, candida albicans, flavonoids hepatotoxicity, inhalation, monoterpenes, subcritical water extraction, toxicity, two-component system, *Zingiber cassumunar*, *Zingiber montanum*, α-humulene, (e)-nerolidol, 8-hydroxy-α-humulene, anti-biofilm, antibiofilm activity, asthma, azazerumbone, *Curcuma heyneana*, dementia, flow cytometry, hydrodistillation, MCF-7, metabolic engineering, palladium, paracetamol, phytoconstituents, phytotherapy, response surface methodology, rhizome, SEM, urease and zingiber	Basic
NF-κB	2.24	60.37	NF-κB, inflammation, oxidative stress, antioxidant, natural products, sesquiterpene, neuropathic pain, anti-inflammation, colorectal cancer, metastasis, phytochemicals, anticancer, chemoprevention, essential oils, macrophages, AKT, cancer, cell invasion, COX-2, diabetic retinopathy, glutathione, mapks, neuroinflammation, acute liver injury, anti-inflammatory, antioxidants, carcinogenesis, chronic constriction injury (CCI), cytochrome p450, detoxification, DNA repair, DPPH, ETBF, gastritis, glioblastoma multiforme, glutathione s-transferase, helicobacter pylori, hepatoprotective, IKK, lipid peroxidation, macrophage, microglia, migration, nephrotoxicity, NF-JB, nitric oxide, phytochemical, radiation, rats, TLR4, toll-like receptor and triple-negative breast cancer	Motor
Molecular docking	0.16	55.00	Molecular docking, ginger, CACO-2, radiosensitivity, signaling pathway, sonic hedgehog and structure-activity relationship	Emerging or declining
Zerumbol	0.00	50.00	Zerumbol and terpenes	Emerging or declining
Antioxidant activity	0.17	44.44	Antioxidant activity, syringa pinnatifolia and cardiac fibrosis	Emerging or declining
Micronucleus	0.21	63.67	Micronucleus, genotoxicity, chromosome aberrations and CHO	Motor
Alzheimer's disease	0.44	50.00	Alzheimer's disease, curcumin, polyphenols and anti-inflammatory activity	Basic
Autophagy	0.42	81.25	Autophagy, hormesis, P62 and ubiquitin-proteasome system	Motor
Medicinal plants	0.00	62.50	Medicinal plants and SARS-COV-2	Niche
Synthesis	0.17	33.33	Synthesis	Niche
Cyclization	0.00	73.61	Cyclization, zerumbone epoxide, zerumbal and zerumbenone	Niche
Angiogenesis	0.13	71.88	Angiogenesis, gastric cancer, vascular endothelial growth factor and vascular endothelial growth factor receptor	Niche
Allodynia	0.25	83.33	Allodynia, hyperalgesia and tumor necrosis factor-α	Motor
Obesity	0.00	50.00	Obesity	Niche
Rat	0.00	76.25	Rat, osteoarthritis, monosodium iodoacetate and neuropeptides	Niche

cluster. These terms represent the key concepts and topics that define the cluster's content. The "Classification" column categorizes each cluster based on its characteristics. The classification categories include Motor, Basic, Emerging or Declining and Niche. These classifications help group clusters based on their relevance, importance and current status within the thematic map. For example, the "Docking" cluster has a high Callon Centrality and Callon Density, indicating its significance and dense connectivity. The associated keywords suggest that this cluster is related to docking, TNF-α, ADMET, atherosclerosis and other topics. It is classified as a "Motor" cluster, indicating its importance in the thematic map. Similarly, other clusters such as "Apoptosis," "Zerumbone," and "NF-κB" also have their respective centrality, density, keywords and classifications provided. The table also includes clusters classified as "Emerging or Declining" and "Niche," which suggests their relative importance and relevance in the thematic map. In summary, the table offers a concise overview of the different clusters within the thematic map, their centrality and density scores, key terms and their classification. This information helps researchers and readers understand the composition and significance of each cluster in the broader context of the thematic map.

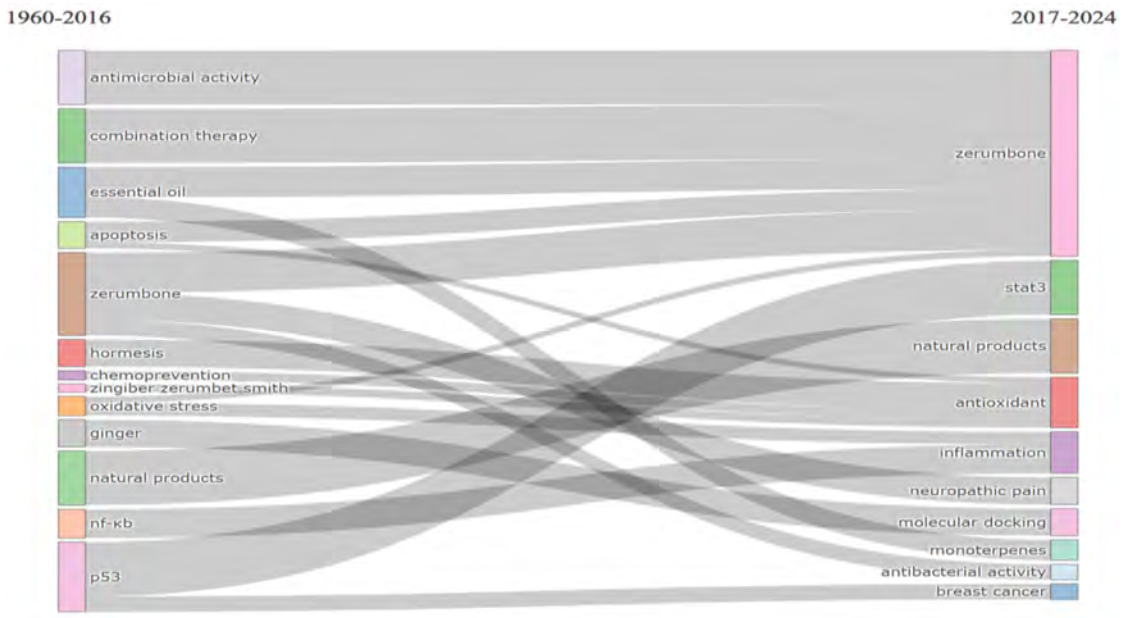

Fig. 7: Thematic evolution

Thematic evolution: The thematic evolution analysis for zerumbone research revealed notable changes and trends over time. The size of the rectangles in Fig. 7 represented the strength or prominence of each cluster. The analysis identified a turning point in the evolution of zerumbone research in 2016. Before 2016, there were 13 clusters identified, indicating a diverse range of research topics related to zerumbone. Some of the prominent clusters during this period included antimicrobial activity, apoptosis, chemoprevention, combination therapy, essential oil, ginger, hormesis, natural products, NF-κB, oxidative stress, p53, zerumbone and *Zingiber zerumbet* Smith. However, after 2016, the number of clusters decreased to 10, suggesting a consolidation or narrowing down of the research focus. The clusters that emerged or remained prominent during this period included zerumbone, antioxidant, inflammation, breast cancer, stat3, antibacterial activity, neuropathic pain and molecular docking. This shift in thematic clusters indicates a transition in the research landscape of zerumbone. The focus expanded from antimicrobial activity, apoptosis, chemoprevention and essential oils in the earlier period to include topics such as antioxidant, inflammation, breast cancer and molecular docking in the later period. Overall, this analysis highlights the changing research trends and shifts in emphasis within the field of zerumbone research. It suggests that after 2016, researchers focused more on specific areas such as antioxidant properties, inflammation, breast cancer and molecular docking.

Emerging themes: Figure 8 illustrated emerging themes in zerumbone research, including cisplatin combination, antimicrobial activity, molecular docking, colorectal cancer, combination therapy, cytotoxicity, anti-cancer effects, inflammation and oxidative stress. They contribute to advancing knowledge and understanding of zerumbone's therapeutic applications.

Mapping of co-authorship

Collaborative research: Figure 9a in the analysis conducted using VOSviewer provides a density visualization of country collaborations in zerumbone research. Countries' collaboration is ranked based on the total link strength (TLS), which measures the strength of connections between countries regarding co-authorship. According to Fig. 9a, Malaysia has the highest total link strength (TLS) of 55, indicating strong collaboration with other countries in zerumbone research. The United States follows with a TLS of 39, indicating significant collaboration as well. Japan has a TLS of 27, indicating moderate collaboration in this research area. Iraq and Saudi Arabia have TLS values of 22 and 17, respectively, suggesting their involvement in collaborative efforts but to a lesser extent than the top three countries. Figure 9b presented a temporal analysis of co-authorship among countries using overlay visualization. The countries with yellow nodes indicate recent involvement in multinational research in zerumbone. Pakistan and Brazil have recently started participating in collaborative efforts related

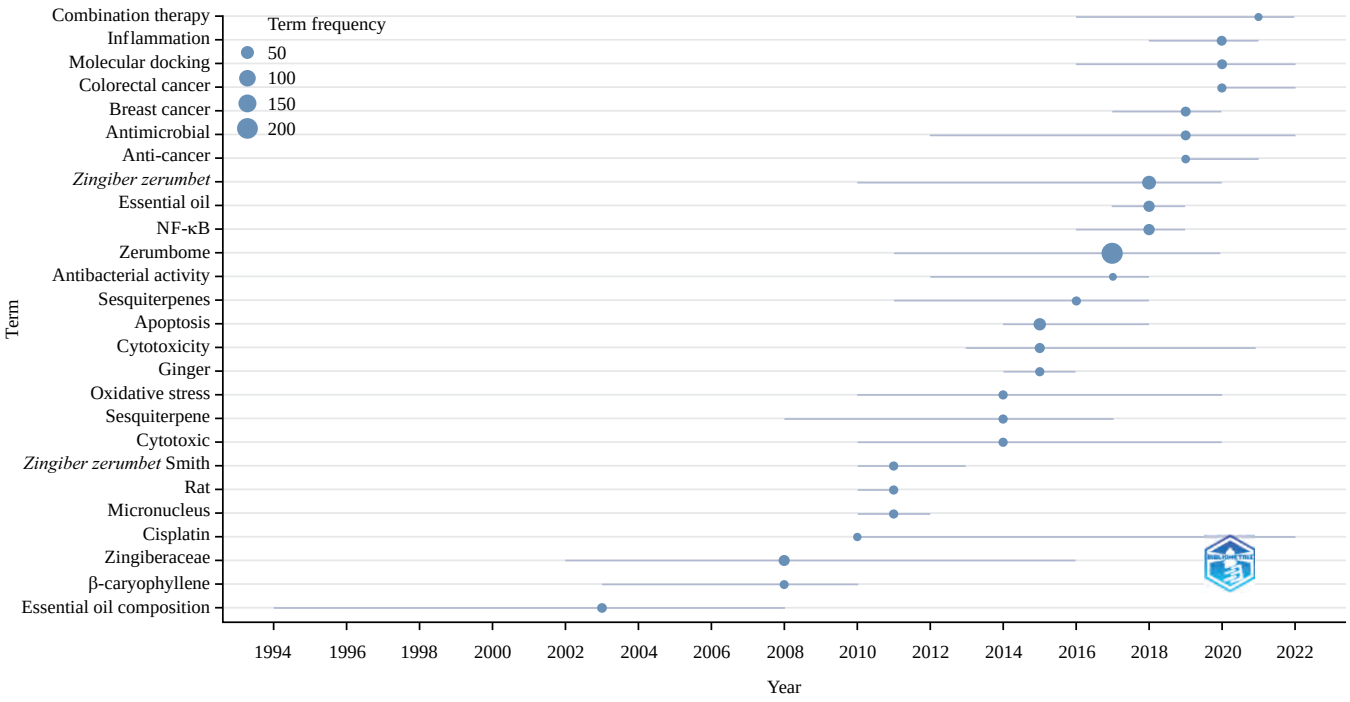

Fig. 8: Emerging themes

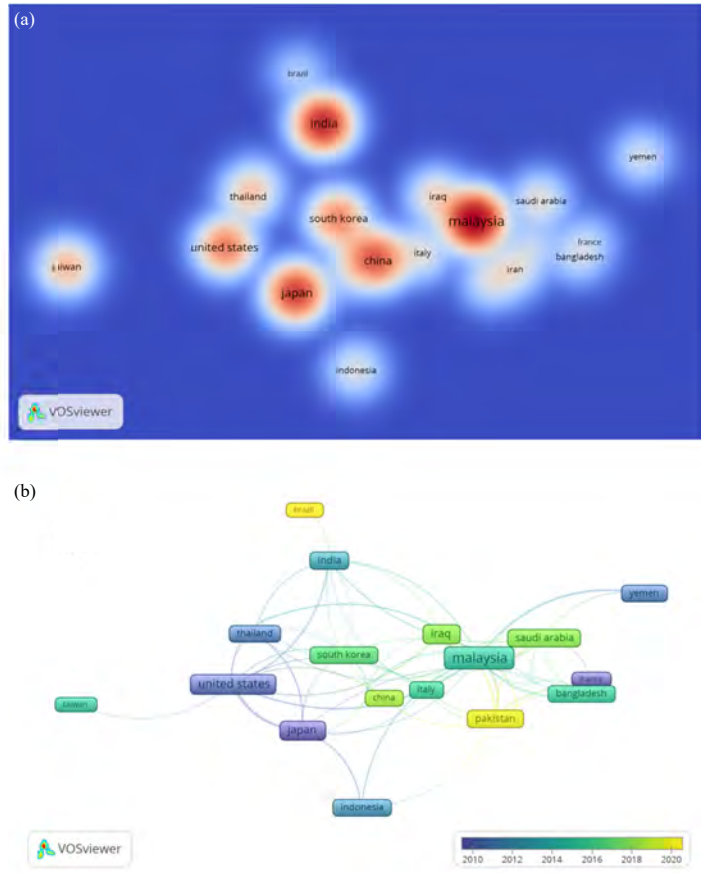

Fig. 9(a-b): Mapping of co-authorship and global collaboration

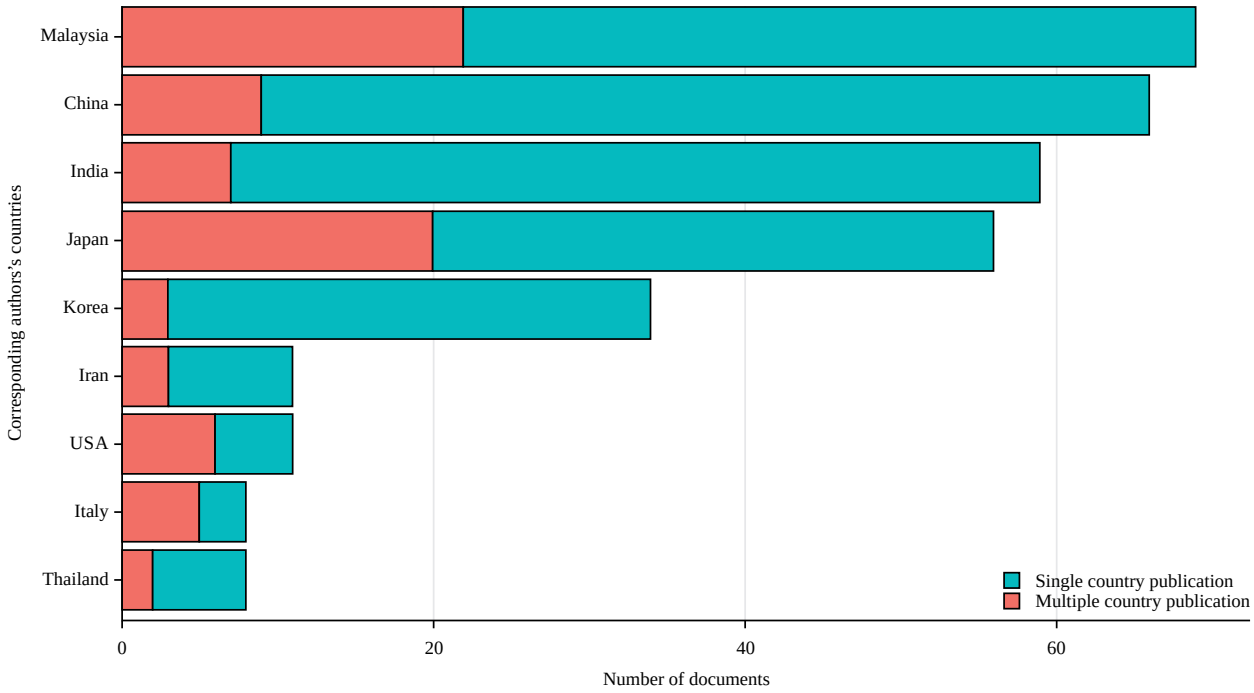

Fig. 10: Single and multiple-country publications

to zerumbone research. Overall, Fig. 9a-b provide insights into the collaborative landscape of zerumbone research, highlighting the countries with the strongest collaboration (based on TLS) and indicating the recent involvement of certain countries through the overlay visualization. These visualizations help researchers understand the patterns and trends in international collaboration within zerumbone research.

Figure 10 provides information on the frequency of single-country publications and the MCP ratio (multiple-country publications ratio) for different countries in a specific analysis based on the corresponding author's country affiliation. The MCP ratio represents the proportion of articles in which at least one author is affiliated with a country other than the corresponding author. According to the table, Italy has the highest MCP ratio at 0.625, indicating that a significant portion of articles from Italy involved authors with affiliations in other countries. The USA follows closely with an MCP ratio of 0.545, suggesting much collaboration between US authors and authors from different countries. Japan ranks third with an MCP ratio of 0.357, indicating a moderate level of international collaboration in their publications. Malaysia, Iran and Thailand have MCP ratios of 0.319, 0.273 and 0.25, respectively, suggesting a considerable involvement of international authors in their publications. China, India and Korea have lower MCP ratios of 0.136, 0.119 and 0.088, respectively, indicating a relatively lower level of international collaboration in their research output. Overall, the MCP ratio provides insights into the extent of international collaboration in scientific publications, specifically regarding the corresponding author's country affiliation. Figure 10 highlights the varying levels of international collaboration across different countries, with Italy and the USA exhibiting higher levels than other nations.

DISCUSSION

The main objective of this study was to examine the growth, impact, thematic evolution and international collaboration patterns in zerumbone (Fig. 11) research. To achieve this, original articles were selected as the primary source of data, excluding reviews, book chapters and editorials. This approach was chosen to ensure a focus on the original research contributions and to capture the most up-to-date and detailed information regarding the thematic trends and collaborative networks in the field of zerumbone.

Asian countries, including Japan, Malaysia, India and China, have emerged as leaders in zerumbone research, surpassing other nations. This can be attributed to the fact that Asia serves as the native region of the plant[27], providing a natural advantage for conducting research on zerumbone. Additionally, the ease of extracting the compound from the

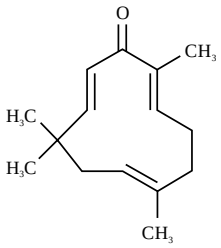

Fig. 11: Chemical structure of zerumbone

essential oils of the plant's rhizomes through simple methods like steam distillation and crystallization using hexane[1] contributes to the accessibility of the resource in these countries. Furthermore, the presence of well-established research expertise and advanced laboratories in these four Asian nations has significantly enriched the quality and breadth of zerumbone research conducted in these regions.

By examining the Sankey diagram in Fig. 3, one can gain a holistic view of the distribution of authors from different countries, the journals they contribute to and the overall landscape of zerumbone research. The diagram showcases the dynamic nature of the field by illustrating changes in the rankings of journals and countries over time[28]. Notably, the top ten most published journals have played a crucial role in reshaping the ranking of key contributors[29]. Furthermore, the diagram reveals that Japan has surpassed Malaysia as the country with the highest number of publications in zerumbone research. These insights underscore the evolving landscape of zerumbone research and highlight the active involvement of various countries and journals in advancing the field. The Sankey diagram provides a visual representation that helps researchers and stakeholders understand the complex interplay between authors, countries and journals in the context of zerumbone research.

The most cited articles in zerumbone research cover a wide range of topics, including its anti-inflammatory, anticancer, antioxidant and antimicrobial properties. These articles have garnered significant attention due to their impactful findings and contributions to understanding zerumbone's potential therapeutic applications. Several key themes emerge from these highly cited articles: Ability of zerumbone to suppress free radical generation, inhibit NF-κB activation, induce apoptosis, downregulate invasion and modulate gene expression involved in cancer progression. Additionally, the articles highlight the effectiveness of zerumbone in inhibiting tumor initiation and promotion, activating drug-metabolizing enzymes and exhibiting antimicrobial activity[5,9,10,16,17,19,30-37]. These studies have provided valuable insights into the mechanisms of action and potential applications of zerumbone, making them highly influential in the field of zerumbone research.

Based on the provided bibliometric data, Murakami, A. (Japan) and Abdul, A.B. (Malaysia) are two authors who have made significant contributions to zerumbone research. Murakami, A. has an h-Index of 20, indicating that they have published at least 20 papers that have each received at least 20 citations. Their g-Index of 24 suggests that their top 24 papers collectively received a total of 576 citations. The m-Index of 0.8 represents the ratio of the h-Index to the g-Index, indicating a relatively high impact compared to the number of highly cited papers. With a total citation count (TC) of 2066 and 24 published papers (NP) since 1999, Murakami, A. has been actively contributing to zerumbone research for a considerable period. Abdul, A.B. has an h-Index of 15, indicating at least 15 of their papers have received 15 citations each. Their g-Index of 21 suggests that their top 21 papers collectively received a total of 441 citations. The m-Index of 0.938 indicates a high impact relative to the number of highly cited papers. With a total citation count (TC) of 942 and 21 published papers (NP) since 2008, Abdul has also made noteworthy contributions to zerumbone research in a relatively shorter time frame. While these bibliometric indicators provide some insight into the impact of these authors, it's important to consider other factors, such as the quality and significance of their research, collaborations and contributions to the field beyond the provided metrics.

The thematic map (Table 3 and Fig. 6) in zerumbone research obtained using Bibliometrix software reveals several distinct clusters and themes within the field. Here's a summary of the major themes identified in the map:

- **Docking:** This cluster focuses on molecular docking studies involving zerumbone and related compounds. It explores topics such as the interaction of zerumbone with target proteins, computational simulations and analytical techniques like HPLC and NMR[14,15,18,38,39]
- **Apoptosis:** This cluster centers around the role of zerumbone in inducing apoptosis (programmed cell death) in various cancer types. It encompasses studies on cytotoxicity, combination therapies, cell cycle regulation, reactive oxygen species (ROS) and the modulation of apoptotic pathways[5,17,19,40]
- **Zerumbone:** This cluster revolves around the fundamental aspects of zerumbone itself, including its chemical properties, essential oil composition, antimicrobial and cytotoxic activities, as well as studies on its derivatives and bioactive constituents[41,42]

- **NF-κB:** This cluster focuses on the modulation of the NF-κB signaling pathway by zerumbone. The NF-κB is a key transcription factor involved in inflammation and cancer progression. Studies in this cluster explore the effects of zerumbone on NF-κB-mediated processes, including inflammation, oxidative stress, metastasis and chemoprevention[11,12]
- **Molecular docking:** This cluster specifically highlights studies that utilize molecular docking techniques to investigate the interaction between zerumbone and various targets, such as proteins involved in signaling pathways and radiosensitivity[43,44]
- **Zerumbol:** This declining cluster focuses on the compound zerumbol and its associations with terpenes[2,45]
- **Antioxidant activity:** This emerging cluster explores the antioxidant properties of zerumbone and its potential effects on conditions like cardiac fibrosis[46]
- **Micronucleus:** This cluster investigates the genotoxic effects of zerumbone, specifically focusing on micronucleus formation, chromosome aberrations and genotoxicity testing[47-50]
- **Alzheimer's disease:** This cluster explores the potential of zerumbone and related compounds in the context of Alzheimer's disease, including their anti-inflammatory activity and effects on polyphenol metabolism[43,51,52]
- **Autophagy:** This cluster examines the role of zerumbone in autophagy, a cellular process involved in maintaining cellular homeostasis and degradation of damaged components[53,54]
- **Medicinal plants:** This niche cluster delves into the broader context of medicinal plants, including their potential applications in the context of SARS-CoV-2 (COVID-19)[4]
- **Synthesis[55], cyclization[13,56], angiogenesis[11,12], allodynia[57], obesity[58] and rat[59,60]:** These niche clusters touch upon specific aspects related to zerumbone research, such as its synthesis, cyclization reactions, angiogenesis in gastric cancer, pain-related phenomena like allodynia and hyperalgesia, obesity-related studies and the use of rat models in research

These thematic clusters represent the major areas of focus and trends within the field of zerumbone research, providing insights into the diverse aspects of its biological activities and potential applications.

The emerging themes in zerumbone research (Fig. 8), such as cisplatin, antimicrobial activity, molecular docking, colorectal cancer, combination therapy, cytotoxicity, anti-cancer effects and inflammation, play significant roles in shaping the future research in this area. Synergistic effects of cisplatin and zerumbone improve cancer treatment[3]. Zerumbone's antimicrobial activity against drug-resistant strains was explored[8]. Molecular docking studies uncovered mechanisms of action[14,15,18,38,44]. Colorectal cancer's molecular targets and signaling pathways are also trending. These themes advance knowledge and guide therapeutic strategies.

Collaboration plays a crucial role in research for several reasons[61]. Firstly, collaboration allows researchers to pool their expertise, skills and resources, leading to more comprehensive and robust research outcomes[62]. Collaboration fosters innovation and creativity in problem-solving by bringing together individuals with diverse perspectives and knowledge[63]. Collaborative research also promotes knowledge sharing, enabling researchers to access a broader range of data, methodologies and techniques[64]. Mapping co-authorship in bibliometrics provides valuable insights into research collaboration patterns. By visualizing co-authorship networks, researchers can identify key collaborators, institutions and countries involved in a particular research field. This mapping helps reveal the extent and nature of collaborations, highlighting trends and dynamics within the scientific community. Understanding co-authorship patterns can aid in identifying potential research partners, fostering interdisciplinary collaborations and promoting knowledge exchange among researchers[65]. While, Japan emerges as the most collaborating country according to VOSviewer mapping and its total link strength (TLS) score, it is important to note that collaboration is not limited to a single country or region. Collaborations can occur on a global scale, transcending geographical boundaries. In the case of Italy, even though it is not an Asian country, it can benefit from collaborating with Asian countries in zerumbone research. Collaborative efforts between Italy and Asian countries can bring together diverse expertise, resources and perspectives to advance research in this field and achieve mutually beneficial outcomes.

CONCLUSION

This thorough bibliometric study offers insightful information about the state of zerumbone research. According to the analysis, there has been a significant increase in research since 1960, especially in recent years, indicating growing interest in the phytochemistry and pharmacology of zerumbone. Underscoring the dynamic nature of collaborations and publication patterns is the shifting landscape of the most productive researchers when taking into account affiliated journals. Important research areas like apoptosis, molecular docking, NF-κB and antioxidant activity were clarified by the identified thematic clusters. The results of this study offer a thorough understanding of the patterns,

partnerships and new areas of zerumbone research, directing subsequent research and advancing scientific understanding in this area. Recommendations include diversifying data sources, considering qualitative assessments, exploring emerging themes and fostering interdisciplinary and international collaborations for further advancement in zerumbone research.

LIMITATIONS

A drawback of this study is its sole dependence on data acquired from the Scopus database. Although Scopus is a comprehensive resource, it may only encompass some pertinent publications in the domain of zerumbone research. An additional constraint of this study is its exclusive focus on articles published in English. The decision to exclude non-English articles may introduce a potential bias and result in omitting pertinent research in other languages. Bibliometric analyses primarily concentrate on published articles, potentially disregarding unpublished or non-peer-reviewed research, resulting in a tendency to favor positive outcomes. Researchers may reference their work more frequently, potentially introducing a bias when assessing research influence or impact.

SIGNIFICANCE STATEMENT

This bibliometric study aimed to quantitatively analyze the impact, trends, collaborations and scientific landscape of zerumbone research, a versatile monosesquiterpene compound derived from the *Zingiber zerumbet* Smith plant. The key findings revealed a significant expansion of zerumbone research over the years, with notable contributions from researchers such as Murakami, A. and Kitayama, T. The thematic map identified major clusters related to apoptosis, docking, NF-κB, angiogenesis, Alzheimer's disease and antioxidant activity, categorizing them as niche, basic, motor, emerging or declining themes. The analysis also highlighted turning points and trending topics in zerumbone research, including cisplatin combination, antimicrobial activity, molecular docking, colorectal cancer and oxidative stress. These findings provide a comprehensive overview that can guide future research, collaborations and decision-making, ultimately advancing our scientific understanding of zerumbone and suggesting potential avenues for further investigation.

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