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Original Research Article

Bibliometric Analysis of Medicinal Plants from Brunei Darussalam: Uncovering Novel Anticancer Targets

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ABSTRACT

Brunei Darussalam boasts a rich biodiversity of medicinal plants, including species like *Piper betel*, *Piper sarmentosum*, *Piper crocatum*, and agarwood, which have demonstrated anticancer properties in previous studies. This bibliometric analysis aimed to explore research trends related to these plants and anticancer activity. A Scopus database search conducted on July 27th, 2024, yielded 210 relevant articles using the keywords "*Piper betel*" OR "*Piper sarmentosum*" OR "*Piper crocatum*" OR "Agarwood" AND "Cancer." VOSviewer was employed for data analysis and visualization. Results indicate a strong association between oral cancer and the four target plants, with agarwood being the second most frequently connected keyword. Notably, research collaboration between these two areas remains limited, suggesting a potential research gap. While East Asian researchers, particularly from Chung Shan Medical University in Taiwan, have been at the forefront of this field, the absence of research originating from Brunei Darussalam presents a significant opportunity for local investigation. Cancer Letters (Elsevier), which has published ten relevant articles, emerges as a potential target journal for future research in this domain. This bibliometric analysis provides valuable insights into research trends and potential avenues for future investigations into the anticancer properties of these Bruneian medicinal plants.

Keywords: Agarwood, Brunei Darussalam, medicinal plants, Oral cancer.

Introduction

Brunei Darussalam, endowed with rich biodiversity, harbors a wealth of medicinal plants that have been integral to traditional healthcare practices for generations. These plants present a promising path for the identification of new medicinal compounds because they are ingrained in the ecological and cultural legacy of the nation. Traditional knowledge has long recognized the efficacy of these plants in addressing various ailments, especially for the indigenous people of Borneo Island in general and Brunei Darussalam in particular. However, scientific validation of their medicinal values remains largely untapped.[1-3] Several medicinal plants grow in Brunei Darussalam whose properties have been studied quite a lot, including *Piper betel*, *Piper sarmentosum*, *Piper crocatum*, and *Aquilaria malaccensis* (agarwood). Some of these plants are known to have various therapeutic properties, including anticancer, antiproliferation, neuropharmacological, analgesic, antioxidant, antiulcerogenic, hepatoprotective, antifertility, antibacterial, antifungal, anti-inflammatory, antineoplastic, antipyretic, anti-hyperglycemic, anti-allergic, and many more.[4-7] Among these various properties, one that is quite interesting is the efficacy of these medicinal plants as anticancer.

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Even with improvements in traditional therapies, cancer is still a major worldwide health concern. There is now more interest in investigating alternative therapeutic approaches due to the increasing prevalence and frequently crippling side effects of synthetic chemotherapeutics.[8] Medicinal plants have become a promising field of study for cancer because of their abundance of bioactive chemicals. For ages, traditional medical systems have used these natural medicines to treat a variety of illnesses, including cancer.[9] While the anticancer properties of certain Bruneian plants, such as *P. betel*, *P. sarmentosum*, *P. crocatum*, and agarwood, have garnered some research attention, a comprehensive understanding of the broader medicinal plant landscape and its anticancer potential remains limited. Bibliometrics is a quantitative research method that employs statistical and mathematical techniques to analyze academic publication patterns and trends within a specific research field. By examining citations, authorship, and other bibliographic data, bibliometric studies can assess the development and impact of research topics. As there are currently no bibliometric analysis reports on the potential of medicinal plants from Brunei Darussalam as anticancer, this study aims to assess existing research on these Bruneian medicinal plants in the context of cancer treatment. By mapping research trends, identifying knowledge gaps, and highlighting potential research avenues, this study seeks to contribute to the sustainable utilization of Brunei's plant resources and inform the development of evidence-based herbal medicines.

Materials and Methods

Materials

For visualizing the outcomes of our analysis, we employed VOSviewer 1.6.20, a software tool developed by the Center for Science and Technology Studies at Leiden University (https://www.vosviewer.com/). The data analyzed in this study was collected from the Scopus database (https://scopus.com/sources.uri?zone=TopNavBar&origin=searchbasic), a comprehensive, complete, and reliable citation database, on July

27th, 2024. It is important to acknowledge that access to Scopus in this research was facilitated by Universitas Airlangga, Surabaya, Indonesia.

Method

Preparation for data collection

The approach used was bibliometric analysis with the Scopus database. A single search was conducted with multiple keywords to identify relevant articles. Apart from analyzing keywords, articles, and journals, analysis was also carried out on the authors, institutions, and the researchers' countries of origin. This bibliometric analysis provides an overview of research developments that have been reported for this scope and information about potential cooperation partners, including appropriate scientific journals to publish related research reports. This study adopted a method as reported by our previous researches.[10,11] The collected data were analyzed according to the procedures outlined in Figure 1.

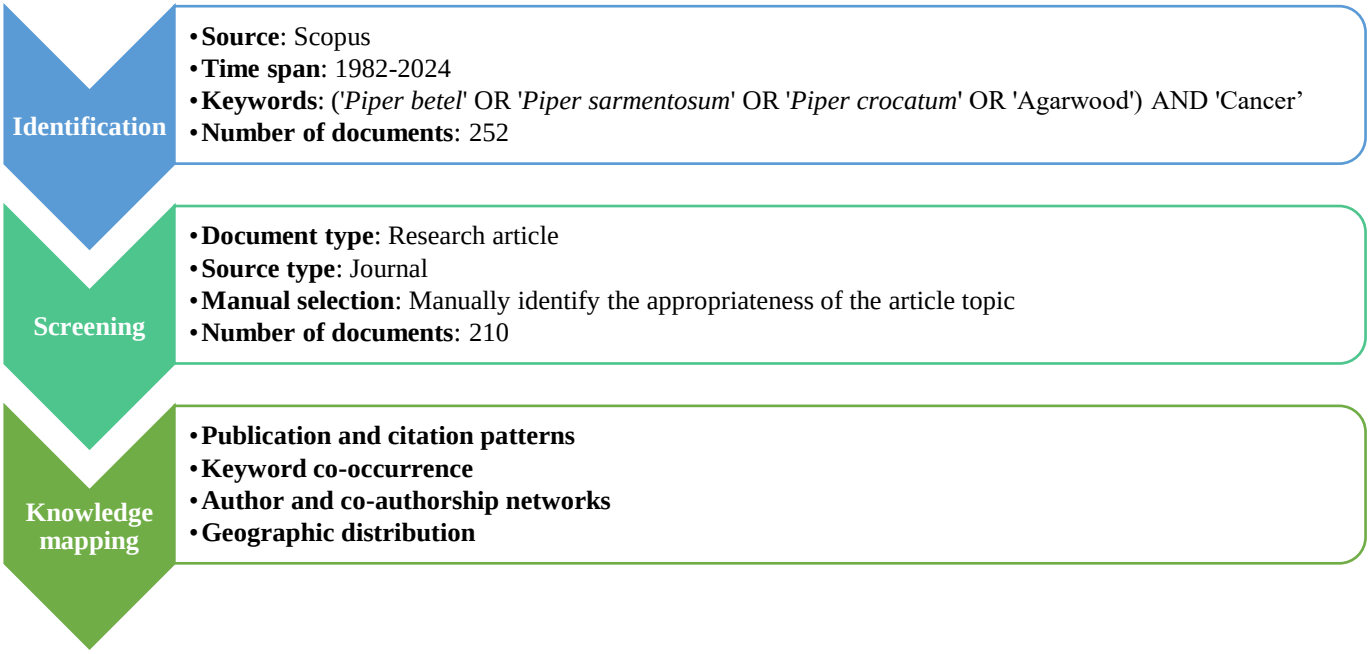


Figure 1: Diagram flow of the research.

Determination of search keywords

To comprehensively identify relevant literature on the anticancer potential of *P. betel*, *P. sarmentosum*, *P. crocatum*, and agarwood, a two-level keyword search strategy was employed. A combination of keywords was used to target articles with these plant species as the subject and cancer as the therapeutic focus. The search string "TITLE-ABS-KEY ('*Piper betel*' OR '*Piper sarmentosum*' OR '*Piper crocatum*' OR 'Agarwood') AND 'Cancer' was used to limit the search to articles where these keywords appeared in the title, abstract, or keyword list. This approach maximized the retrieval of relevant studies that directly addressed the anticancer properties of the target plant species.[12]

Initial search results

All search results for the specified keywords were included in the Scopus database without limitations. The complete content of these documents, excluding metadata, was accessed. A total of 252 documents were identified that contained the search terms in their titles, abstracts, or keywords.

Refinement of search results

The initial search yielded a broad dataset that was subsequently refined using several inclusion and exclusion criteria. While the Scopus database offers numerous search parameters (including access type, year of publication, author, subject area, document type, publication stage, source title, keywords, affiliation, funding sponsor, country, source type, and language), this study focused solely on journal articles to ensure a high level of evidence and avoid potential redundancy with book chapters and other tertiary sources.[13] These search parameters resulted in a pool of 210 relevant research articles for further analysis.

Compile preliminary data statistics

Filtered data was exported in CSV format from the Scopus database, encompassing citations, bibliography, abstracts, keywords, funding details, and other relevant metadata. Bibliometric analysis and visualization were performed using VOSviewer 1.6.20 software. In line with our previous researches,[10,11] the analysis focused on publication and citation patterns, keyword co-occurrence, author and co-authorship networks, and geographic distribution of research.

Results and Discussion

Publication and Citation Patterns

A total of 210 relevant documents were identified in the Scopus database, with publication dates ranging from 1982 to 2024. The peak publication year was 2010, with 18 articles published. While 14 of the 210 articles appeared in journals subsequently removed from the Scopus index, these articles were published prior to the delisting date and therefore included in the analysis. Table 1 provides a comprehensive overview of the search results.

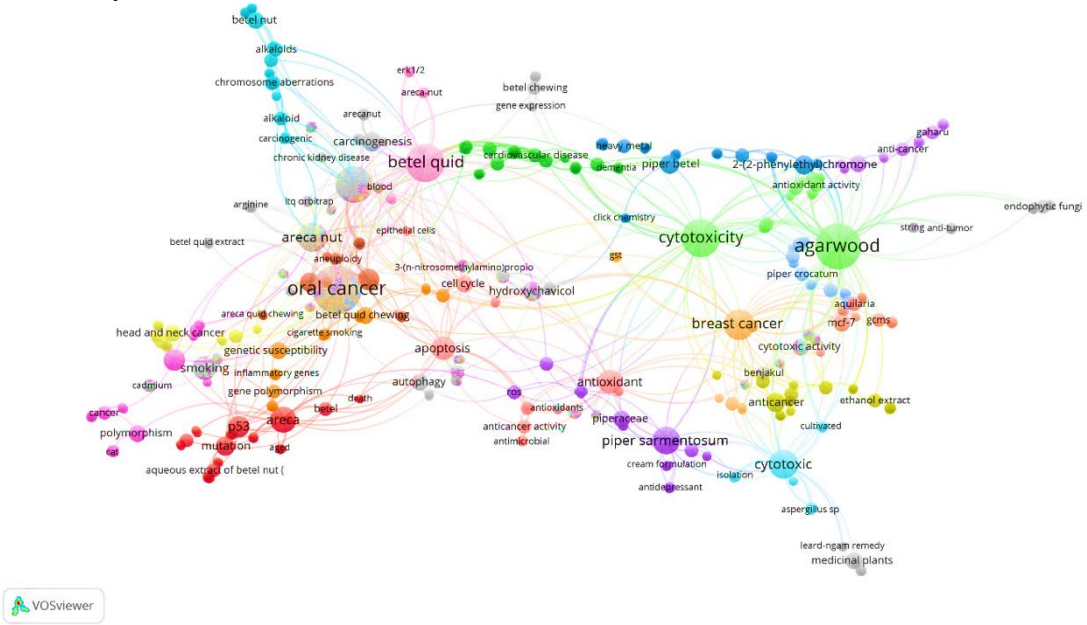
Data collection and analysis were conducted at the journal and publisher level. A keyword search yielded 143 journals and 63 publishers publishing articles related to the specified keywords. The journals with the highest number of publications were Cancer Letters (Elsevier) with ten articles, PLoS ONE (Public Library of Science) with eight, and Mutation Research – Genetic Toxicology and Environmental Mutagenesis (Elsevier) with six. Elsevier was the most prolific publisher, contributing 66 articles across 32 journals. Despite other factors, publishing research in the Environmental Health Perspectives (Public Health Services, US Dept of Health and Human Services) tends to lead to a higher number of citations compared to other journals. This is supported by the fact that one article published in 2005 within this journal has already accumulated 662 citations.[14] This number surpasses the combined citations of ten articles published in Cancer Letters between 1993 and 2006, which totaled 628 citations. Typically, a longer publication history correlates with a higher citation count.[15] However, this trend was not observed in our analysis. Overall, there were 7035

citations of all articles related to these keywords. This highlights the potential for high-impact publications in this field. Complete data is presented in Table 2.

Keyword Co-Occurrence

In-depth keyword analysis revealed a complex network of research connections, as shown in Figure 2a. Of the 582 identified keywords, 'oral cancer' (n=25, link strength=105) and 'agarwood' (n=22, link strength=87) emerged as the most prominent terms. However, a notable absence of connections between these two keywords suggests a potential research gap.

A total of 33 keyword clusters were identified, with the largest cluster comprising 28 terms. Key terms within this cluster included 'betel', 'areca', 'p53', and 'mutation', all closely linked to 'oral cancer'. This suggests a focus on the role of *P. betel* and areca, particularly *Areca catechu*, in oral cancer development, potentially linked to p53 mutations.[16] *Areca catechu* has been established as a carcinogen, while *P. betel*, often consumed together in betel quid, has been hypothesized to possess neutralizing effects on the carcinogenic properties of *A. catechu*.[17-19] These findings underscore the need for further research to explore the potential synergistic effects of *P. betel* and *A. catechu* in oral cancer prevention or treatment. Additionally, investigating the underlying mechanisms, including the role of p53 mutations, is warranted to inform the development of targeted therapeutic strategies.[20]



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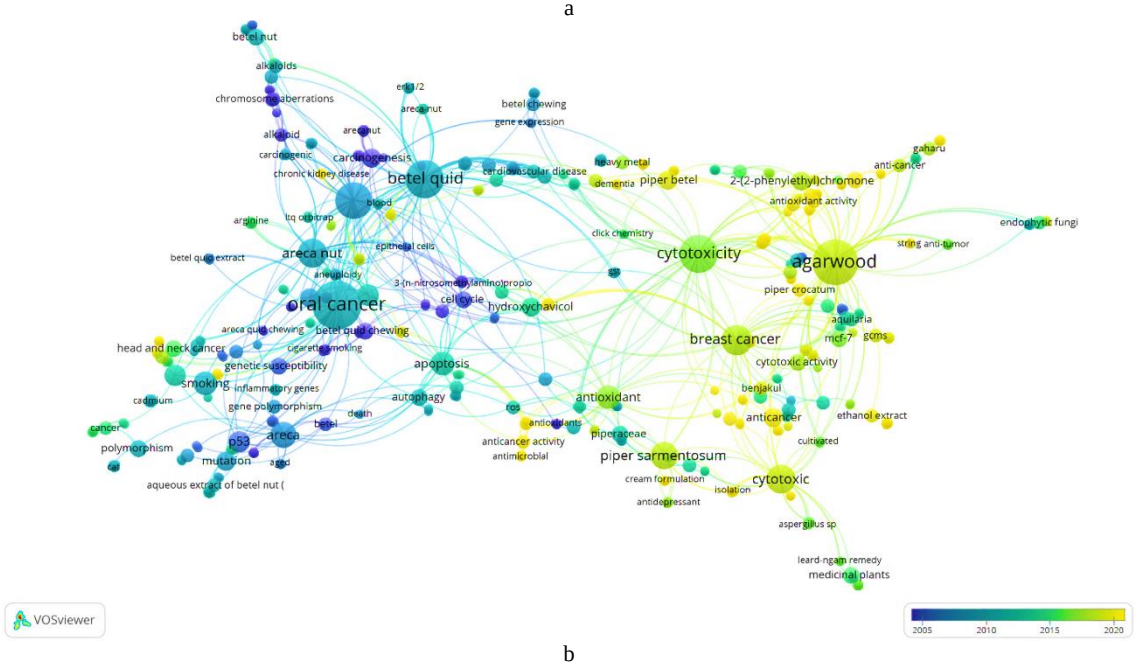

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Figure 2. Network (**a**) and overlay (**b**) visualizations of the keywords "*Piper betel*" OR "*Piper sarmentosum*" OR "*Piper crocatum*" OR "Agarwood" AND "Cancer".

Another cluster analysis revealed a distinct grouping of 18 items centered around the keyword "agarwood" (Cluster 11). This cluster exhibited strong associations with terms such as "cytotoxicity," "cytotoxic," "breast cancer," and "2-(2-phenylethyl)chromone." It is evident that this cluster primarily focuses on the anticancer properties of 2-(2-phenylethyl)chromone, a secondary metabolite derived from agarwood, with a particular emphasis on breast cancer research.[21,22] Intriguingly, no direct connections were observed between this "agarwood" cluster and the previously identified "oral cancer" cluster. This lack of overlap suggests a potential research gap and highlights the need for further exploration into the anticancer properties of agarwood-

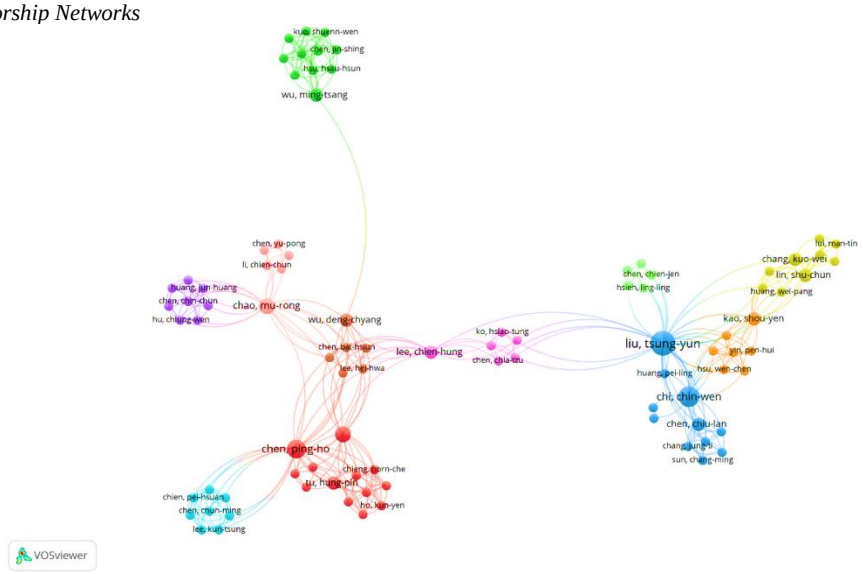
derived compounds against a broader spectrum of cancer types. In particular, investigating the efficacy of 2-(2-phenylethyl)chromone against oral cancer cells, especially those with p53 mutations, could be a promising avenue for future research. Additionally, exploring the synergistic effects of 2-(2-phenylethyl)chromone in combination with other chemotherapeutic agents could offer promising avenues for developing more effective cancer treatments. Furthermore, understanding the underlying molecular mechanisms of action of these compounds is crucial for optimizing their therapeutic potential.

As depicted in Figure 2b, research on agarwood (and to a lesser extent, *P. betel*) has consistently garnered interest, with publication rates remaining robust into the mid-2020s. In contrast, research on oral cancer, particularly in relation to p53 mutations, peaked in the early 2010s, with subsequent studies becoming less frequent. This contrasting trajectory between a mature research field (oral cancer) and an emerging one (agarwood) presents a promising opportunity to explore synergistic research avenues that could lead to significant advancements.[20] While research on oral cancer has been extensive,[23] the emerging interest in agarwood offers a unique opportunity to identify novel therapeutic targets and develop innovative treatment strategies. Future studies could focus on elucidating the precise mechanisms of action of agarwood compounds, optimizing their delivery systems, and investigating their potential to overcome drug resistance.

Author and Co-Authorship Networks

The study examined author and institutional data using the Scopus database. Due to inconsistencies in how institutions were recorded on Scopus, the analysis focuses on the entire university or institutional level, including specific departments, laboratories, or faculties. Instead of analyzing individual authors (which would limit each author to one contribution per article), the study looked at citation data for the entire document to provide a more comprehensive view of author impact.[24] Among the 1041 identified authors, Tsung Yun Liu from National Yang Ming Chiao Tung University, as well as Hao Fu Dai and Wen Li Mei from the Chinese Academy of Tropical Agricultural Sciences, were the most prolific with seven publications each. While Tsung Yun Liu's work garnered the highest citation count (357), Hao Fu Dai and Wen Li Mei exhibited the strongest collaboration networks with 56 links apiece.[25,26]

Network analysis revealed eleven interconnected author clusters. The largest cluster comprised eleven authors led by Ping Ho Chen from Kaohsiung Medical University, with four publications in collaboration with researchers from various institutions, including Chung Shan Medical University (Figure 3a). However, this cluster's most recent publication dates back to the mid-2010s.[27] In contrast, the group led by Chia Tzu Chen from National Yang Ming Chiao Tung University represents the most recent research activity in this field which were published in the early 2020s (Figure 3b).[28]



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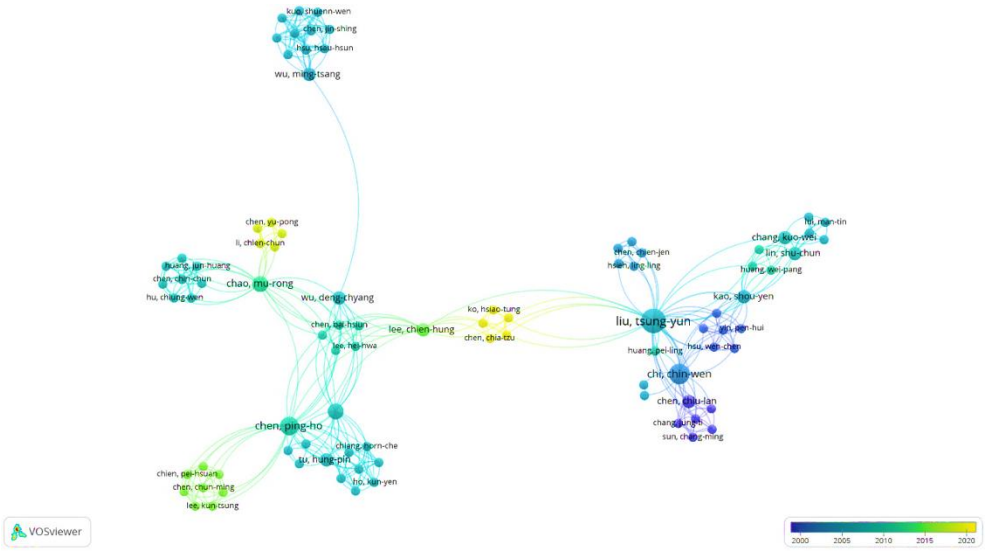

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Figure 3. Network (**a**) and overlay (**b**) visualizations of authorship of the keywords "*Piper betel*" OR "*Piper sarmentosum*" OR "*Piper crocatum*" OR "Agarwood" AND "Cancer".

Analysis of author affiliations revealed that Chung Shan Medical University, specifically the Institute of Medicine, was the most prolific institution, contributing eight documents. Despite generating only 233 citations (Figure 4a), this institution exhibited the highest total link strength with 63 connections. This contrasts with the work of Ward *et al*.[14] from the National Cancer Institute, which garnered 663 citations. The disparity in citation counts can be attributed to the publication timeline.[29] While the work of Ward *et al*.[14] dates back to the mid-2000s, allowing for greater citation accumulation, the research from Chung Shan Medical University primarily falls within the last decade (Figure 4b). Consequently, shorter publication timelines often correlate with lower citation rates, further compounded by journal impact factors.[30]

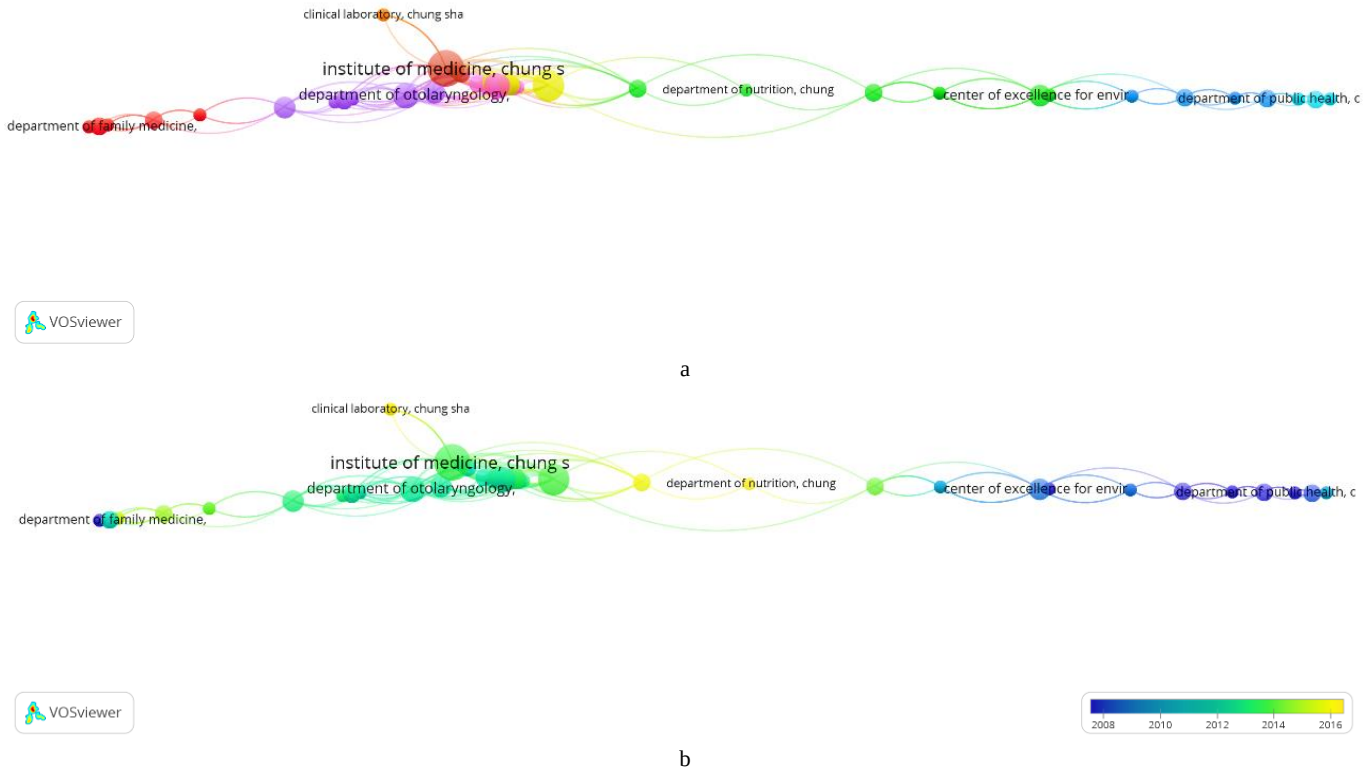

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Figure 4. Network (**a**) and overlay (**b**) visualizations of institutions of the keywords "*Piper betel*" OR "*Piper sarmentosum*" OR "*Piper crocatum*" OR "Agarwood" AND "Cancer".

Geographic Distribution of Research

The analysis was extended to investigate the geographic distribution of research contributions. Among the 210 analyzed documents, authors from 35 countries were represented, often in collaborative efforts (Figure 5a). Taiwan emerged as the leading contributor, with 70 publications garnering 2649 citations. In contrast, researchers from the United States exhibited the strongest collaborative network, with 25 links to research institutions in ten other countries. Despite producing only 21 documents, this network generated a substantial 1758 citations. As demonstrated by Ward *et al*.,[14] the largest cross-country collaboration involves researchers from the US, Netherlands, Canada, Denmark and Slovakia.

While Taiwan led in overall publication volume (followed by India with 52 documents), a surprising trend emerged regarding publication recency. Although Taiwan's research peaked in the mid-2010s, China demonstrated a more recent research surge, with a peak in the early 2020s (Figure 5b). This discrepancy is primarily attributed to the significant contributions of the Chinese Academy of Tropical Agricultural Sciences, which produced ten documents, eight within the past five years.[31] This contrasts sharply with Taiwan's National Yang Ming Chiao Tung University,[28] which, despite having the highest overall publication count (70), demonstrated a lower proportion of recent publications (six within the past five years). Consequently, while Taiwan holds a historical advantage in this research field, China exhibits more recent and active research engagement. This dynamic highlight the evolving landscape of research on these medicinal plants and underscores the importance of continuous monitoring for emerging trends.[32]

A notable finding is the absence of research contributions from Brunei Darussalam, despite the endemic nature of the studied medicinal plants in the region and their traditional use by local populations.[33] This gap in research represents a significant opportunity for future investigations into the anticancer potential of these plants. The lack of involvement from Bruneian institutions highlights the need for increased research capacity and collaboration within the country. Establishing collaborations with researchers from other countries where these plants are also prevalent could be a strategic approach to accelerating research progress in this area.[34]

The findings of this bibliometric analysis provide valuable insights into the current state of research on the anticancer potential of *P. betel*, *P. sarmentosum*, *P. crocatum*, and agarwood. While significant progress has been made, particularly in understanding the molecular mechanisms underlying their anticancer effects, there remains ample scope for further investigation. Future research should focus on exploring the synergistic effects of these plants in combination with conventional therapies, optimizing their formulations for improved bioavailability and therapeutic efficacy, and conducting clinical trials to evaluate their safety and efficacy in human subjects. Additionally, the underrepresentation of research from Brunei Darussalam, despite the endemic nature of these plants, underscores the need for increased investment in local research infrastructure and collaborative efforts with international researchers to unlock the full potential of these medicinal plants.

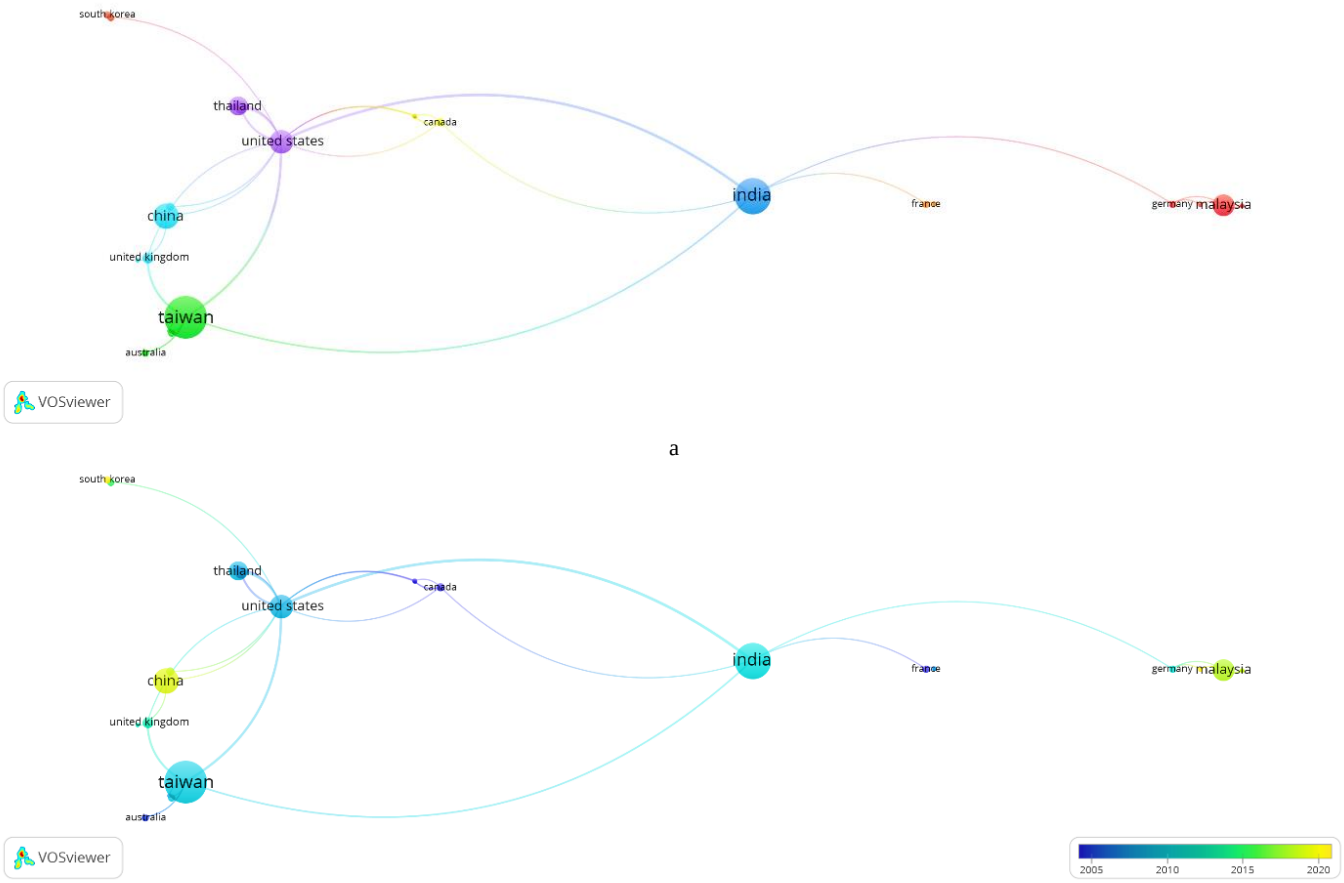

Figure 5. Network (**a**) and overlay (**b**) visualizations of countries of the keywords "*Piper betel*" OR "*Piper sarmentosum*" OR "*Piper crocatum*" OR "Agarwood" AND "Cancer".

Table 1. Articles on Scopus with the keywords "*Piper betel*" OR "*Piper sarmentosum*" OR "*Piper crocatum*" OR "Agarwood" AND "Cancer". Articles in red indicate discontinued status in the Scopus database

No	Publication year	Authors	Title	Journal	Publisher	Number of citations
1	2005	Ward *et al*.	Workgroup report: Drinking-water nitrate and health - Recent findings and research needs	Environmental Health Perspectives	Public Health Services, US Dept of Health and Human Services	662
2	1994	Hoffmann *et al*.	Tobacco-specific n-nitrosamines and arecaderived n-nitrosamines: Chemistry, biochemistry, carcinogenicity, and relevance to humans	Journal of Toxicology and Environmental Health	Taylor & Francis	311
3	2006	Manosroi *et al*.	Anti-proliferative activity of essential oil extracted from Thai medicinal plants on KB and P388 cell lines	Cancer Letters	Elsevier	275
4	2010	Mahavorasirikul *et al*.	Cytotoxic activity of Thai medicinal plants against human cholangiocarcinoma, laryngeal and hepatocarcinoma cells in vitro	BMC Complementary and Alternative Medicine	Springer Nature	195

5	2000	Merchant *et al*.	Paan without tobacco: An independent risk factor for oral cancer	International Journal of Cancer	John Wiley & Sons	172
6	2004	He *et al*.	Identification of tumor-associated proteins in oral tongue squamous cell carcinoma by proteomics	Proteomics	John Wiley & Sons	148
7	2015	Lee *et al*.	IL-1β promotes malignant transformation and tumor aggressiveness in oral cancer	Journal of Cellular Physiology	John Wiley & Sons	147
8	2004	Chang *et al*.	The induction of prostaglandin E2 production, interleukin-6 production, cell cycle arrest, and cytotoxicity in primary oral keratinocytes and KB cancer cells by areca nut ingredients is differentially regulated by MEK/ERK activation	Journal of Biological Chemistry	American Society for Biochemistry and Molecular Biology Inc.	119
9	2008	Tsai *et al*.	Arecoline, a major alkaloid of areca nut, inhibits p53, represses DNA repair, and triggers DNA damage response in human epithelial cells	Toxicology	Elsevier	110
10	2006	Kietthubthew *et al*.	Polymorphism in DNA repair genes and oral squamous cell carcinoma in Thailand	International Journal of Hygiene and Environmental Health	Elsevier	109
11	2008	Lin *et al*.	Betel nut chewing is associated with increased risk of cardiovascular disease and all-cause mortality in Taiwanese men	American Journal of Clinical Nutrition	Elsevier	94
12	1992	Rosin, M.P.	The use of the micronucleus test on exfoliated cells to identify anti-clastogenic action in humans: a biological marker for the efficacy of chemopreventive agents	Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis	Elsevier	93
13	2010	Zaveri *et al*.	Chemistry and pharmacology of Piper longum L	International Journal of Pharmaceutical Sciences Review and Research	Global Research Online	91
14	2015	Joseph *et al*.	Human health risk assessment from arsenic exposures in Bangladesh	Science of the Total Environment	Elsevier	88
15	2006	Lin *et al*.	Functional polymorphism in NFKB1 promoter is related to the risks of oral squamous cell carcinoma occurring on older male areca (betel) chewers	Cancer Letters	Elsevier	87
16	2001	Lee *et al*.	Accumulation of mitochondrial DNA deletions in human oral tissues - Effects of betel quid chewing and oral cancer	Mutation Research - Genetic Toxicology and Environmental Mutagenesis	Elsevier	81
17	2006	Dasgupta *et al*.	Immunosuppression, hepatotoxicity and depression of antioxidant status by arecoline in albino mice	Toxicology	Elsevier	80

18	2009	Zainal Ariffin *et al*.	Intrinsic anticarcinogenic effects of Piper sarmentosum ethanolic extract on a human hepatoma cell line	Cancer Cell International	Springer Nature	75
19	2002	Chen *et al*.	Hydroxyl radical formation and oxidative dna damage induced by areca quid in vivo	Journal of Toxicology and Environmental Health - Part A	Taylor & Francis	73
20	2013	Talukdar *et al*.	Epigenetic, Genetic and Environmental Interactions in Esophageal Squamous Cell Carcinoma from Northeast India	PLoS ONE	Public Library of Science	72
21	2011	Cui *et al*.	Antitumor and antimicrobial activities of endophytic fungi from medicinal parts of Aquilaria sinensis	Journal of Zhejiang University: Science B	Zhejiang University	72
22	2018	Wang *et al*.	Agarwood essential oil ameliorates restrain stress-induced anxiety and depression by inhibiting HPA axis hyperactivity	International Journal of Molecular Sciences	Multidisciplinary Digital Publishing Institute (MDPI)	67
23	2010	Chattopadhyay *et al*.	Genome-wide analysis of chromosomal alterations in patients with esophageal squamous cell carcinoma exposed to tobacco and betel quid from high-risk area in India	Mutation Research - Genetic Toxicology and Environmental Mutagenesis	Elsevier	67
24	2010	Lu *et al*.	Areca nut extract induced oxidative stress and upregulated hypoxia inducing factor leading to autophagy in oral cancer cells	Autophagy	Taylor & Francis	66
25	2014	Gundala *et al*.	Hydroxychavicol, a betel leaf component, inhibits prostate cancer through ROS-driven DNA damage and apoptosis	Toxicology and Applied Pharmacology	Elsevier	65
26	2007	Chiang *et al*.	Characterization of erecoline-induced effects on cytotoxicity in normal human gingival fibroblasts by global gene expression profiling	Toxicological Sciences	Oxford University Press	65
27	2002	Boonyaphiphat *et al*.	Lifestyle habits and genetic susceptibility and the risk of esophageal cancer in the Thai population	Cancer Letters	Elsevier	65
28	2012	Chu *et al*.	Impacts of microRNA gene polymorphisms on the susceptibility of environmental factors leading to carcinogenesis in oral cancer	PLoS ONE	Public Library of Science	63
29	2011	Yuan *et al*.	Possible association between nickel and chromium and oral cancer: A case-control study in central Taiwan	Science of the Total Environment	Elsevier	63
30	2006	Lai & Lee	Genetic damage in cultured human keratinocytes stressed by long-term exposure to areca nut extracts	Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis	Elsevier	62

31	2018	Wang *et al.*	CYP450-mediated mitochondrial ROS production involved in arecoline N-oxide-induced oxidative damage in liver cell lines	Environmental Toxicology	John Wiley & Sons	60
32	2009	Wu *et al*.	Impact of chewing betel-nut (Areca catechu) on liver cirrhosis and hepatocellular carcinoma: A population-based study from an area with a high prevalence of hepatitis B and C infections	Public Health Nutrition	Cambridge University Press	58
33	2006	Lee *et al*.	Prolonged exposure to arecoline arrested human KB epithelial cell growth: Regulatory mechanisms of cell cycle and apoptosis	Toxicology	Elsevier	57
34	2016	Liao *et al*.	2-(2-Phenylethyl)chromone derivatives in artificial agarwood from Aquilaria sinensis	Fitoterapia	Elsevier	56
35	2012	Lin *et al*.	Effects of NFKB1 and NFKBIA gene polymorphisms on susceptibility to environmental factors and the clinicopathologic development of oral cancer	PLoS ONE	Public Library of Science	55
36	2001	Kietthubthew *et al*.	Genetic and environmental interactions on oral cancer in Southern Thailand	Environmental and Molecular Mutagenesis	John Wiley & Sons	55
37	2004	Wu *et al*.	Clastogenic effect for cigarette smoking but not areca quid chewing as measured by micronuclei in exfoliated buccal mucosal cells	Mutation Research - Genetic Toxicology and Environmental Mutagenesis	Elsevier	52
38	2005	Katiyar *et al*.	p53 gene mutation and human papillomavirus (HPV) infection in esophageal carcinoma from three different endemic geographic regions of India	Cancer Letters	Elsevier	51
39	2006	Chang *et al*.	Betel nut chewing and other risk factors associated with obesity among Taiwanese male adults	International Journal of Obesity	Springer Nature	49
40	2004	Jeng *et al*.	Reactive oxygen species are crucial for hydroxychavicol toxicity toward KB epithelial cells	Cellular and Molecular Life Sciences	Springer Nature	49
41	2016	Dahham *et al*.	In vivo toxicity and antitumor activity of essential oils extract from agarwood (Aquilaria crassna)	BMC Complementary and Alternative Medicine	Springer Nature	48
42	2003	Tan *et al*.	Novel heteroplasmic frameshift and missense somatic mitochondrial DNA mutations in oral cancer of betel quid chewers	Genes Chromosomes and Cancer	John Wiley & Sons	48

43	2013	Paranjpe *et al*.	Piper betel leaf extract: Anticancer benefits and bio-guided fractionation to identify active principles for prostate cancer management	Carcinogenesis	Oxford University Press	47
44	2007	Cheng *et al*.	Carotenoids suppress proliferating cell nuclear antigen and cyclin D1 expression in oral carcinogenic models	Journal of Nutritional Biochemistry	Elsevier	47
45	2004	Wu *et al*.	Influences of lifestyle habits and p53 codon 72 and p21 codon 31 polymorphisms on gastric cancer risk in Taiwan	Cancer Letters	Elsevier	47
46	2020	Hung *et al*.	Assessment of the risk of oral cancer incidence in a high-risk population and establishment of a predictive model for oral cancer incidence using a population-based cohort in Taiwan	International Journal of Environmental Research and Public Health	Multidisciplinary Digital Publishing Institute (MDPI)	46
47	2016	Li & Xing	Ethnobotanical study on medicinal plants used by local Hoklos people on Hainan Island, China	Journal of Ethnopharmacology	Elsevier	45
48	2010	Yadav *et al*.	Polymorphisms of glutathione-S-transferase genes and the risk of aerodigestive tract cancers in the northeast indian population	Genetic Testing and Molecular Biomarkers	Mary Ann Liebert	45
49	2007	Lo *et al*.	S100A8 is identified as a biomarker of HPV18-infected oral squamous cell carcinomas by suppression subtraction hybridization, clinical proteomics analysis, and immunohistochemistry staining	Journal of Proteome Research	American Chemical Society	45
50	2014	Hashim *et al*.	Screening of anticancer activity from agarwood essential oil	Pharmacognosy Research	Phcog.Net	44
51	2011	Pan *et al*.	Bioassay-guided isolation of constituents of Piper sarmentosum using a mitochondrial transmembrane potential assay	Journal of Natural Products	American Chemical Society	43
52	2007	Lan *et al*.	Areca nut chewing and mortality in an elderly cohort study	American Journal of Epidemiology	Oxford University Press	43
53	1999	Jeng *et al*.	Arecoline cytotoxicity on human oral mucosal fibroblasts related to cellular thiol and esterase activities	Food and Chemical Toxicology	Elsevier	42
54	2010	Kazi *et al*.	Interaction of cadmium and zinc in biological samples of smokers and chewing tobacco female mouth cancer patients	Journal of Hazardous Materials	Elsevier	41
55	2008	Yen *et al*.	A prospective community-population-registry-based cohort study of the association between betel-quid chewing	American Journal of Clinical Nutrition	Elsevier	40

			and cardiovascular disease in men in Taiwan (KCIS no. 19)			
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57	2005	Wu *et al*.	Effects of pH on nicotine-induced DNA damage and oxidative stress	Journal of Toxicology and Environmental Health - Part A	Taylor & Francis	38
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61	2014	Chen *et al*.	Identification of cucurbitacins and assembly of a draft genome for Aquilaria agallocha	BMC Genomics	Springer Nature	36
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63	1996	Jin *et al*.	Studies on promoting activity of Taiwan betel quid ingredients in hamster buccal pouch carcinogenesis	European Journal of Cancer Part B: Oral Oncology	Elsevier	35
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65	2015	Yang *et al*.	A systematic gene-gene and gene-environment interaction analysis of DNA repair genes XRCC1, XRCC2, XRCC3, XRCC4, and oral cancer risk	OMICS A Journal of Integrative Biology	Mary Ann Liebert	34
66	2007	Tovosia *et al*.	Prevalence and associated factors of betel quid use in the Solomon Islands: A hyperendemic area for oral and pharyngeal cancer	American Journal of Tropical Medicine and Hygiene	American Society of Tropical Medicine and Hygiene	34
67	2009	Wicaksono *et al*.	Antiproliferative effect of the methanol extract of Piper crocatum Ruiz & Pav leaves on human breast (T47D) cells in-vitro	Tropical Journal of Pharmaceutical Research	Pharmacotherapy Group	33
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114	2019	Wang *et al.*	Agarwood extract mitigates intestinal injury in fluorouracil-induced mice	Biological and Pharmaceutical Bulletin	Pharmaceutical Society of Japan	15
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116	2013	Sharkar *et al*.	Ethnomedicinal importance of the plants in villages in kushtia sador and mirpur upozila, bangladesh	Journal of Herbs, Spices and Medicinal Plants	Taylor & Francis	14
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125	2014	Lin *et al*.	Relationship between betel quid chewing and risks of cardiovascular disease in older adults: A cross-sectional study in Taiwan	Drug and Alcohol Dependence	Elsevier	12
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129	2018	Aswini & Soundhari	Production of camptothecin from endophytic fungi and characterization by high-performance liquid chromatography and anticancer activity against colon cancer cell line	Asian Journal of Pharmaceutical and Clinical Research	Asian Journal of Pharmaceutical and Clinical Research	11

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146	2019	Zhao *et al.*	Three new 2-(2-phenylethyl)chromone derivatives from agarwood of Aquilaria crassna Pierre ex Lecomte (Thymelaeaceae)in Laos	Phytochemistry Letters	Elsevier	8
147	2015	Kumar *et al.*	Synthetic modification of hydroxychavicol by Mannich reaction and alkyne-azide cycloaddition derivatives depicting cytotoxic potential	European Journal of Medicinal Chemistry	Elsevier	8
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152	2021	Wang *et al.*	Two new 2-(2-phenethyl)chromone derivatives from agarwood of Aquilaria walla and their cytotoxicity	Phytochemistry Letters	Elsevier	7
153	2020	Tian *et al.*	Two new sesquiterpenoids from agarwood originated from Aquilaria sp.	Journal of Asian Natural Products Research	Taylor & Francis	7
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158	2020	Hsiao *et al*.	Investigating the health disparities in the association between lifestyle behaviors and the risk of head and neck cancer	Cancer Science	John Wiley & Sons	6
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164	2022	Sangavi *et al*.	Identification and Validation of Hydroxychavicol from Betel Leaf as a Promising Breast Cancer Inhibitor: An In vitro and In silico Analysis	Current Enzyme Inhibition	Bentham Science Publishers	5
165	2021	Hussain *et al*.	Anticancer and antimicrobial peptides from medicinal plants of Borneo island in Sarawak	Advances in Traditional Medicine	Springer Nature	5
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167	2019	Gameil *et al*.	Anticancer potential and chemical profile of agarwood hydrosol	Malaysian Journal of Fundamental and Applied Sciences	Penerbit UTM Press	5

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176	2013	Kangralkar & Kulkarni	In vitro antitumor activity of alcoholic extract of piper betel leaf	Research Journal of Pharmaceutical, Biological and Chemical Sciences	RJPBCS	4
177	2023	Huang *et al.*	Aquilariperoxide A, a Sesquiterpene Dimer from Agarwood of Aquilaria sinensis with Dual Antitumor and Antimalarial Effects	Journal of Organic Chemistry	American Chemical Society	3
178	2023	Satapathy *et al.*	Bioactive components of piper betel could be potential anticancer agents: A short review on pre-clinical inves-tigations and practical challenges	Current Trends in Biotechnology and Pharmacy	Association of Biotechnology and Pharmacy	3
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188	2019	Abbas *et al*.	Uninfected agarwood branch extract possess cytotoxic and inhibitory effects on mcf-7 breast cancer cells	Marmara Pharmaceutical Journal	Marmara University	2
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190	2014	Chang *et al*.	Detection of SF3B3 gene mutations in oral cancer by high resolution melting analysis	Clinical Laboratory	Verlag Klinisches Labor GmbH	2
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192	2010	Chen *et al*.	Mechanism of DNA damage induced by arecaidine: The role of Cu(II) and alkaline conditions	Food Chemistry	Elsevier	2
193	2005	Heepchantree *et al*.	A comparative biomonitoring study of populations residing in regions with low and high risk of lung cancer using the chromosome aberration and the micronucleus tests	Mutation Research - Genetic Toxicology and Environmental Mutagenesis	Elsevier	2
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196	2021	Widayat *et al*.	Metabolite profiles of agarwood Gyrinops versteegii (Gilg) domke leaves collected from different locations	Research Journal of Biotechnology	Research Journal of BioTechnology	1
197	2008	Thiéry *et al*.	Betel quid and oral cancer: Case report | Chique de bétel et cancers oraux: À propos d'une observation	Medecine Tropicale	Institut de Medecine Tropicale	1
198	2024	Hossain *et al*.	Malondialdehyde and heavy metal contents in Piper betel: Possible risks of heavy metals in human health	Journal of Food Composition and Analysis	Elsevier	0
199	2024	Duenngai *et al*.	Antioxidant and Anticancer Potentials and Metabolic Profiling of Benjakul, A Thai Herbal Preparation	Tropical Journal of Natural Product Research	Faculty of Pharmacy, University of Benin	0
200	2024	Zhang *et al*.	Determination of Antitumor Active Ingredients in Agarwood Essential Oil by Gas Chromatography-Mass Spectrometry (GC-MS) and Grey Relational Analysis	Analytical Letters	Taylor & Francis	0
201	2023	Nursyarah *et al*.	Red Betel Leaf Bioactive Compounds as ERα Receptor Inhibitors In Silico and MCF-7 Cell Anticancer In Vitro	HAYATI Journal of Biosciences	Institut Pertanian Bogor	0
202	2022	Su *et al*.	Three new 2-(2-phenylethyl)chromones from ‘Chong-lou’ agarwood of Aquilaria sinensis	Phytochemistry Letters	Elsevier	0
203	2022	Jang *et al*.	Agarwood (Aquilaria crassna) Inhibits Beta-amyloid and Tau-protein Formation in a Mouse Obesity Model	Journal of Animal Health and Production	ResearchersLinks Ltd	0
204	2021	Lisna *et al*.	String Analysis to identify the Activity of Gyrinops versteegii derived Lauric Acid against Breast Cancer	Research Journal of Biotechnology	Research Journal of BioTechnology	0
205	2020	Ghazali *et al*.	Antioxidant and cytotoxicity activity of phenolic compounds from piper sarmentosum roxb. Against T47D human breast cancer cell	Natural Products Journal	Bentham Science Publishers	0
206	2015	Chitra	Role of irradiation and status of A-feto protein, B2-microglobulin and carcinoembryonic antigen in different stages of oral cancer patients	International Journal of Pharma and Bio Sciences	International Journal of Pharma and Bio Sciences	0
207	2013	Kulkarni Rajesh	Tobacco consumption and associated morbidities-a community based cross sectional study among rural agricultural workers in North Karnataka	International Journal of Pharma and Bio Sciences	International Journal of Pharma and Bio Sciences	0

208	2011	Ghosh *et al*.	High α - Radioactivity level in betel leaf (piper betel) and chewing tobacco	Indian Journal of Environmental Protection	Kalpana Corporation	0
209	2009	Shashi *et al*.	Oral and respiratory cancer: A clinical and epidemiological case study	Asian Journal of Microbiology, Biotechnology and Environmental Sciences	Global Publications	0
210	2003	Moore *et al*.	Epidemiology of the major cancers in the Asian Pacific	Proceedings of the Japan Academy Series B: Physical and Biological Sciences	Japan Academy	0
			Total			**7035**

Table 2. Comparison of each journal and publisher with the keywords "*Piper betel*" OR "*Piper sarmentosum*" OR "*Piper crocatum*" OR "Agarwood" AND "Cancer". Journals in red indicate discontinued status in the Scopus database.

No	Journal	Publisher	Total articles	Total citations
1	Cancer Letters	Elsevier	10	628
2	PLoS ONE	Public Library of Science	8	316
3	Mutation Research - Genetic Toxicology and Environmental Mutagenesis	Elsevier	6	253
4	Fitoterapia	Elsevier	4	96
5	Archives of Toxicology	Springer Nature	4	61
6	Toxicology	Elsevier	3	247
7	Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis	Elsevier	3	178
8	Food and Chemical Toxicology	Elsevier	3	116
9	International Journal of Environmental Research and Public Health	Multidisciplinary Digital Publishing Institute (MDPI)	3	90
10	Journal of Natural Products	American Chemical Society	3	82
11	Environmental Toxicology	John Wiley & Sons	3	77
12	Mutagenesis	Oxford University Press	3	51
13	Journal of the Medical Association of Thailand	Medical Association of Thailand	3	21
14	Phytochemistry Letters	Elsevier	3	15
15	BMC Complementary and Alternative Medicine	Springer Nature	2	243
16	Science of the Total Environment	Elsevier	2	151
17	American Journal of Clinical Nutrition	Elsevier	2	134
18	International Journal of Hygiene and Environmental Health	Elsevier	2	128
19	Journal of Toxicology and Environmental Health - Part A	Taylor & Francis	2	111
20	Autophagy	Taylor & Francis	2	85
21	Environmental and Molecular Mutagenesis	John Wiley & Sons	2	79
22	Journal of Ethnopharmacology	Elsevier	2	76
23	International Journal of Molecular Sciences	Multidisciplinary Digital Publishing Institute (MDPI)	2	75

24	Genetic Testing and Molecular Biomarkers	Mary Ann Liebert	2	51
25	Clinica Chimica Acta	Elsevier	2	49
26	Medical Hypotheses	Elsevier	2	45
27	Planta Medica	Thieme	2	44
28	Tropical Journal of Pharmaceutical Research	Pharmacotherapy Group	2	36
29	Archives of Oral Biology	Elsevier	2	32
30	Nutrition and Cancer	Taylor & Francis	2	32
31	European Journal of Medicinal Chemistry	Elsevier	2	25
32	Environmental Toxicology and Pharmacology	Elsevier	2	23
33	Molecules	Multidisciplinary Digital Publishing Institute (MDPI)	2	19
34	Tropical Journal of Natural Product Research	Faculty of Pharmacy, University of Benin	2	2
35	Research Journal of Biotechnology	Research Journal of BioTechnology	2	1
36	International Journal of Pharma and Bio Sciences	International Journal of Pharma and Bio Sciences	2	0
37	Environmental Health Perspectives	Public Health Services, US Dept of Health and Human Services	1	662
38	Journal of Toxicology and Environmental Health	Taylor & Francis	1	311
39	International Journal of Cancer	John Wiley & Sons	1	172
40	Proteomics	John Wiley & Sons	1	148
41	Journal of Cellular Physiology	John Wiley & Sons	1	147
42	Journal of Biological Chemistry	American Society for Biochemistry and Molecular Biology Inc.	1	119
43	International Journal of Pharmaceutical Sciences Review and Research	Global Research Online	1	91
44	Cancer Cell International	Springer Nature	1	75
45	Journal of Zhejiang University: Science B	Zhejiang University	1	72
46	Toxicological Sciences	Oxford University Press	1	65
47	Toxicology and Applied Pharmacology	Elsevier	1	65
48	Public Health Nutrition	Cambridge University Press	1	58
49	Cellular and Molecular Life Sciences	Springer Nature	1	49
50	International Journal of Obesity	Springer Nature	1	49
51	Genes Chromosomes and Cancer	John Wiley & Sons	1	48
52	Carcinogenesis	Oxford University Press	1	47
53	Journal of Nutritional Biochemistry	Elsevier	1	47
54	Journal of Proteome Research	American Chemical Society	1	45
55	Pharmacognosy Research	Phcog.Net	1	44
56	American Journal of Epidemiology	Oxford University Press	1	43
57	Journal of Hazardous Materials	Elsevier	1	41
58	DNA and Cell Biology	Mary Ann Liebert	1	39
59	BMC Genomics	Springer Nature	1	36
60	European Journal of Cancer Part B: Oral Oncology	Elsevier	1	35
61	American Journal of Tropical Medicine and Hygiene	American Society of Tropical Medicine and Hygiene	1	34
62	OMICS A Journal of Integrative Biology	Mary Ann Liebert	1	34
63	Chemico-Biological Interactions	Elsevier	1	31
64	American Journal of Pharmacology and Toxicology	Science Publications	1	29

65	Journal of Nutrition, Health and Aging	Elsevier	1	29
66	Journal of Analytical Toxicology	Preston Publications	1	28
67	Journal of Experimental Zoology Part A: Ecological Genetics and Physiology	John Wiley & Sons	1	28
68	Analytica Chimica Acta	Elsevier	1	25
69	Cancer Genetics	Elsevier	1	25
70	Population Health Metrics	Springer Nature	1	25
71	Ethnicity and Health	Taylor & Francis	1	24
72	Journal of Chromatography A	Elsevier	1	23
73	Bulletin of the World Health Organization	World Health Organization	1	22
74	Journal of Clinical Laboratory Analysis	John Wiley & Sons	1	22
75	Public Health	Elsevier	1	22
76	Toxicology Mechanisms and Methods	Taylor & Francis	1	22
77	Asian Pacific Journal of Tropical Biomedicine	Wolters Kluwer Health	1	21
78	Sains Malaysiana	Penerbit Universiti Kebangsaan Malaysia	1	20
79	BMC Cell Biology	Springer Nature	1	19
80	Recent Patents on Drug Delivery and Formulation	Bentham Science Publishers	1	18
81	Biological and Pharmaceutical Bulletin	Pharmaceutical Society of Japan	1	15
82	Biochemical and Biophysical Research Communications	Elsevier	1	14
83	Journal of Herbs, Spices and Medicinal Plants	Taylor & Francis	1	14
84	Journal of Toxicology and Environmental Health - Part A: Current Issues	Taylor & Francis	1	14
85	Journal of Cellular Biochemistry	John Wiley & Sons	1	13
86	Drug and Alcohol Dependence	Elsevier	1	12
87	Annals of Clinical Biochemistry	SAGE	1	11
88	Asian Journal of Pharmaceutical and Clinical Research	Asian Journal of Pharmaceutical and Clinical Research	1	11
89	Human Genetics	Springer Nature	1	11
90	Journal of Applied Pharmaceutical Science	MediPoeia	1	11
91	Microscopy Research and Technique	John Wiley & Sons	1	11
92	Asian Pacific Journal of Cancer Prevention	Asian Pacific Organization for Cancer Prevention	1	10
93	Environmental Pollution	Elsevier	1	10
94	Human and Experimental Toxicology	SAGE	1	10
95	International Journal of Human Genetics	Kamla-Raj Enterprises	1	10
96	Anti-Cancer Drugs	Wolters Kluwer Health	1	9
97	Journal of Mass Spectrometry	John Wiley & Sons	1	9
98	Anticancer Research	International Institute of Anticancer Research	1	8
99	Scientific World Journal	Hindawi	1	8
100	Teratogenesis, Carcinogenesis, and Mutagenesis	John Wiley & Sons	1	8
101	Indian Journal of Biochemistry and Biophysics	National Institute of Science Communication and Policy Research	1	7
102	Journal of Asian Natural Products Research	Taylor & Francis	1	7
103	Journal of Tropical Forest Science	Forest Research Institute Malaysia	1	7
104	Applied Physics A: Materials Science and Processing	Springer Nature	1	6
105	Cancer Science	John Wiley & Sons	1	6
106	Journal of Agricultural and Food Chemistry	American Chemical Society	1	6

107	Journal of Pharmaceutical and Biomedical Analysis	Elsevier	1	6
108	Advances in Traditional Medicine	Springer Nature	1	5
109	Annales de Toxicologie Analytique	EDP Sciences	1	5
110	British Food Journal	Emerald Publishing	1	5
111	Current Enzyme Inhibition	Bentham Science Publishers	1	5
112	International Journal of Pharmacy and Pharmaceutical Sciences	IJPPS	1	5
113	International Journal on Advanced Science, Engineering and Information Technology	INSIGHT - Indonesian Society for Knowledge and Human Development	1	5
114	Journal of Complementary and Integrative Medicine	Walter de Gruyter	1	5
115	Malaysian Journal of Fundamental and Applied Sciences	Penerbit UTM Press	1	5
116	Environmental Chemistry Letters	Springer Nature	1	4
117	Research Journal of Pharmaceutical, Biological and Chemical Sciences	RJPBCS	1	4
118	Research Journal of Pharmacy and Technology	A and V Publication	1	4
119	Tianran Chanwu Yanjiu yu Kaifa	Science China Press	1	4
120	Asia-Pacific Journal of Molecular Biology and Biotechnology	Universiti Putra Malaysia	1	3
121	Current Trends in Biotechnology and Pharmacy	Association of Biotechnology and Pharmacy	1	3
122	Iranian Journal of Cancer Prevention	Shahid Beheshti Medical University	1	3
123	Journal of Organic Chemistry	American Chemical Society	1	3
124	Turkish Journal of Biochemistry	Turk Biyokimya Dernegi	1	3
125	Annals of Tropical Medicine and Public Health	Africa Health Research Organization	1	2
126	Chinese Traditional and Herbal Drugs	Editorial Office of Chinese Traditional and Herbal Drugs	1	2
127	Clinical Laboratory	Verlag Klinisches Labor GmbH	1	2
128	Food Chemistry	Elsevier	1	2
129	Journal of Pure and Applied Microbiology	Journal of Pure and Applied Microbiology	1	2
130	Jurnal Teknologi	Penerbit UTM Press	1	2
131	Marmara Pharmaceutical Journal	Marmara University	1	2
132	Rasayan Journal of Chemistry	Rasayan Journal of Chemistry, c/o Dr. Pratima Sharma	1	2
133	Medecine Tropicale	Institut de Medecine Tropicale	1	1
134	Pertanika Journal of Tropical Agricultural Science	Universiti Putra Malaysia	1	1
135	Phytochemical Analysis	John Wiley & Sons	1	1
136	Analytical Letters	Taylor & Francis	1	0
137	Asian Journal of Microbiology, Biotechnology and Environmental Sciences	Global Publications	1	0
138	HAYATI Journal of Biosciences	Institut Pertanian Bogor	1	0
139	Indian Journal of Environmental Protection	Kalpana Corporation	1	0
140	Journal of Animal Health and Production	ResearchersLinks Ltd	1	0
141	Journal of Food Composition and Analysis	Elsevier	1	0
142	Natural Products Journal	Bentham Science Publishers	1	0
143	Proceedings of the Japan Academy Series B: Physical and Biological Sciences	Japan Academy	1	0
	Total		**210**	**7035**

Conclusion

While extensive research has explored the anticancer properties of several medicinal plants endemic to Brunei Darussalam, including *P. betel*, *P. sarmentosum*, *P. crocatum*, and agarwood, a notable gap exists in the literature regarding the association between agarwood and oral cancer. This presents a promising avenue for future research, particularly for researchers in countries with a significant focus on oral cancer, such as Taiwan and China.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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