

Potential of Polyisoprenoid of Mangroves as Antimicrobial and Anticancer: A Bibliometric Analysis

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Abstract

Mangroves are plants that hope to inhibit coastal abrasion because they can adapt to seawater and withstand beach posture. Polyisoprenoid compounds contained in mangroves have been known to have an important role in the process of adaptation to seawater salt stress. Publications in the Scopus database were collected using the keywords mangrove, polyisoprenoid, polyisoprene, and dolichol until December 2021. The articles obtained were analyzed bibliometrically using VOSviewer. Totally 129,406 documents were collected with the dominant topics apoptosis and antibacterial activity. Polyisoprenoid appeared 9 times with relevance values 1.1. Polyprenol and dolichol did not link with antibacterial, anticancer, or other biological activities. Several 106,679 (82.5%) are original research articles, 13,907 (10.8%) papers have been published this year (2021). English was mostly used in the language in the publication (95.5%). The countries with the largest publications were the United States, then China, India, Australia, Brazil, United Kingdom, Germany, Japan, France, and Indonesia. The Marine Pollution Bulletin was the most publisher 1,875 documents. Four of the top ten funding sponsors are from China. Wang YS was the main collaborator who has publication links with 50 authors with a total link strength of 32. The field of studies is still in the biological, environmental, social, and pharmaceutical sciences. The study of mangroves and polyisoprenoids related to antimicrobial assays and anticancer increases over time and still needs a lot of scientific studies. Greater research collaboration involving more authors were the hope until the clinic stage.

Keywords

Mangrove, Polyisoprenoid, Polyprenol, Dolichol, Antibacterial, Anticancer

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1. INTRODUCTION

Mangroves grow widely in the tropics and subtropics, are distributed 75% in 15 countries and 22.6% in Indonesia (Giri et al., 2011). They play a role in the community's socio-economic development, especially in the Sumatra Utara regency. Firewood and charcoal are some of its products; besides, they were also used to treat the communities (Bandaranayake, 1998).

Polyisoprenoid has an essential role in living things, including in mangroves closely related to biosynthesis of isoprenoid secondary metabolites. Triterpenoid and phytosterol compounds are the most numerous (Skorupinska-Tudek et al., 2008; Inafuku et al., 2018). Polyisoprenoid content in mangroves generally into dolichol and polyprenol (Basyuni et al., 2018; Basyuni et al., 2017). The general structure of this compound was composed of isoprenoid isomers with a long number of carbon chains. Polyisoprenoid members consist of

polyprenol, dolichol, and bombiprenon (Figure 4). The yield of polyisoprenoid from mangrove leaves growing on the coast of Langkat Regency, North Sumatra, Indonesia is shown in Table 3.

The articles include study mangroves related chemical content, role in biosynthesis and biological activity have reached more than hundreds of thousands of documents in the Scopus database and more than 6 million documents in the Google Engine database. Knowledge of the role of mangroves in human life needs to be explored, especially in solving problems of infection and cancer, still the main issues in the world.

The bibliometric method is a systematic literature review method that can be used to analyze scientific articles with specific topics with mathematical calculations (Chen et al., 2014). This method can assess the quality of a study, analyze critical areas of researches, and predict the future. Scopus online database contains almost all important global articles and

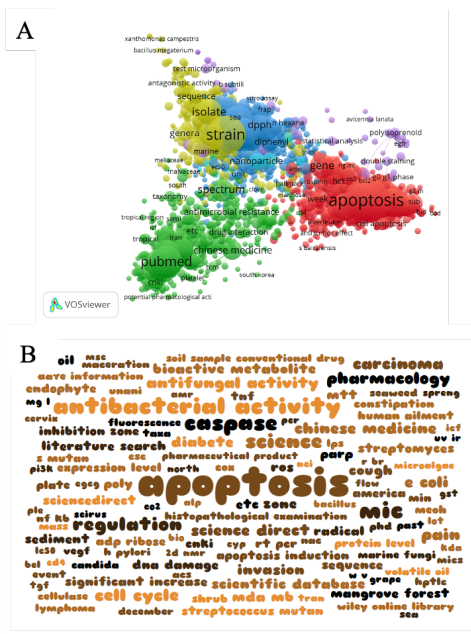


Figure 1. Bibliometric Analysis of The Keywords in Publication of Mangrove; Polyisoprenoid; Polyprenol; Dolichol. (A) Co-Occurance of Keyword. The Size of The Node Indicated The Frequency with which The Keyword Appeared. A Shorter Distance Indicates a Greater Amount of Co-Occurrence Between Two Keywords. (B) Word Cloud Consisted of 1943 Keywords that Appear with a Frequency of 3 or More Times. The Text Size Indicated The Repetition frequency.

has analysis tools to produce representative graphs. Furthermore, the export results are analyzed using software, including VOSviewer.

Currently, no bibliometric analysis of the role of mangroves as an antimicrobial and anticancer has been carried out, till now. More comprehensive information based on literature will provide benefits to the community. Therefore, our study was performed to understand potential mangroves, polyisoprenoid, polyprenol, and dolichol as antibacterial and anticancer.

2. EXPERIMENTAL SECTION

2.1 Methods

Global library of mangroves, polyisoprenoids, polyprenols, and dolichol detected in the Scopus database on 25 November 2021. The keywords used in the search field include “mangroves” or “polyisoprenoid” or “polyprenol” or “dolichol”. The information extracted for the year of publication, language, journal, author, affiliation, keywords, document type, abstract, and the number cited convert to CSV and RIS extension. VOSviewer application version 1.6.17 is used to analyze co-authorship, co-occurrence, citation, bibliographic coupling, co-citation, and themes. The distance attribute of each value is used to assess the “link” and “total link strength” attributes (Jalal, 2019).

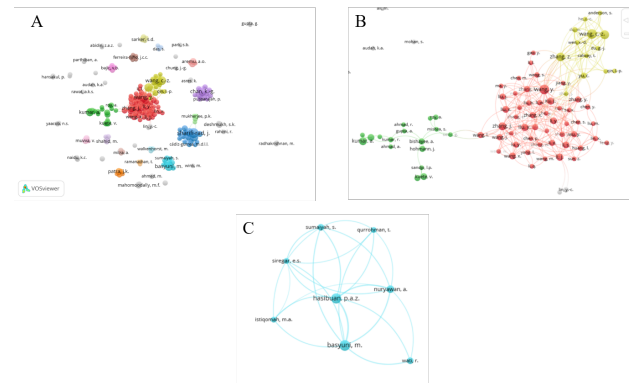


Figure 2. Bibliometric Analysis of Co-Authorship. (A) Citations of Authors. Fouthy Four Clusters were Shown in Different Colors. Top Six Cluster with The Largest Number of Authors. (B) Wang Y is The Most Collaborator with Purple Cluster Color. (C) Eight Authors from Indonesia Who have Relationship Publications.

3. RESULT AND DISCUSSION

3.1 Publication Yield in Bibliometric Analysis

Total of 129,342 documents related to the topic of mangroves” or “polyisoprenoid” or “polyprenol” or “dolichol were identified in the Scopus database. 106,679 (82.5%) original research articles, 9,646 (7.5%) review articles, 5,504 (4.3%) conference papers, 5,176 (4.0%) book chapters, 877 (0.7%) books, 424 (0.3%) note, 288 (0.2%) editorial and 748 other publications including short survey, letter, erratum, conference review, data paper, retracted, abstract report, etc.

The publications detected in the 1846-2022 range show 410 (0.3%) papers published in 2022. Papers, 13,907 (10.8%) have been published this year (2021), and 12,451 (9.6%) articles were published in 2020, while lower years have a minor trend. The increasing trend indicates that research was intensive and diverse globally.

The six official languages of the United Nations are Arabic, Chinese, English, French, Russian and Spanish. English is the most widely used language globally, including the Scopus database. This language dominated 12.4129 (95.5%) and followed by Chinese, Spanish, Portuguese, French, Japanese, German, Russian, Korean, Persian, Turkish, Polish, Italian, Malay, Czech, Arabic, Croatian, Thai, Lithuanian, Hungarian, Swedish, Ukrainian, Bulgarian, Indonesian, Serbian, and Slovak (Table 1).

Based on the stages, the papers classified 128,063 (99%) in final articles, while 1,279 (1%) articles in press. These articles collected were dominantly published documents that have gone through the review process, while a small portion has a scheduled launch.

3.2 The Keywords in Bibliometric Analysis

The keyword used by the author in the search in the articles was set to a threshold of 3 times from the Scopus database

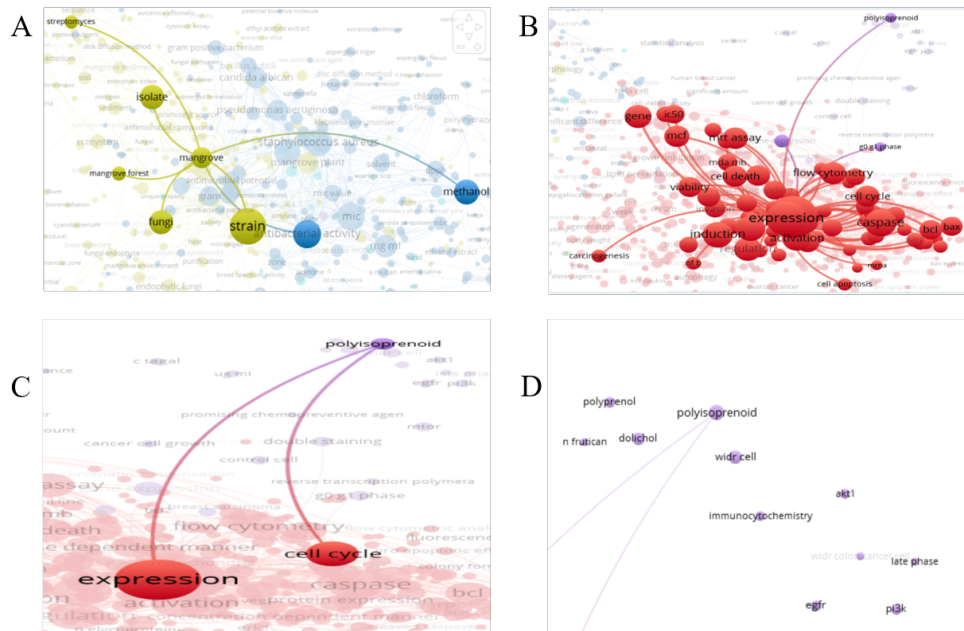


Figure 3. (A) Keyword Mangrove with Total Link Strength 599 and Related Antibacterial Activity and Fungal Assay. (B) Term of Expression in Molecule, Gen, and Cycle Cells Linked to Polyisoprenoid. (C) Occurrence of Polyisoprenoid was Nine with Total Link Strength 198. Related Keywords were Expression and Cell Cycle

in the form of RIS extension. A total of 27,293 keywords appeared 3,238 times. The most frequently occurring keyword was apoptosis (198 times and relevance score 0.56), followed by antibacterial activity, phytochemistry, mangrove plant, cell death, etc. (Figure 1A). While polyisoprenoid has frequency 9 and relevance score 1.1 (Figure 3C). Meanwhile, polyprenol and dolichol have occurrences of 5 and 6 times but still have a small link value and frequency.

The graphic of word cloud showed the largest keyword size was apoptosis followed by antibacterial activity, antifungal activity, diabetes, and carcinoma, but the difference in frequency was not significant (Figure 1B).

3.3 Bibliometric Analysis of The Publication

The largest number of published articles has been grouped by country, language, funding sponsor, subject area, affiliation, source title, and author name showed Table 1. The majority of the studies were biological, environmental, social, and pharmaceutical sciences, focusing on the study of apoptosis, antibacterial, antifungal, and pharmacological activities. Investigations leading to clinical science have not been a concern yet.

The country that has the largest publication was the United States, followed by China, India, Australia, Brazil, United Kingdom, Germany, Japan, France, and Indonesia, with the majority of language usage being English, while the largest publisher was the Chinese Academy of Science (5223) even most of the affiliate comes from China.

The Marine Pollution Bulletin published 1,875 publications with CiteScore: 7.9 SJR: 1,548 SNIP: 1,566 in 2020. In

addition, there were also more than a thousand articles published by Science of The Total Environment (CiteScore: 10.5 SJR: 1,795 SNIP: 2,015), Estuarine Coastal and Shelf Science (CiteScore 4.6 SJR: 0.852 SNIP: 1.135), Plos One (CiteScore: 5.3 SJR: 0.99 SNIP: 1.349), IOP Conference Series Earth and Environmental Science (CiteScore: 0.5 SJR: 0.179 SNIP: 0.436) and Marine Ecology Progress Series (CiteScore: 4.4 SJR: 1.151 SNIP: 0.958).

The citescor value, scimago journal range (SJR), Source Normalized Impact per Paper (SNIP) is the value calculated from the number of publications, the frequency of citations per paper, and subject area so that it can be used as a parameter for the quality of a publisher or article.

More than eighty percent of publications scientific articles with the top ten funding and publication of articles in the Scopus database was the National Natural Science Foundation of China with more than ten thousand articles (Table 1).

Hyde Kevin D from Mae Fah Luang University, Chiang Rai, Thailand was the most prominent author with 317 publications and has been cited as many as 51,152 times, followed Tam, Lovelock, Dahdouh-Guebas, F, Duarte, Basyuni, Connolly, Proksch, Proksch, Kathiresan, and Gu have publications, respectively 217; 187; 166; 162; 159; 158; 158; 146; 145 documents (Table 1).

3.4 Analysis of Co-Authorship

There were 5,790 authors who participated in the publication of mangroves, polyisoprenoids, polyprenols, and polyphenols. In this analysis, the authors filtered at least three published documents. A total of 199 authors were selected to measure

Table 1. Top Ten Countries, Languages, Organizations, Funding Sponsors, Source Title, Document Type, Subject Area, Author Name with Publications Related to Mangroves, Polyisoprenoid, Polyprenol, and Dolichol

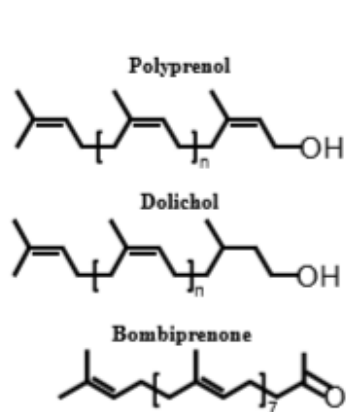
Subject	Number of Publication	Subject	Number of Publication
Countries		Affiliation	
United States	25659	Chinese Academy of Sciences	5223
China	23064	Ministry of Education China	3317
India	12698	University of Chinese Academy of Sciences	1968
Australia	9964	CNRS Centre National de la Recherche Scientifique	1798
Brazil	7993	Universidade de São Paulo	1457
United Kingdom	7777	The University of Queensland	1278
Germany	6527	Sun Yat-Sen University	1184
Japan	5670	James Cook University	1104
France	5193	Xiamen University	1049
Indonesia	4366	Ocean University of China	980
Language		Source Title	
English	124129	Marine Pollution Bulletin	1875
Chinese	2872	Science Of The Total Environment	1579
Spanish	1072	Estuarine Coastal And Shelf Science	1465
Portuguese	785	Plos One	1272
French	447	Iop Conference Series Earth And Environmental Science	1221
Japanese	148	Marine Ecology Progress Series	1057
German	131	Environmental Science And Pollution Research	956
Russian	100	Remote Sensing	888
Korean	58	Scientific Reports	737
Persian	35	Hydrobiologia	716
Funding Sponsor		Document Type	
National Natural Science Foundation of China	10413	Article	106679
National Science Foundation	3565	Review	9646
Conselho Nacional de Desenvolvimento Científico e Tecnológico	2594	Conference Paper	5504
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior	1857	Book Chapter	5176
National Key Research and Development Program of China	1823	Book	877
Ministry of Science and Technology of the People's Republic of China	1557	Note	424
Chinese Academy of Sciences	1546	Editorial	288
National Institutes of Health	1539	Short Survey	258
Japan Society for the Promotion of Science	1430	Letter	215
Ministério da Ciência, Tecnologia e Inovação	1316	Erratum	105
Subject Area		Author Name	
Agricultural and Biological Sciences	59690	Hyde, K.D.	317
Environmental Science	45174	Tam, N.F.Y.	207
Biochemistry, Genetics and Molecular Biology	25359	Lovelock, C.E.	187
Earth and Planetary Sciences	24631	Dahdouh-Guebas, F.	166
Chemistry	9653	Duarte, C.M.	162
Immunology and Microbiology	8979	Basyuni, M.	159
Medicine	8521	Connolly, R.M.	158
Pharmacology, Toxicology and Pharmaceutics	7477	Proksch, P.	158
Social Sciences	7013	Kathiresan, K.	146
Engineering	6593	Gu, J.D.	145
Year			
2021	13907		
2020	12451		
2019	10553		
2018	9730		
2017	8299		
2016	7683		
2015	6917		
2014	6325		
2013	5848		
2012	5271		

Table 2. Biological Activities of Polyisoprenoid

Species	IC ₅₀ viability WiDr Cell ($\mu\text{g/mL}$)	IC ₅₀ scavenging DPPH	Inhibition growth of <i>E. coli</i> (mm)	Inhibition growth of <i>S. aureus</i> (mm)
<i>Acacia auriculiformis</i>	1,425.46	17,100	13.17	12.29
<i>Acrostichum aureum</i>	314.623	nt	nt	nt
<i>Avicennia lanata</i>	305.928	14,681	10.19	13.25
<i>Avicennia marina</i>	209.693	13,561	10.85	10.52
<i>Avicennia officinalis</i>	1,444.45	4,515	12.66	8.85
<i>Avicennia alba</i>	nt	12,250	na	9.24
<i>Barringtonia asiatica</i>	1,831.74	4,427	12.83	9.6
<i>Bruguiera gymnorrhiza</i>	350.395	nc	10.16	11.645
<i>Bruguiera gymnorrhiza yellow leaf</i>	1,853.57	nt	nt	nt
<i>Calophyllum inophyllum</i>	275.829	1,463	9.65	8.66
<i>Ceriops tagal</i>	276.055	5,680	9.14	13.48
<i>Hibiscus tiliaceus</i>	409.821	2,018	10.52	11.57
<i>Nypa fruticans</i>	180.186	2,438	14.48	11.66
<i>Pandanus odoratissimus</i>	513.598	nc	12.49	12.38
<i>Pongamia pinnata</i>	386.77	5,100	10.19	10.96
<i>Rhizophora mucronata</i>	278.335	9,195	na	11.09
<i>Ricinus communis</i>	1,890.00	27,620	10.16	8.23
<i>Stachytarpheta jamaicensis</i>	285.492	971	9.99	11.35

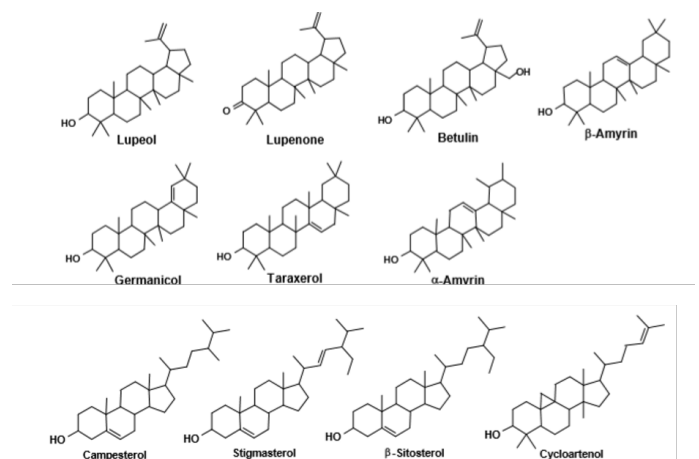
Note: nt: not test; na: not active

Data obtained from (Sari et al., 2018; Sumardi et al., 2018)

**Figure 4.** Isoprenoid Composed Polyisoprenoid Compounds (Basyuni et al., 2018)

total link strength. The six most significant clusters of total authors can be categorized as having total links. The first cluster consisted of 50 authors, with the main collaborator was Wang, the total link strength 32. The second cluster consisted of 17 authors; Kumar has the most links. The third cluster consisted of 16 authors as the most collaborators on Sharifi-Rad. The fourth cluster consists of 13 authors as the most collaborators on Wang and Yuan. The fifth cluster consists of 11 authors, with Chan and Lee as main collaborators. Besides that, the sixth cluster consists of 8 authors and Basyuni M as the main collaborator, with the affiliation from North Sumatra University.

The participative of researchers, official institutions, coun-

**Figure 5.** Phytomedicine Content of The Leaves and Roots of Some Mangroves (Basyuni et al., 2017)

tries, and collaborative funding will benefit the global community. The scientific studies were used for nature and maintaining its sustainability.

3.5 Anticancer Activity of Polyisoprenoid

At least ten mangrove species have known polyisoprenoid activity on WiDr cancer cell culture. Polyisoprenoid with predominant dolichol from *Avicennia marina* has toxicity properties with a value IC₅₀ 155 $\mu\text{g/mL}$ against colon cancer cells with a selective index 5.2. In the cell cycle, the dominant polyisoprenoid suppresses the G₀-G₁ phase. Analysis using flowcytometry showed apoptotic induction by increasing expression p52 and gen Bcl-2. COX-2 gene expression can be suppressed directly

Table 3. The Yield of Polyisoprenoid from Mangrove Leaves

Species	Polyisoprenoid (mg/g dw)	Yield (%)
<i>A. auriculiformis</i>	28	2.8
<i>B. asiatica</i>	133	13
<i>C. equisetifolia</i>	65	6.5
<i>C. inophyllum</i>	25	2.5
<i>H. tiliaceus</i>	14	1.4
<i>M. candidum</i>	140	14
<i>M. citrifolia</i>	119	12
<i>P. odoratissima</i>	23	2.3
<i>P. pinnata</i>	12	1.2
<i>R. communis</i>	20	2
<i>S. hydrophyllacea</i>	138	13.8
<i>S. jamaicensis</i>	19	1.9
<i>S. portulacastrum</i>	53	5.3
<i>T. catappa</i>	65	6.5

proportional to increased doses (Illian et al., 2018; Sari et al., 2018a; Sari et al., 2018b; Sari et al., 2018c). It can still be considered as an anticancer or complementary candidate. The methanol, water, and n-hexane extract of leaves have effective cytotoxic against HL-60, HCT-116, and NCI-H23 cells besides inhibiting antiproliferative HepG2 and MCF-7 cell culture (Albinhassan et al., 2021; Reddy and Ratna, 2016).

Dolichol from *Avicennia lanata* has IC₅₀ 306 µg/mL for colon cancer cells with selective index 1.9. The cell cycle did not indicate suppressive activity and was lower than *Avicennia marina*.

Polyisoprenoid from *Rhizophora mucronata* and *Ceriops tagal* had toxic on WiDr cell cultures with IC₅₀ 278 and 276 µg/mL, respectively. The compounds inhibit the cell cycle in the S and G2/M phases; besides that expressed Bcl-2 and cyclin D1 genes were suppressed (Sari et al., 2018c). *Nypa fruticans* showed the highest cytotoxic activity and moderate category with IC₅₀ 180.186 µg/mL. WiDr cell culture, this compound inhibits the cell cycle in S and G2/M phase (Sari et al., 2018b).

3.6 Antimicrobial Activity of Polyisoprenoid

Sixteen mangrove species with varying polyisoprenoids have obtained twelve as antibacterial potential, following *Acacia auriculiformis*, *Avicennia lanata*, *Avicennia marina*, *Avicennia officinalis*, *Barringtonia asiatica*, *Bruguiera gymnorhiza*, *calophyllum inophyllum*, *Hibiscus tiliaceus*, *Nypa fruticans*, *Pandanus odoratissimus*, *Pongamia pinnata*, and *Ricinus communis*, shown on Table 2.

The polar portion of mangroves was reported to act as antibacterial. They were *Avicennia marina*, *Acacia auriculiformis*, *Barringtonia asiatica*, *Hibiscus tiliaceus*, *Bruguiera gymnorhiza*, *Avicennia lanata*, *Avicennia officinalis*, *Avicennia alba*, *Pandanus odoratissimus*, *Ricinus communis* (Gurmeet and Amrita, 2015; Khan and Omoloso, 2002; Mandal et al., 2005; Manilal et al., 2016; Naz and Bano, 2012; Thatoi et al., 2016). Further develop-

ment of studies related to mechanical action and safety was still needed to find out active compounds that can be used as biomarkers.

Analysis of the chemical content of the non-polar parts of the leaves and roots of six mangroves, *Acanthus ilicifolius* (Acanthaceae), *Bruguiera parviflora* (Rhizophoraceae), *Ceriops tagal* (Rhizophoraceae), *Rhizophora apiculata* (Rhizophoraceae), *Sonneratia caseolaris* (Sonneratiaceae), and *Xylocarpus granatum* (Meliaceae), by using GC-MS analysis the chemical information has been obtained. Namely: lupeol, lupenone, betulin, β-amyrin, germanicol, taraxerol, α-amyrin, campesterol, stigmasterol, β-sitosterol, and cycloartenol, as shown in Figure 5.

4. CONCLUSION

Mangroves are potential plants that grow along the coastline and provide benefits in aspect of life. Publication of academic documents on mangroves regarding biological content and activity continues to increase, and there is even a publication plot in 2022. Evaluation of specific and in-depth topics from scientific articles on mangroves is still much needed in developing and resolving global health problems. Research in microbiology and cancer still has an excellent opportunity to be explored and requires collaboration with authors with various disciplines.

5. ACKNOWLEDGEMENT

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