

Bibliometric Study of Microwave-Assisted Synthesis of Flavanone Derivatives

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Abstract

This study aims to describe various studies related to synthesizing flavanone derivatives using the microwave-assisted method with a bibliometric approach. Metadata information was collected from Scopus on June 30th, 2023, with three keywords (microwave-assisted OR microwave, synthesis, and flavanone) searched for article titles, abstracts, and keywords. Analysis and research mapping were carried out with VOSviewer. Of the 33 articles relevant for analysis, 15 keyword clusters were obtained, most of which contained a list of flavanone derivatives. Interestingly, none of these clusters contain keywords for well-known compounds from the flavanone group, such as pinostrobin, pinocembrin, or hesperetin. In other words, there is an excellent opportunity to obtain novelty for microwave-assisted derivatization studies of flavanones. The chances of publication of these studies are greater in Chemistry of Heterocyclic Compounds (Springer Nature), Oriental Journal of Chemistry (Scientific Publishers), and Tetrahedron Letters (Elsevier), each with three documents. Meanwhile, most researchers on this topic come from India with 13 documents. This information allows researchers on this topic to determine potential flavanones that have the opportunity to be derivatized by the microwave-assisted method.

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INTRODUCTION

Flavanones are a class of flavonoid compounds, a subclass of polyphenolic compounds found in various plants. Flavanones are characterized by their chemical structure, consisting of a 15-carbon skeleton with a ketone (carbonyl) group at the C4 position. They are derived from flavonoids by removing a double bond in the C2-C3 position of the flavonoid structure¹. Flavanones are known for their antioxidant properties and are commonly found in various fruits and vegetables. Citrus fruits, such as oranges, lemons, and grapefruits, are prosperous sources of flavanones². Some well-known flavanones found include pinostrobin, hesperetin, or naringenin. These compounds have been studied for their potential health benefits, including their role in reducing oxidative stress, inflammation, and their potential to support cardiovascular health³. Flavanones are also being investigated for their anti-cancer and anti-inflammatory properties⁴.

Obtaining derivatives of flavanones typically involves modifying the parent organic molecule to introduce specific functional groups or structural changes. Derivatization is a common technique in organic chemistry used for various purposes, such as enhancing the compound's stability, reactivity, or analytical properties. It's important to note that the specific methods and reagents used to obtain organic derivatives can vary widely depending on the structure of the original compound and the desired modification. Safety precautions, proper lab techniques, and knowledge of organic chemistry principles are essential when working with organic compounds and their derivatives⁵.

One of the most advanced, innovative, and environmentally friendly ways to obtain flavanone derivatives is to utilize microwaves using a microwave. Using a microwave can not only save material usage but can also shorten reaction time⁶. For example, our previous research⁷ obtained prenyl derivatives from pinostrobin, a type of flavanone isolated from

Boesenbergia pandurata, with a yield of 96% in 30 minutes using microwave assistance, which was proven to show anti-breast cancer activity 4-5 times better than pinostrobin. Therefore, microwave-assisted synthesis of flavanone derivatives is a feasible strategy for discovering new lead compounds with various pharmacological activities. However, no research exclusively reviews previous studies regarding the use of this method for flavanone derivatives. Therefore, this brief study aims to describe research related to the microwave-assisted synthesis of flavanone derivatives using a bibliometric approach

MATERIALS AND METHODS

Materials

The software used to visualize the analysis results was VOSViewer 1.6.19 (<https://www.vosviewer.com/>) from the Center for Science and Technology Studies, Leiden University. All analyzed articles were obtained from the Scopus database (<https://www.scopus.com/sources.uri>) on June 30th, 2023. In this study, access to Scopus was provided by Universitas Airlangga, Surabaya, Indonesia.

Methods

The approach used was bibliometric analysis with the Scopus database. Search keywords were made in one search level consisting of three keywords. Apart from analyzing articles and journals, analysis was also carried out on the authors 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 research⁸ as follows:

Determination of search keywords

In this study, the keywords used consist of one level, which consists of three keywords. The first keyword was the method used: "microwave-assisted OR microwave". The use of the 'OR' operator is indicated because of the probability of using other terms by the authors, so the term 'microwave' is used, which is more general. The second keyword was "synthesis" as the target carried out, while the third keyword was "flavanone" as the object studied. The criteria chosen for these keywords were the article's title, abstract, and keywords, assuming that articles that specifically address this topic must contain keywords specified in one of the three criteria.

Initial search results

Search results by keyword were presented as a whole in the Scopus database. Data collection of a number of Scopus documents is carried out without any restrictions, and no metadata is downloaded. In total, 34 documents contained titles, abstracts, or keywords containing the three previous search keywords.

Refinement of search results

The initial search results obtained were filtered based on several categories. Several parameters that could be limited in the Scopus database include access type, year of publication, author's name, subject area, document type, publication stage, source title, keywords, affiliation, funding sponsor, country, source type, and language. In this study, these parameters were not restricted to obtaining comprehensive results, except for the type of sources limited to journals. This limitation is made with the assumption that other types of sources, such as books, book series, and book chapters, contain tertiary information that is already available in journal articles. From the limitations, 33 relevant research articles were obtained for further analysis.

Compile preliminary data statistics

The filtered data was then downloaded in CSV format. Exported information includes citations, bibliography, abstract and keywords, funding details, and other information.

Data analysis

Bibliometric analysis of the downloaded data was performed and visualized using VOSviewer 1.6.19. As in our previous study, the parameters analyzed consisted of publications and citation structures, authors and co-authorship relations, and country of study location.

RESULTS AND DISCUSSION

Publications and citation structures

Of the 33 published documents in Scopus Indexed Journals obtained based on searches, the most publications occurred during 2012 with five documents. The oldest publication was reported in 1999, and as of 2023, there are two publications on the topic. However, of the 33 articles, six were published in four journals that are no longer indexed by Scopus. Still, discontinued status applies to journals and articles published after the year of determination, while the articles analyzed were published earlier so the six articles are still used in the analysis. The article's complete results from the search results for these keywords were presented in **Table I**.

Table I. Articles on Scopus with the keywords "Microwave-assisted OR Microwave", "Synthesis", and "Flavanone". Articles in red indicate discontinued status in the Scopus database

No	Publication year	Authors	Title	Journal	Publisher	Number of citations
1	2007	Polshettiwar, Vivek; Varma, Rajender S.	Tandem bis-aldol reaction of ketones: A facile one-pot synthesis of 1,3-dioxanes in aqueous medium	Journal of Organic Chemistry	American Chemical Society	86
2	2011	Neves, Marta Perro; Cidade, Honorina; Pinto, Madalena; Silva, Artur M.S.; Gales, Luís; Damas, Ana Margarida; Lima, Raquel T.; Vasconcelos, M. Helena; Nascimento, Maria De São José	Prenylated derivatives of baicalein and 3,7-dihydroxyflavone: Synthesis and study of their effects on tumor cell lines growth, cell cycle and apoptosis	European Journal of Medicinal Chemistry	Elsevier	62
3	2012	Bonfield, Kevin; Amato, Erica; Bankemper, Tony; Agard, Hannah; Steller, Jeffrey; Keeler, James M.; Roy, David; McCallum, Adam; Paula, Stefan; Ma, Lili	Development of a new class of aromatase inhibitors: Design, synthesis and inhibitory activity of 3-phenylchroman-4-one (isoflavanone) derivatives	Bioorganic and Medicinal Chemistry	Elsevier	52
4	2001	Patonay, Tamás; Varma, Rajender S.; Vass, András; Lévai, Albert; Dudás, József	Highly diastereoselective Michael reaction under solvent-free conditions using microwaves: Conjugate addition of flavanone to its chalcone precursor	Tetrahedron Letters	Elsevier	47
5	2005	Sagrera, Gabriel J.; Seoane, Gustavo A.	Microwave accelerated solvent-free synthesis of flavanones	Journal of the Brazilian Chemical Society	Sociedade Brasileira de Química	36
6	2006	Hemanth Kumar K.; Perumal P.T.	A simple and facile solventless procedure for the cyclization of 2'-amino- and 2'-hydroxy-chalcones using silica-supported sodium hydrogen sulphate as heterogenous catalyst	Canadian Journal of Chemistry	NRC Research Press	35
7	2011	Mondal, Rina; Gupta, Arpita Das; Mallik, Asok K.	Synthesis of flavanones by use of anhydrous potassium carbonate as an	Tetrahedron Letters	Elsevier	33

8	2012	Albogami, Abdullah; Karama, Usama; Mousa, Ahmed Amine; Khan M.; Al-Mazroa, Sara Abdullah; Alkhathlan, Hamad Z.	inexpensive, safe, and efficient basic catalyst Simple and efficient one step synthesis of functionalized flavanones and chalcones	Oriental Journal of Chemistry	Scientific Publishers	26
9	2008	Ashok D.; Shrivani D.	One-pot synthesis of novel spiro 2,3,7,8-tetrahydro-benzo[1,2-b:5,4-b']dipyran-4,6-dione and 2,3,8,9-tetrahydro-benzo[1,2-b:4,3-b']dipyran-4,10-dione derivatives	Tetrahedron Letters	Elsevier	24
10	2012	Kahriman, Nuran; Iskender, Nagihan Yilmaz; Yücel, Murat; Yayli, Nurettin; Demir, Emine; Demirbağ, Zihni	Microwave-assisted synthesis of 1,3'-diazaflavone/ flavone and their alkyl derivatives with antimicrobial activity	Journal of Heterocyclic Chemistry	Wiley-Blackwell	20
11	2019	Rocha, Djenisa H.A.; Vaz, Patrícia A.A.M.; Pinto, Diana C.G.A.; Silva, Artur M.S.	Synthesis chalcones and their isomerization into flavanones and azaf flavanones	Methods and Protocols	Multidisciplinary Digital Publishing Institute (MDPI)	16
12	1999	Matloubi Moghaddam, Firouz; Ghaffarzadeh, Mohammad; Abdi-Oskoui, Seyed Hossein	Tandem fries reaction-conjugate addition under microwave irradiation in dry media; one-pot synthesis of flavanones	Journal of Chemical Research – Part S	Science Reviews Ltd.	14
13	2011	Kamboj, Ramesh C.; Sharma, Geeta; Kumar, Dinesh; Arora, Rita; Sharma, Chetan; Aneja K.R.	An environmentally sound approach for the synthesis of some flavanones and their antimicrobial activity	International Journal of ChemTech Research	Sphinx Knowledge House	12
14	2006	Nie, Aihua; Huang, Ziwei	Microwave-assisted reaction of 2'-hydroxychalcones with hydrazides to synthesize flavanone hydrazone and 4,5-dihydropyrazole derivatives	Journal of Combinatorial Chemistry	American Chemical Society	10
15	2020	Leitão, Emília P. T.	Chalcones: Retrospective synthetic approaches and mechanistic aspects of a privileged scaffold	Current Pharmaceutical Design	Bentham	9
16	2016	Ashok, Dongamanti; Kumar, Rayagiri Suneel; Gandhi, Devulapally Mohan; Jayashree, Anireddy	Solvent-free microwave-assisted synthesis and biological evaluation of auronones and flavanones based on 2,2-dimethylchroman-4-one	Chemistry of Heterocyclic Compounds	Springer Nature	8
17	2012	Vaz, Patrícia A. A. M.; Pinto, Diana C. G. A.; Rocha, Djenisa H. A.; Silva, Artur M. S.; Cavaleiro, José A. S.	New syntheses of 3-aryloflavone derivatives; Knoevenagel condensation and oxidation versus one-pot synthesis	Synlett	Thieme	8
18	2011	Shakil N.A.; Singh, Manish K.; Sathiyendiran M.; Kumar J.	Microwave accelerated solvent-free synthesis and antifungal evaluations of flavanones	Archives of Phytopathology and Plant Protection	Taylor & Francis	8
19	2020	Schultze, Christiane; Foß, Stefan; Schmidt, Bernd	8-Prenylflavanones through Microwave Promoted Tandem Claisen Rearrangement/6-endo-trig Cyclization and Cross Metathesis	European Journal of Organic Chemistry	Wiley-Blackwell	7
20	2016	Ashok, Dongamanti; Padmavati, Kadiyala; Vijaya Lakshmi,	Microwave-assisted one-pot synthesis of pyrazoly-substituted benzochroman-	Chemistry of Heterocyclic Compounds	Springer Nature	7

		Bommidi; Sarasija, Madderla	4-one derivatives and evaluation of their anticancer activity			
21	2020	Urmann, Corinna; Riepl, Herbert	Semi-Synthetic Approach Leading to 8-Prenylaringenin and 6-Prenylaringenin: Optimization of the Microwave-Assisted Demethylation of Xanthohumol Using Design of Experiments	Molecules	Multidisciplinary Digital Publishing Institute (MDPI)	6
22	2021	Murti, Yogesh; Pathak, Devender; Pathak, Kamla	Green chemistry approaches to the synthesis of flavonoids	Current Organic Chemistry	Bentham	5
23	2017	Sheng, Xiao; Jia, Xinyu; Tang, Fei; Wang, Yang; Hou, Ai-Jun	The total synthesis of (\pm)-sanggenol F	Tetrahedron	Elsevier	5
24	2010	Boob, Sonal D.; Rajput P.R.	A facile solvent free microwave induced synthesis of chlorine containing pyrazoline and Isoxazoline derivatives and their phytotic impact on some flowering plants and antimicrobial activity	Oriental Journal of Chemistry	Scientific Publishers	5
25	2016	Dongamanti, Ashok; Naji, Hayder Hasan; Bommidi, Vijaya Lakshmi; Madderla, Sarasija	Microwave-assisted one-pot synthesis and antimicrobial evaluation of 2-(1-phenyl-3-(2-thienyl)-1H-pyrazol-4-yl)chroman-4-one derivatives	Heterocyclic Communications	Walter de Gruyter	4
26	2014	Al-Bogami, Abdullah S.; Alkhatlan, Hamad Z.; Saleh, Tamer S.; Elazzazy, Ahmed M.	Microwave-assisted synthesis of potent antimicrobial agents of flavanone derivatives	Oriental Journal of Chemistry	Scientific Publishers	4
27	2017	Ramana Kishore N.; Ashok, Dongamanti; Rao, Boddu Ananda; Sarasija, Madderla; Murthy, Nandula Y. S.	Simple and efficient route for the synthesis of functionalized 2,3,7,8-tetrahydro-4H,6H-pyrano[3,2-g]chromene-4,6-diones	Chemistry of Heterocyclic Compounds	Springer Nature	3
28	2016	Sayyahi, Soheil; Heidari, Somayeh	Polymer-supported basic ionic liquid as an efficient heterogeneous catalyst system for straightforward synthesis of flavanones	Iranian Journal of Catalysis	Islamic Azad University	3
29	2012	Al-Bogami, Abdullah S.	Microwave-assisted synthesis of chalcones, flavanones and 2-pyrazolines: Theoretical and experimental study	Letters in Organic Chemistry	Bentham	3
30	2020	Gomes, Claudia R B; de Souza, Marcus V N; Facchinetti, Victor	A Review on Onychine and its Analogs: Synthesis and Biological Activity	Current Organic Synthesis	Bentham	2
31	2019	Ashok D.; Nagaraju N.; Dharavath, Ravinder; Ram Reddy M.; Ramakrishna K.; Sarasija M.	A novel method for synthesis and their antimicrobial activity of 1H-tetrazole based flavones and flavanone derivatives under ultrasonic and microwave irradiation methods	Asian Journal of Chemistry	Asian Publication Corporation	1
32	2023	Van, Pham Thi Bich; Huy, Le Thanh; Thuy, Nguyen Thi Bich; Nga, Vo Thi; Tam, Le Minh; Phuong, Ho; Hao, Hoang Minh	Solvent-free, microwave-assisted, solid-catalyzed synthesis and α -Glucosidase inhibition of chalcones	Vietnam Journal of Chemistry	Wiley-Blackwell	0

33	2023	Kalar, Pankaj Lal; Agrawal, Swatantra; Kushwaha, Sandhya; Gayen, Shovanlal; Das, Kalpataru	Recent Developments on Synthesis of Organofluorine Compounds Using Green Approaches	Current Organic Chemistry	Bentham	0
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Apart from authorship, data collection and analysis are conducted at the journal and publisher where the article is published. Analysis was carried out on these keyword combinations, and the results showed that 26 journals and 16 publishers published articles with these keyword combinations. Most articles were published in three journals: Chemistry of Heterocyclic Compounds (Springer Nature), Oriental Journal of Chemistry (Scientific Publishers), and Tetrahedron Letters (Elsevier), each with three articles. Meanwhile, the publishers with the most journals are Elsevier and Bentham, each with four journals. However, more articles are published in Elsevier journals than Bentham (6 versus 5). Nevertheless, considering the number of citations of published papers, publishing an article in the Journal of Organic Chemistry (American Chemical Society) is advantageous because it shows the highest chance of obtaining multiple citations (86 citations from 1 article) Complete data is presented in **Table II**.

Table II. Comparison of each journal and publisher with the keywords “Microwave-assisted OR Microwave”, “Synthesis”, and “Flavanone”. Journals in red indicate discontinued status in the Scopus database

No	Journal	Publisher	Total articles	Total citations
1	Tetrahedron Letters	Elsevier	3	104
2	Journal of Organic Chemistry	American Chemical Society	1	86
3	European Journal of Medicinal Chemistry	Elsevier	1	62
4	Bioorganic and Medicinal Chemistry	Elsevier	1	52
5	Journal of the Brazilian Chemical Society	Sociedade Brasileira de Quimica	1	36
=6	Oriental Journal of Chemistry	Scientific Publishers	3	35
=6	Canadian Journal of Chemistry	NRC Research Press	1	35
8	Journal of Heterocyclic Chemistry	Wiley-Blackwell	1	20
9	Chemistry of Heterocyclic Compounds	Springer Nature	3	18
10	Methods and Protocols	Multidisciplinary Digital Publishing Institute (MDPI)	1	16
11	Journal of Chemical Research – Part S	Science Reviews Ltd.	1	14
12	International Journal of ChemTech Research	Sphinx Knowledge House	1	12
13	Journal of Combinatorial Chemistry	American Chemical Society	1	10
14	Current Pharmaceutical Design	Bentham	1	9
=15	Archives of Phytopathology and Plant Protection	Taylor & Francis	1	8
=16	Synlett	Thieme	1	8
17	European Journal of Organic Chemistry	Wiley-Blackwell	1	7
18	Molecules	Multidisciplinary Digital Publishing Institute (MDPI)	1	6
=19	Current Organic Chemistry	Bentham	2	5
=19	Tetrahedron	Elsevier	1	5
21	Heterocyclic Communications	Walter de Gruyter	1	4
=22	Iranian Journal of Catalysis	Islamic Azad University	1	3
=22	Letters in Organic Chemistry	Bentham	1	3
24	Current Organic Synthesis	Bentham	1	2
25	Asian Journal of Chemistry	Asian Publication Corporation	1	1
26	Vietnam Journal of Chemistry	Wiley-Blackwell	1	0
Total			33	561

Further analysis based on keywords from each article shows exciting results, with several keywords with prominent link strength outside the search keywords (Microwave-assisted OR Microwave, Synthesis, and Flavanone). The keyword 'flavonoids' shows the highest occurrences (18) and link strength (300). However, 'microwave' and 'microwave-assisted' only showed 5 and 1 occurrences and 94 and 17 link strengths, respectively. The most popular keyword related to microwave technique is 'microwave irradiation' with 17 occurrences and 277 link strengths. In other words, the term 'microwave irradiation' seems more popular than 'microwave-assisted'.

Another interesting point is that all the lead compounds used are written using IUPAC names, none of which are written in the title, abstract, and keywords using the trivial name of the compound. In addition, an analysis of the various lead

compounds also showed that most of the well-known flavanones, such as pinostrobin, pinocembrin, or hesperetin, did not appear in search terms. Naringenin (in 6-prenylnaringenin or 8-prenylnaringenin) and sanggenol F are the only well-known flavanones that appear. Moreover, most authors focus on synthesizing flavanone compounds with starting materials such as chalcone rather than synthesizing existing flavanones. Even if there is, the majority use reflux method, as reported by Sinyeue *et al*⁹. Thus, the microwave-assisted synthesis of flavanone derivatives has been shown to offer a tremendous novelty opportunity due to the lack of previous studies, at least those published in Scopus-indexed journals, as shown in **Figure 1**.

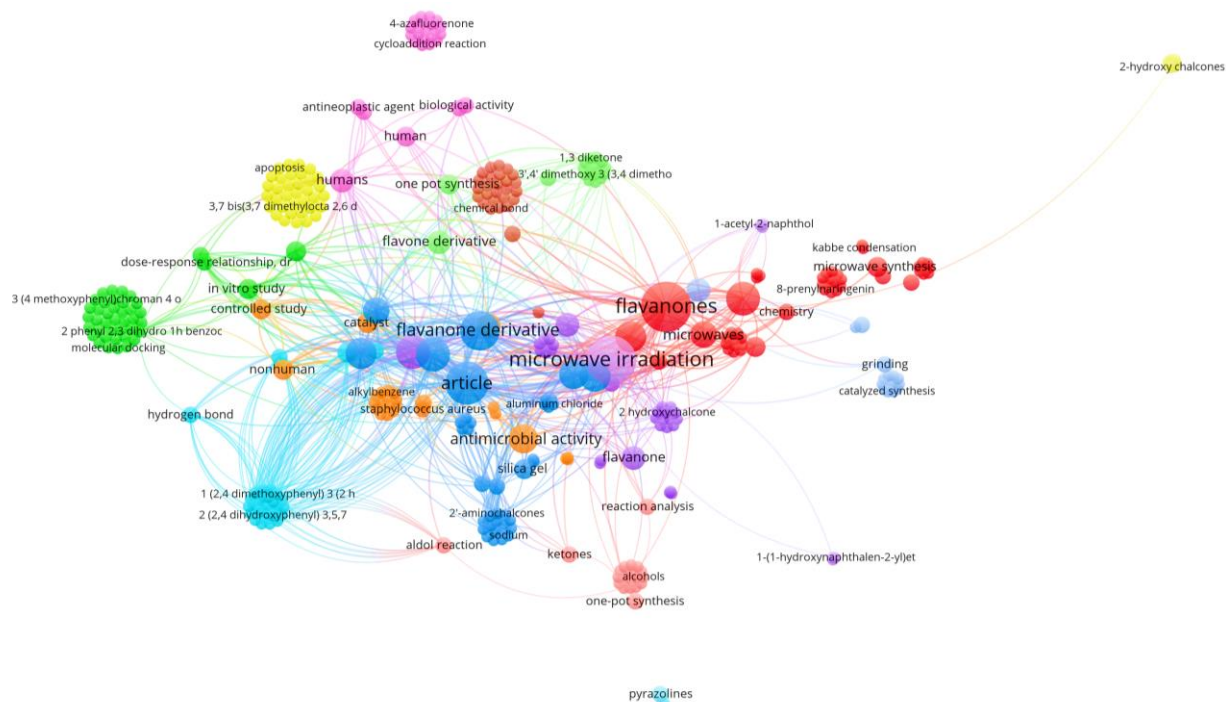


Figure 1. Network visualization of the keywords “Microwave-assisted OR Microwave”, “Synthesis”, and “Flavanone”.

Authors and co-authorship relations

Author institutional analysis with the Scopus database was not carried out due to inconsistent institutional writing due to non-harmonized institutional indexation on Scopus⁸. Instead, the analysis was performed on the authors and their agencies only. The analysis was performed based on the citation results of the entire document because these parameters can diversify each author instead of a direct author analysis (which only counts one author per article). The analysis results show that 13 authors show link strength above 500, but only six have citations above 10. The six authors were then identified with the most significant influence on the topics studied, especially those published in Scopus-indexed journals. The author with the most citations (26) is Rajender S. Varma from Technická Univerzita v Liberci, Czech Republic, with 758 link strength and last published an article on the related topic in 2007, indicating that this researcher is the most considered regarding this topic. However, the author with the most documents is Dongamanti Ashok from Osmania University, India, with five documents that were last published in 2019, as shown in **Figure 2**. Thus, these two researchers deserve to be role models for research on microwave-assisted synthesis of flavanone derivatives¹⁰.

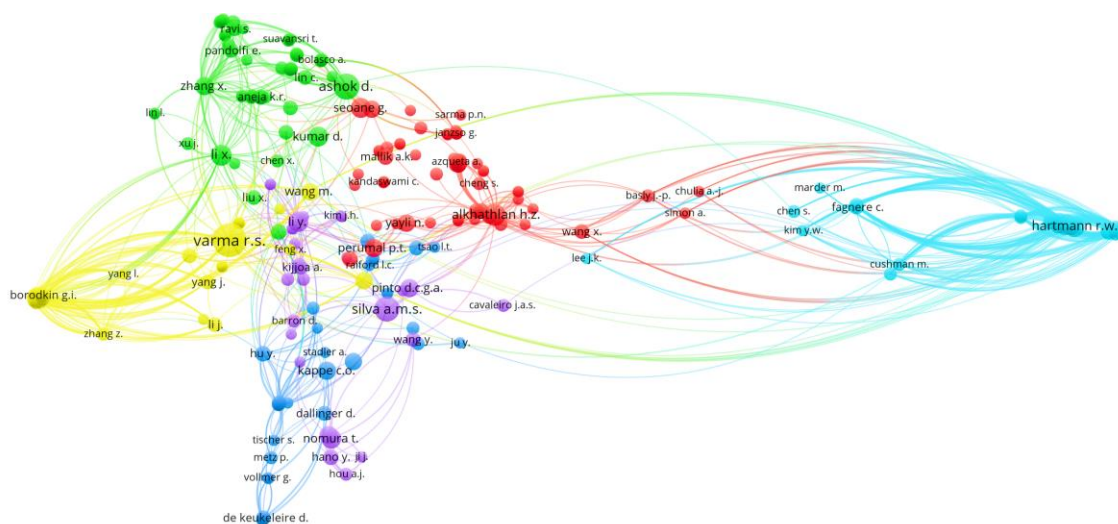


Figure 2. Network visualization of authorship of the keywords “Microwave-assisted OR Microwave”, “Synthesis”, and “Flavanone”.

Country of study location

Finally, the analysis is carried out on the country of origin of the researcher, or in other words, the country of origin of the researcher's institution. The 33 documents were published by researchers from 12 countries, both individually and in collaboration between countries, as shown in **Figure 3**. There is only one document produced by cross-country collaboration: between the US (US Environmental Protection Agency) and Hungary (University of Debrecen and University of Kaposvár). India produced the most articles on this topic, with 13 documents, followed by the US and Portugal, with four documents each. Of the 13 documents, six were published by researchers from Osmania University, Hyderabad, the same affiliate as Dongamanti Ashok, the researcher with the most documents on the topic. In other words, the institution is the global epicenter of research on microwave-assisted synthesis of flavanone derivatives.



Figure 3. Network visualization of countries of the keywords “Microwave-assisted OR Microwave”, “Synthesis”, and “Flavanone”.

CONCLUSION

This study found that several previous studies have reported microwave-assisted synthesis of flavanone derivatives but not some well-known flavanone derivatives such as pinostrobin, hesperetin, or naringenin. This information is valuable for medicinal chemistry researchers to carry out the microwave-assisted synthesis of these flavanone derivatives as a novel research topic.

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AUTHORS' CONTRIBUTION

HP: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing. **MR:** data curation, formal analysis, investigation, methodology, resources, validation, visualization, writing – original draft, writing – review & editing.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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