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Global research landscape on two coumarin derivatives: A scientometric study of trends and innovations from 1990 to 2022

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ABSTRACT

Daphnetin(7,8-dihydroxycoumarin) and esculin (6,7-dihydroxycoumarin-β-D-glucopyranoside) are natural coumarins that have gained increasing research attention over the years due to their therapeutic applications in a wide range of human ailments. This study assessed the current research status and future research trends of daphnetin and esculin through bibliometric analysis. Relevant articles on these compounds published between 1990 and 2022 were identified in the Web of Science and Scopus databases. "Daphnetin"* or "Esculin"* were used as the search terms to retrieve articles in the "Topic" field of both databases, and RStudio and VOSviewer were used for bibliometric analysis and visualization of *meta*-data from the retrieved documents. A total of 2172 publications on both compounds were identified. Research outputs on daphnetin and esculin have increased steadily over the years with an annual growth rate of 4.46%. China (576 articles, 28.2%) and USA (198 articles, 9.7%) are the top countries researching on daphnetin and esculin with China being the main country in the international cooperation network. International Journal of Systematic and Evolutionary Microbiology (215 articles), Journal of Clinical Microbiology (71 articles), International Journal of Systematic Bacteriology (29 articles), Archives of Microbiology (24 articles), and Antonie Van Leeuwenhoek (21 articles) are the top five journals publishing articles on these compounds. The most common research topics for both compounds were their biological activities, including anti-microbial, antibiotic resistance, anticancer, anti-inflammatory and antioxidant effects. With an average citation of 21.83 per document, citation analysis revealed that both compounds have been cited a considerable number of times, indicating their significance in the scientific community. Taken together, findings from this review provide insights into the status and trends of daphnetin and esculin research, thus highlighting their increasing interest and potential applications in the medical field.

1. Introduction

Coumarins, which are oxygenated heterocyclic compounds, are found in various plants, fungi, and bacteria, with around 1300 chemoforms documented. These compounds have derivatives present in different parts of plants, including leaves (*Murraya paniculata* Kaneh.), roots (*Ferulago campestris* (Besser) Grecescu), seeds [(tonka beans) (*Dipteryx odorata* (Aubl.) Forsyth f.)], and fruits (*Aegle marmelos* (L.) Corrêa) (Stefanachi et al., 2018). Many studies have explored the therapeutic potentials of coumarins to develop assays for their efficacy, toxicity, detection, and synthesis (Sovrlić & Manojlović, 2017).

The word coumarin was derived from the French word "coumarou"

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for Tonka bean, and was first obtained as a plant-derived compound in 1820 (Deiters & Martin, 2004). Due to the polar ring of coumarins, they are typically found in a free state and exhibit blue fluorescence when exposed to ultraviolet light. The long conjugation in the rings of coumarins with electron-rich and charge-transfer properties allows them to interact with ions and molecules. The chemical structure of coumarins (Fig. 1a) is derived from the fusion of a pyran-2-one and a benzene ring, and its systematic name is 2H-1-benzopyran-2-one (Rawat & Reddy, 2022; Stefanachi et al., 2018). Typically, in coumarins, the oxygen atom is regarded as position 1, followed by the carbonyl carbon at position 2, and then the other atoms. In addition to their potent pharmacological properties, coumarin derivatives are widely used in cosmetics to enhance fragrance.

Coumarins can have a simple, dimeric, or trimeric ring structure. Within the genus *Daphne*, various coumaric compounds such as daphnetin (Fig. 1b), daphnin, esculin (Fig. 1c), umbelliferone, daphnetin-8-glucoside, and acetyl-umbelliferon have been identified (Manojlović et al., 2012; Sovrlić et al., 2015). The *Daphne* L. species alone contain over 50 different coumarins. Among the coumarins, daphnetin and esculin have attracted significant research attention due to their potential therapeutic applications in treating various human ailments.

Daphnetin (7,8-dihydroxy coumarin) (DAP) (Fig. 1b) is a white, tasteless, and odorless compound that is soluble in methanol, ethanol, and dimethyl sulfoxide, but only sparingly soluble in aqueous solutions (Shan et al., 2011). It has a molecular weight of 178.14 g/mole and a melting point of 262.0 °C (Liao et al., 2013). Daphnetin exhibits high permeability and solubility and is metabolized through phase 1 metabolism via CYP3A4 with a half-life of 15 min. However, it has poor

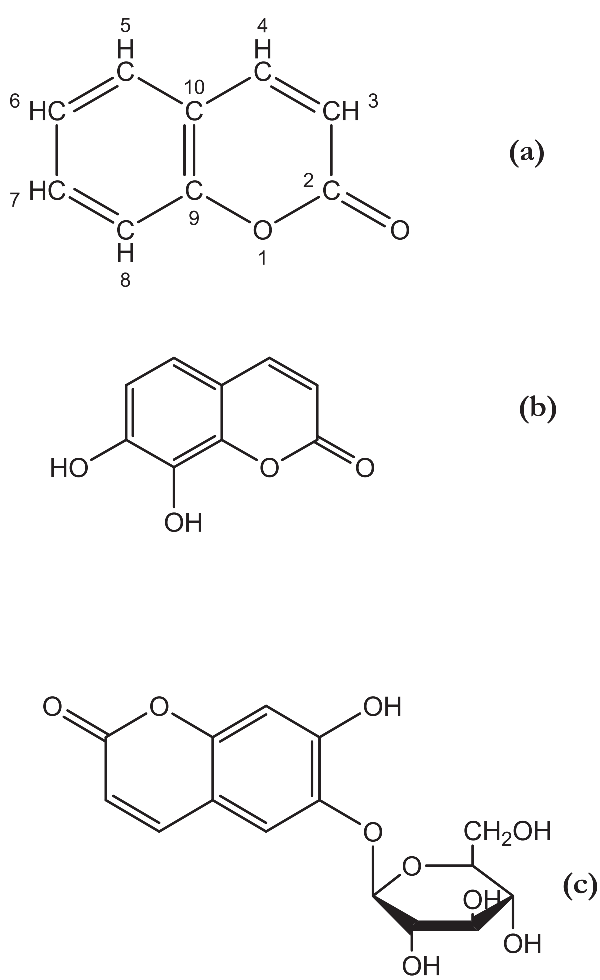

Fig. 1. (a) General structure of coumarins (b) daphnetin (c) esculin.

bioavailability and is taken up by passive diffusion in the intestine. During metabolism, daphnetin is converted to sulfonate, glucuronide, and methyl-conjugated intermediates (Du et al., 2009; Liang et al., 2010, 2017, 2015; Xia et al., 2018; Yang et al., 1999; Zhang et al., 2014). The metabolism of daphnetin has been studied, with some works focusing on glucuronidation while others provided little information on other conjugated metabolites such as methylation and sulfonation. The methylation cascade showed a higher rate of clearance compared to sulfonation and glucuronidation (Liang et al., 2016).

Daphne, one of the sources of daphnetin, is a genus of shrubs with about 70 to 95 species of perennial and evergreen shrubs, mostly found in North Africa, India, and Europe. These plants are unique for their strong aroma from their flowery part and coloured fruit (Riveiro et al., 2010). Daphnetin and its derivatives are found in different species of *Daphne,* such as *D. odora* Thunb, *D. giraldii* Nitsche, *D. gnidium* L., *D. Koreana* Nakai, *D. oleoides* Tscherniaeff ex Meisn. *D. mezereum* L. and *D. tangutica* Maxim. Daphnetin has also be isolated from the stem and leaves of *D. pedunculata* H.F.Zhou ex C.Y.Chang (Moshiashvili et al., 2020). The glucoside of daphnetin (daphnetin-8-glucoside) is derived from daphnetin-7-glucoside in *D. odora* and other 16 scaffolds were derived from *D. oleoides* (Brown, 1986; Han et al., 2020; Khouchlaa et al., 2021; Riaz et al., 2016). In East Asia, the dried and ripe seeds of *Euphorbia lathyris* Georgi (also called *Euphorbia semen*) are another source of daphnetin and other coumarins, and recently, it was reported that simple coumaric compounds such as esculin, esculetin and daphnetin were isolated from *Euphorbia semen* (Masamoto et al., 2003; Zhu et al., 2018). Synthesized or naturally occurring daphnetin is an oxygenated heterocyclic compound with a framework of benzo-α-pyrone (Xia et al., 2018). It is naturally synthesized from a shikimate cascade, with L-Phenylalanine and L-Tyrosine as the precursors. The compound can also be chemically synthesized from malic acid and pyrogallol in the presence of heated concentrated H_2SO_4 and nitrogen, as well as from umbelliferone via hydroxylation reaction as shown in Fig. 2 (NDong et al., 2003; Pan et al., 2017; Wang et al., 2020).

Esculin (6,7-Dihydroxycoumarin-β-D-glucopyranoside) (Fig. 1c) is a coumarin glycoside found in plants such as the species of the genus *Fraxinus* L. and *Aesculus hippocastanum* L. (Liang et al., 2017; Mokdad-Bzeouich et al., 2015). It consists of a monosaccharide (glucose) unit and a dihydroxy coumarin scaffold and is a fine blue, fluorescent solution (Mokdad-Bzeouich et al., 2015). A pharmacokinetic study of esculin and its derivative, esculetin, in rats, showed that esculin has a higher peak concentration (1850.39 ng/mL) and a longer time to reach maximum concentration (10.25 h) in plasma compared to esculetin (Y. Li et al., 2012; Wang et al., 2018). Metabolic studies in rats revealed that esculin undergoes biotransformation through a variety of phase I and phase II reactions, including deglycosylation, dehydrogenation, glucuronidation, hydroxylation, hydrolysis, sulfation, methylation, and glycine conjugation (Wang et al., 2016).

To comprehend a research domain and identify areas for future investigation, researchers must conduct a thorough literature search when new ideas and discoveries arise. While narrative reviews provide a broad perspective on a topic, they may not retrieve all relevant records, and authors may face challenges in selecting criteria for article retrieval (Olisah et al., 2022). Mapping the evolution of a particular field is crucial for academics and organizations and assessing its underlying knowledge framework is necessary to understand its dynamics and progress. Bibliometric tools have been used to retrieve literature and quantitatively analyze research progression by summarizing bibliographic information and visualizing trends in various subject areas (Mikhail et al., 2020). We used this tool to analyze published works on daphnetin and esculin statistically. This was important to gain a better understanding of advancements and track the evolution of knowledge on these important coumarin compounds given their reported potential pharmacological activities. On this basis, a comprehensive bibliometric analysis was conducted along with a review of the contents in the eligible articles.

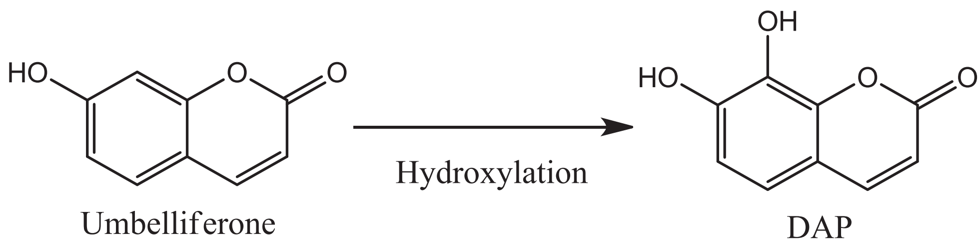

Fig. 2. Chemical synthesis of daphnetin from umbelliferone via hydroxylation.

2. Methodology

2.1. Data retrieval

We used the Web of Science (WoS) and Scopus databases to extract metadata for daphnetin and esculin found in the literature. The WoS database, housed by Clarivate Analytics, was chosen because it contains data from several disciplines. This includes the physical and biological sciences, which are the focus of the current study. Elsevier launched the Scopus database in 2004 and was chosen because it includes extensive information on a vast number of disciplines relating to citation and abstract (Olisah et al., 2018). Following the procedure highlighted in Olatunji et al. (Olatunji et al., 2021) and Olisah et al. (Olisah et al., 2022). We mapped out the research indices from retrospective encoded metadata indexed in published literature. To identify studies conducted on daphnetin and esculin, a search term: TI = ("daphnetin") OR TI = (esculin) was typed into the topic module of the WoS database and this was used to retrieve data published between January 1, 1990, to December 2022. Only articles (n = 838), reviews (n = 16), book chapters (n = 5), and editorials" (n = 1) were targeted. We excluded document types such as proceeding paper (20), meeting abstract (n = 17), note (n = 8), early access (n = 5), letter (n = 5), and retracted publications (n = 2). After exclusion, a total of 860 articles were identified and satisfied the search criteria (Fig. 3). A similar search string was used in the Scopus Database in the following manner: TITLE-ABS-KEY ("daphnetin ") OR TITLE-ABS-KEY ("esculin"). The search focused on articles (n = 1736), reviews (n = 97), book chapters (n = 9), and editorials (n = 4). Other documents, such as conference papers (n = 33), notes (n = 17), letters (n = 14), short surveys (n = 7), and erratum (n = 2) were excluded. The search yielded 1846 documents (Fig. 3). The search for each database was conducted on the 22nd of February 2023.

2.2. Data processing

A total of 860 from the WoS and 1846 documents from the Scopus database were downloaded in Bibtex format and uploaded into the RStudio (Version 1.4.1106; 2009 – 2021) for scientometric analysis. Duplicate records from the database were merged using R commands, thus giving a total of 2172 unique documents. Codes published in Aria and Cuccurullo (2017) were used to analyze bibliometric indices (yearly frequency of article publication, number of articles, authors and publication citation metrics, country collaboration pathways, and country productivity). The VOSviewer (version 1.6.15 © 2009 – 2020) was used to visualize thematic areas related to daphnetin and esculin research. Statistical codes for Kolmogorov-Smirnoff (K-S) p-value, the goodness of fit, and the β-coefficient were used to understand the annual production frequency of publication.

3. Results and discussion

3.1. Publication type and publication trend

In this study, 2172 records on daphnetin and esculin from 1990 to 2022 were identified and classified into nine types (Table 1). Most of these publications were articles (93.92 %) and reviews (4.60 %). Given that the highest publication types were articles, we focused on analyzing

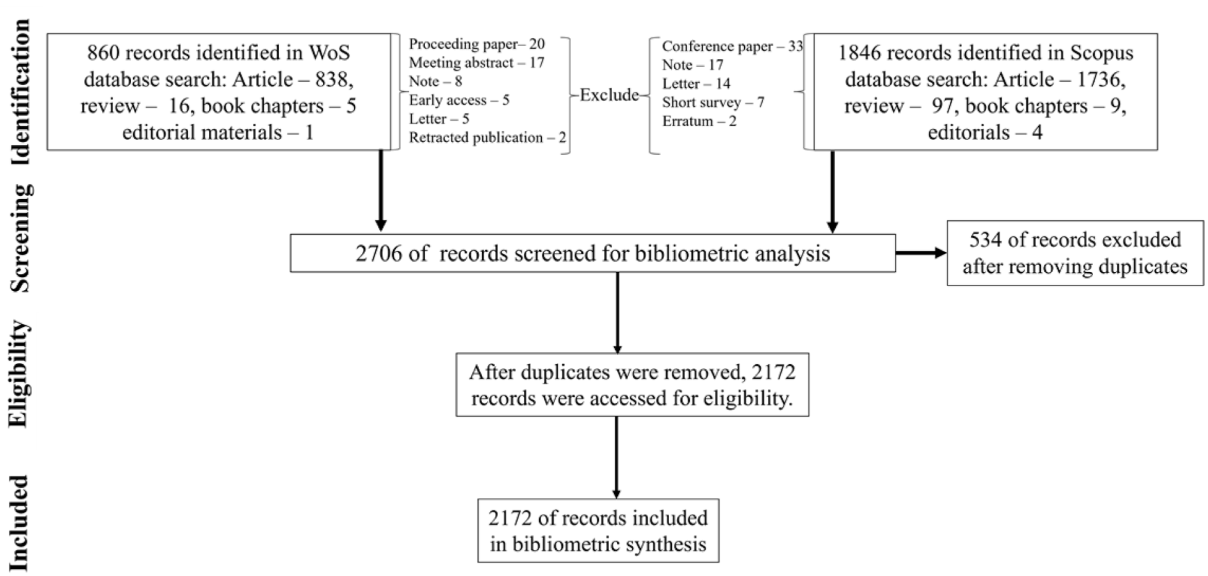

Fig. 3. Schematic diagram showing the selection criteria pathway of studies related to daphnetin and esculin published in the Web of Science and Scopus databases from 1990 to 2022.

Table 1
Bibliographic information on research conducted on daphnetin and esculin (1990–2022) retrieved from Web of Science and Scopus databases.

General data	
Time Span	1990:2022
Database	Scopus and Web of Science
Sources (Journals, books, etc)	847
Documents	2172
Average years from publications	12
Average citations per document	21.83
Average citations per year per document	1.798
References	67,476
Document types	
Article	2040
Book chapter	12
Proceedings	11
Editorial material	4
Review	100
Keyword analysis	
Keyword Plus (ID)	16,776
Author's Keywords (DE)	5015
Author's contribution	
Authors	6667
Single authored documents	45
Multi-authored documents	1995
Collaboration index	3.11
Authors of single-authored documents	43
Authors of multi-authored documents	6624
Authors per document	3.07
Co-Authors per document	5.28

and evaluating these publications, to reflect the developmental trend in these coumarin compounds. A total of 6667 scholars conducted studies on daphnetin and esculin with a publication per author and author per publication ratio of 0.33 and 3.07, respectively. While there were 43 single-authored publications, the majority were multiple-authored (n = 6624), retrieved from 847 journal sources. On average, these publications accumulated 1.79 citations per year and 21.83 citations per publication. Additionally, a collaboration index of 3.11 indicated a high level of co-authorship per publication in this study, which reflects the significant interest of the scientific community in the compound. The interest in these compounds stems from their potential therapeutic effects, and researchers continue to explore their potential applications in medicine and healthcare. For example, Garg et al. (Garg et al., 2020) reported esculetin (esculin) and daphnetin among the notable biologically active coumarins, displaying bioactivities such as neuroprotection, hepatoprotection (Javed et al., 2022), anti-inflammatory, antioxidant (Kılıç, 2022) and anticancer (Desam & Al-Rajab, 2022) effects.

Fig. 4 illustrates the growth trend of daphnetin and esculin research articles from 1990 to 2022. A linear model was utilized to describe the relationship between the publication year and the number of publications. The number of articles slowly increased from 18 in 1990 to 40 in 2000. From 2011 to 2013, there was a fluctuating increase in publications, and from 2014 to 2022, the number of publications exponentially increased, surpassing 100. However, there was a decline in publications in 2018. In the last decade, a total of 1183 studies on daphnetin and esculin were published, accounting for 54.46 % of all included studies.

Upon examining the relationship between the number of publications and years, a linear regression showed an R^2 value of 0.7812, indicating a direct connection between the two variables. To analyze the authorship distribution pattern, Lotka's inverse square law of author productivity was used (Ekundayo & Okoh, 2018). Our examination of scientific outputs using Lotka's law revealed a β-coefficient of 2.29 and a constant of 0.49, with a K-S goodness-of-fit score of 0.95 ($p = 0.08$, two-sample t-test). Based on the 4.46 % annual growth rate, a significant increase in the number of articles on daphnetin and esculin can be expected in the coming years.

3.2. Country publications distribution and collaboration

Fig. 5 shows the global distribution of daphnetin and esculin publications. Although over 50 different countries or territories published related articles, a small number of countries produced most of the publications, which is typical in scientific fields (Wu et al., 2022). Among the 2,040 articles with author addresses, 52.40 % (1,069) originated from four countries: China, USA, India, and North and South Korea. China had the highest contribution with 576 articles (28.2 %), followed by USA (198 articles, 9.7 %) and India (154 articles, 7.5 %) (Table 2). These top four countries contributing to publications on daphnetin and esculin are known to have a strong tradition of using natural products in medicine and have made significant contributions to the field of natural product research (Yuan et al., 2016). Other common factors possibly driving research output in natural product research in these countries are a combination of technological and scientific advances (Atanasov et al., 2021), rich natural resources, government support, academic expertise, and economic incentives (Marginson, 2022). In terms of citations, the top two countries, China (9248 total citations) and USA (6996 total citations) corresponded with the top two most publishing countries on daphnetin and esculin research between 1990 and 2022. Other countries with relatively high total citations were Japan (2669 total citations), Spain (2355 total citations) and Korea (2220 total citations).

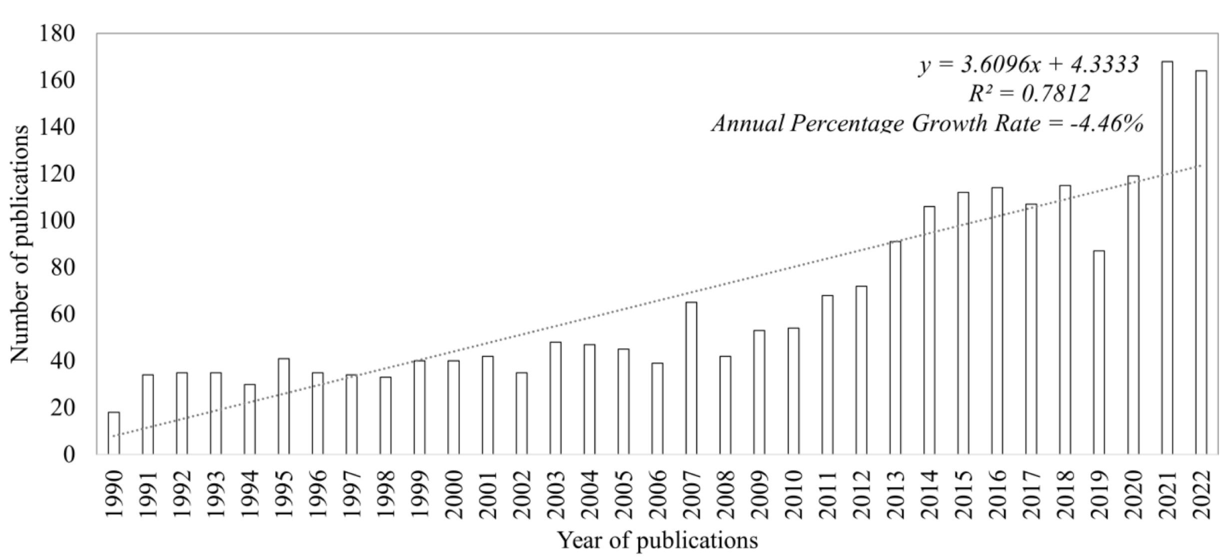

Fig. 4. Annual publication frequencies of research on daphnetin and esculin in Web of Science and Scopus databases from 1990 to 2022.

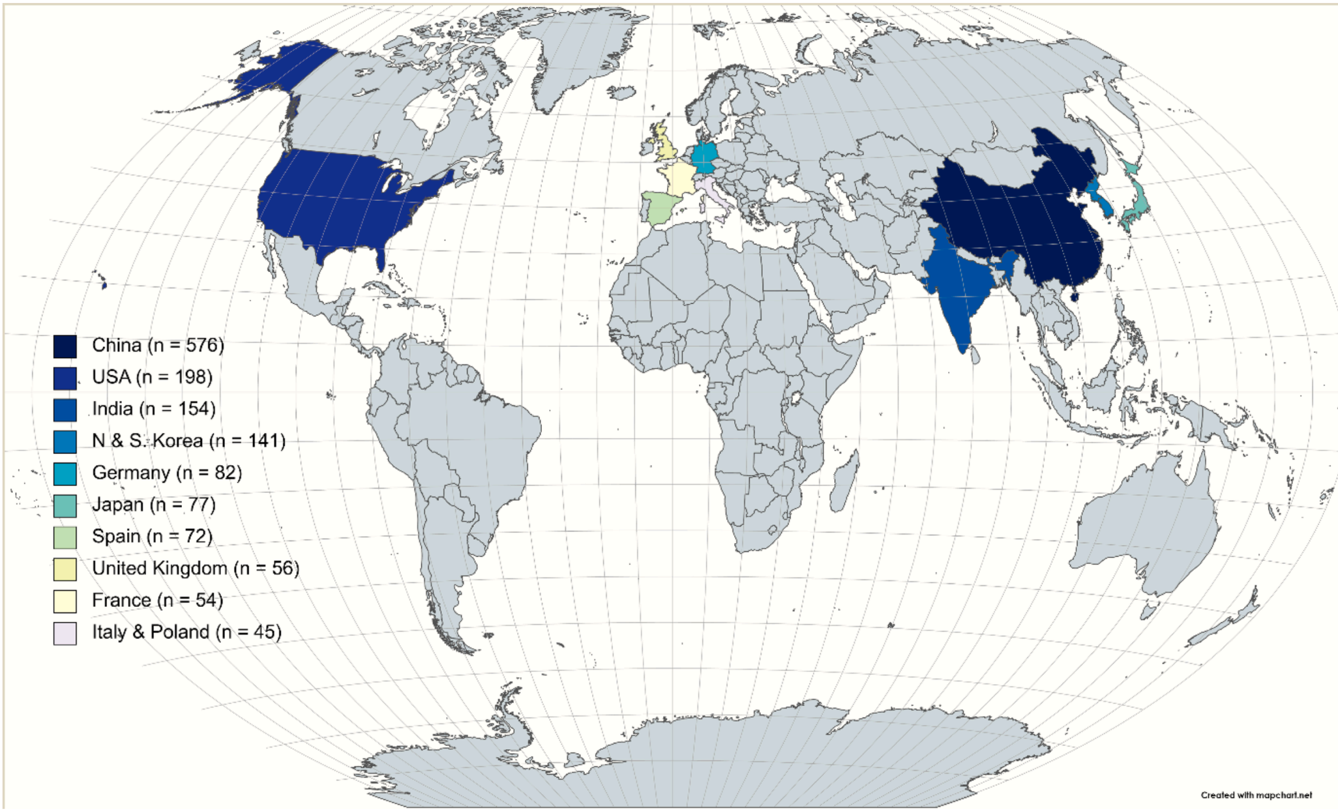

Fig. 5. Top 10 most productive countries in daphnetin and esculin research in terms of article production in the Web of Science and Scopus databases from 1990 to 2022. Countries shaded in grey colored indicate those not considered in the collection.

Table 2
Twenty most published and most cited countries of daphnetin and esculin-related publications from 1990 to 2022.

Rank	Countries	Articles	Frequency	SCP	MCP	MCP/P Ratio	Article citations	Citation average
1	China	576	0.2881	551	25	0.0434	9248	16.06
2	USA	198	0.099	180	18	0.0909	6996	35.33
3	India	154	0.077	148	6	0.039	1723	11.19
4	Korea	141	0.0705	133	8	0.0567	2220	15.74
5	Germany	82	0.041	70	12	0.1463	2067	25.21
6	Japan	77	0.0385	75	2	0.026	2669	34.66
7	Spain	72	0.036	69	3	0.0417	2355	32.71
8	United Kingdom	56	0.028	49	7	0.125	1752	31.29
9	France	54	0.027	48	6	0.1111	1853	34.31
10	Italy	45	0.0225	40	5	0.1111	1146	25.47
11	Poland	45	0.0225	42	3	0.0667	575	12.78
12	Brazil	41	0.0205	39	2	0.0488	991	24.17
13	Turkey	27	0.0135	23	4	0.1481	592	21.93
14	Iran	26	0.013	23	3	0.1154	425	16.35
15	Pakistan	25	0.0125	25	0	0	204	8.16
16	Bulgaria	24	0.012	24	0	0	1257	52.38
17	Canada	21	0.0105	19	2	0.0952	692	32.95
18	Czech Republic	21	0.0105	21	0	0	337	16.05
19	Belgium	20	0.01	16	4	0.2	1059	52.95
20	Serbia	20	0.01	19	1	0.05	444	22.2

Countries are classified based on single country publications (SCP), multiple country publications (MCP), and multiple country publications per publication(MCP/P).

In conducting scientific research, collaboration among a diverse team with various backgrounds and ideas is often necessary to overcome the most significant challenges. Incorporating different perspectives and approaches can make it easier to achieve research objectives. In some cases, government agencies require collaboration initiatives as part of their funding conditions to promote research progression (Olisah et al., 2022). In our study, RStudio was used to examine the collaboration pathways among the top countries in daphnetin and esculin research. The size of the node in the network collaboration map (Fig. 6) denotes the number of papers in which an author from a particular country is enlisted as a co-author, with larger nodes indicating more papers, and the thickness of connecting lines shows the frequencies between countries (Li et al., 2019). The network collaboration map among various countries revealed that China had the most frequent collaboration with USA, India, Japan, Korea and Germany.

3.3. Authorship pattern and citation analysis

Bibliometric analysis is also valuable in identifying how authors contribute to a research topic in terms of publications and citation

Fig. 6. Collaboration network of countries involved in Daphnetin and Esculin research.

counts (Hirsch, 2005). One way to evaluate this contribution is through citation indicators, such as the H-index. The H-index measures both the productivity and impact of an author's publications and it is commonly used for research evaluation (Kamrani et al., 2021). Studies have shown that the H-index is related to the number of publications and citations related to an author (Hirsch, 2005). This study used different citation metrics, including the H-index, g-index and total citations to identify the top 20 authors in daphnetin and esculin research over the last two decades (Fig. 7 and Table 3). The authors were chosen based on their contributions to more than 20 publications.

In Fig. 7, embedded circles indicate the total number of articles and citations for articles published each year. A total of 6667 authors were involved in the publication of research on daphnetin and esculin between 1990 and 2022. The top five most productive authors are Wang Y. (52 articles), Li Y. (43 articles) Liu Y. (38 articles), Zhang X. and Zhang Y. (37 articles). In terms of the relative impact based on citation, Kostava I, (1211 citations), Wang Y. (717 citations), Wang X. (667 citations), Li J. (659 citations) and Velázquez E. (549 citations) were the most cited authors. It is interesting to note that only one of the top five most published authors (Wang Y.) made the list of the top five most cited authors on daphnetin and esculin research. This may be attributed to the quality of the research, and other factors such as the extent of collaborations with other researchers, the journals in which the research is published, and the visibility of the research to other researchers. Additionally, citation count can be influenced by citation practices within a particular field, such as self-citations and the citation of highly influential papers. Even though a high citation count can be an indication of research impact and influence, it is important to consider other factors that may have contributed to the difference in citation count among authors (Alonso et al., 2009).

3.4. Most cited publications

The number of citations an article receives is commonly used as a measure of its impact and importance in a particular research field (Caon et al., 2020). A high number of citations typically indicates that an article has been deemed relevant and valuable by other researchers. Additionally, an author's overall impact and contributions to the field

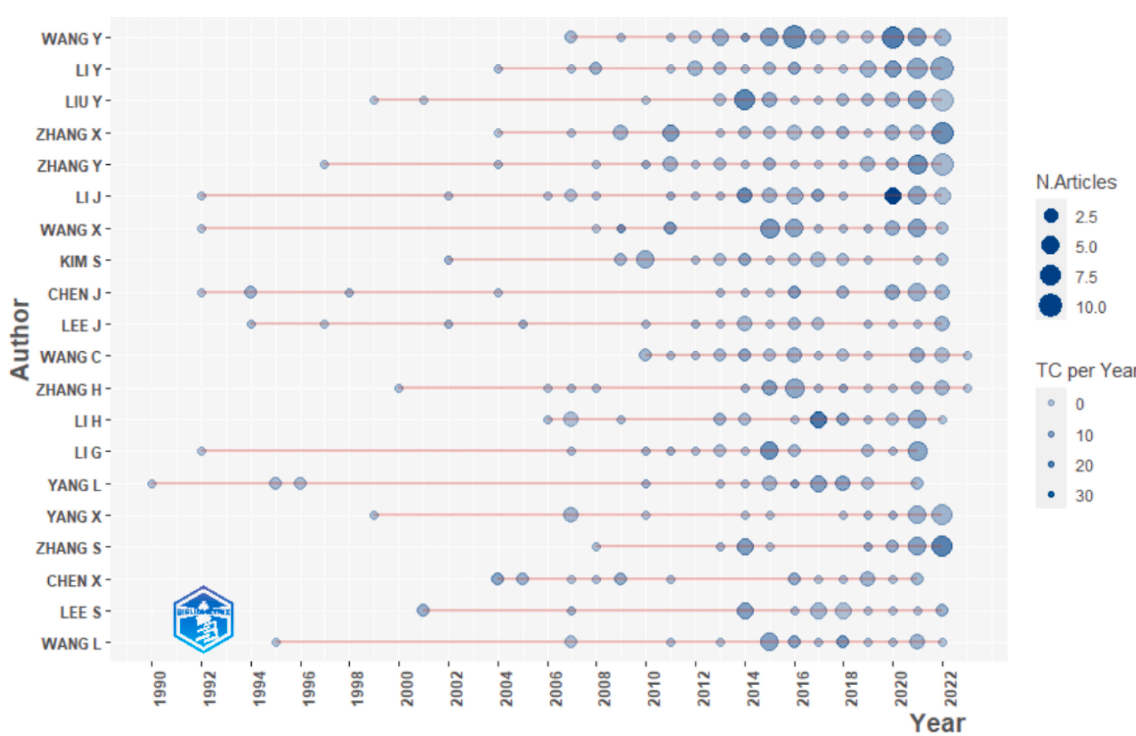

Fig. 7. Top 20 most productive researchers of daphnetin and esculin publications from 1990 to 2022.

Table 3
The top 20 most productive authors on daphnetin and esculin from 1990 to 2022 were categorized in terms of number of publications, citation indices, total citation (TC), and publication start year (PY).

Rank	Authors	Publications	h_index	g_index	m_index	TC	PY_start
1	Wang Y	52	16	25	0.9411765	717	2007
2	Li Y	43	14	20	0.7	485	2004
3	Liu Y	38	12	18	0.5217391	368	2001
4	Zhang X	37	12	18	0.6	404	2004
5	Zhang Y	37	10	19	0.3703704	403	1997
6	Li J	33	12	25	0.5454545	659	2002
7	Wang X	30	13	25	0.40625	667	1992
8	Kim S	26	11	19	0.5	409	2002
9	Chen J	25	12	21	0.375	478	1992
10	Lee J	25	9	20	0.3	442	1994
11	Wang C	24	10	15	0.7142857	22	2010
12	Zhang H	24	11	19	0.4583333	380	2000
13	Li H	23	10	17	0.5882353	312	2007
14	Li G	22	9	18	0.6428571	357	2010
15	Yang L	22	11	20	0.3793103	408	1995
16	Yang X	22	6	11	0.24	154	1999
17	Zhang S	22	10	16	0.625	279	2008
18	Chen X	21	10	20	0.5	510	2004
19	Lee S	21	8	18	0.3478261	346	2001
20	Liu J	21	10	16	0.5	432	2004

can be evaluated by the number of citations they receive over time (Wang et al., 2019).

In the current bibliometric analysis on research about daphnetin and esculin, the top 20 most cited publications during the study period were identified (Supplementary Table 1). These articles received total citations ranging from 185 to 805, with an average of 13.4 to 40.15 citations per year. Among the top five most cited articles, only one was single-authored (Kostova, 2005), while the other four were multi-authored. The authors of these articles were predominantly from developed countries such as Greece, Argentina, and the United Kingdom, with only two articles (Kostova, 2005; Kostova et al., 2012) from developing countries, specifically Bulgaria. Four of the top five most cited articles were review articles that focused on the therapeutic properties of coumarin compounds, including their antioxidant, antiviral, antimicrobial, and anti-inflammatory effects. For example, the top cited article published by Fylaktakidou et al. is a review article and focused on the biological activities of natural products containing a coumarin moiety. It discusses how coumarins may affect the formation and scavenging of reactive oxygen species (ROS) and influence processes involving free radical-mediated injury. The work highlights the anti-inflammatory and antioxidant properties of coumarin and its derivatives, including esculetin, fraxetin, and daphnetin, and describes the efforts made by researchers to prepare new compounds with single or more complicated systems, including heterocyclic rings (Fylaktakidou et al., 2005).

3.5. Journal types

Research on daphnetin and esculin has been published in 847 primary reference works, including journals, books, letters, and conference proceedings. Table 4 shows the top 20 publishing journals in daphnetin and esculin-related research. Springer, Elsevier, American Society for Microbiology, and Microbiology Society were the top publishers, while the remaining journals were published by different publishers. The top 10 most productive journals in terms of the number of articles published on daphnetin and esculin research were the International Journal of Systematic And Evolutionary Microbiology (215 articles), Journal of Clinical Microbiology (71 articles), International Journal of Systematic Bacteriology (29 articles), Archives of Microbiology (24 articles), Antonie Van Leeuwenhoek (21 articles), Current Microbiology (21 articles), Journal of Ethnopharmacology (21 articles), PLoS ONE (19 articles), Applied and Environmental Microbiology (16 articles), and Food Chemistry (16 articles). In terms of the 5-year impact factor (IF), the Journal of Clinical Microbiology and Food Chemistry ranked highest with an impact factor of 11.67 and 9.231 respectively, while Antonie Van Leeuwenhoek had the lowest impact factor (2.745). The impact factor is commonly used to evaluate the relative importance of a journal within its field and to measure the frequency with which the “average article” in a journal has been cited in a particular period. Journal which publishes more review articles often have the highest IFs. Journals with higher IFs are believed to be more important than those with lower ones (Sharma et al., 2014).

Table 4
Top 20 most publishing journals of daphnetin and esculin research from 1990 to 2022.

S/N	Sources	Articles
1	International Journal of Systematic and Evolutionary Microbiology	215
2	Journal of Clinical Microbiology	71
3	International Journal of Systematic Bacteriology	29
4	Archives of Microbiology	24
5	Antonie Van Leeuwenhoek	21
6	Current Microbiology	21
7	Journal of Ethnopharmacology	21
8	PloS ONE	19
9	Applied and Environmental Microbiology	16
10	Food Chemistry	16
11	Journal of Food Protection	15
12	Molecules	15
13	Phytochemistry	15
14	Plant Disease	15
15	Chinese Traditional and Herbal Drugs	14
16	Systematic and Applied Microbiology	14
17	European Journal of Pharmacology	13
18	Journal of Chromatography A	13
19	Journal of Diary Science	13
20	Phytomedicine	13

Daphnetin and esculin have been found to have antimicrobial properties. Studies have shown that they can inhibit the growth of a wide range of bacteria, including Gram-positive and Gram-negative bacteria, as well as some fungi strains (Mercer et al., 2013). These compounds are effective against some antibiotic-resistant strains of bacteria, making them potentially useful in the development of new antimicrobial agents (Kostova et al., 1993). These may explain the high number of articles published in Microbiology related journals mentioned above.

3.6. Keyword analysis and thematic classification

Keywords in scientific articles provide a concise representation of the research focus, content, methodology, and contributions. They aid in categorization, indexing, discoverability, and interdisciplinary connections, contributing to effective communication and dissemination of research (Mikhail et al., 2020; Yeasmen et al., 2021). In the current scientometric analysis, the top 20 most relevant keywords [author's keywords (DE) and keyword-plus (ID)] in daphnetin and esculin research were recorded (Supplementary Table 2). The top keywords were "Daphnetin", "Esculin", "Coumarin", "Coumarins", "Esculetin", "Antioxidant", "Taxonomy", "Beta-glucosidase", "Polyphasic taxonomy", "Flavonoids", "Aesculin", "Inflammation", "Mastitis", "Oxidative stress", "Identification", "Apoptosis", "Enterococci", "Fraxin" and "Bacteria". To assess the thematic areas of daphnetin and esculin-related articles, a co-occurrence network analysis was conducted on keywords associated with these compounds during the study period. The analysis revealed three keyword clusters, each representing a thematic domain (Fig. 8). The colored circles within each cluster indicate the most used keywords, while the lines between terms indicate their frequency of occurrence in the literature.

In Fig. 8, the red cluster (cluster 1) shows the pharmacological research thematic area. This cluster encompasses various experimental approaches, including *in vivo*, *in vitro*, preclinical, and human clinical studies, used to evaluate the pharmacological potentials of daphnetin and esculin. Numerous studies have consistently demonstrated the broad therapeutic effects of these compounds. For example, daphnetin has been utilized as a therapeutic scaffold for various ailments, such as cancer, rheumatoid arthritis, fever, and lumbago (Tu et al., 2012; Wang et al., 2013), and has been reported to possess multiple therapeutic properties, including antioxidant, anti-inflammatory, antiarthritic (Lv et al., 2018), antipyretic, analgesic (Singh et al., 2021), antiproliferative (Kostova et al., 2012), neuroprotective (Singh et al., 2021), antibacterial (Cottigli et al., 2001), anti-stroke, nephroprotective, hepatoprotective, cardioprotective, anti-coagulation disorders, anticancer, and anti-ischemic brain injury (Boulebd & Khodja, 2021; Pinto & Silva, 2017; Zhang et al., 2018). Daphnetin has been used for an extended time in managing coagulation disorders without exhibiting marked toxic effect (Du et al., 2014). The compound can ameliorate endotoxin and heavy metal toxicity in the lungs (Yu et al., 2014). Additionally, the compound was found to improve osteoporosis and alleviate chronic skin inflammatory diseases that are characterized by impaired keratinocyte differentiation, defective inflammatory cell infiltration, and excessive proliferation (Gao et al., 2020). In another study, daphnetin exhibited immunosuppressive effects in BALB/c mice at concentrations of 20, 10, and 5 mg/kg when administered via the intraperitoneal route. The compound downregulated OVA-specific antibodies (IgG1 and IgG2b) and reduced the growth of Th1 and Th2 cytokines (Song et al., 2021). At concentrations of 40, 20, 10, and 1 μM, daphnetin enhanced cell viability in streptozotocin-treated rat insulinoma cells and improved insulin secretion, depicting its antidiabetic effects (Vinayagam & Xu, 2017). The authors suggested that the antidiabetic effect of the compound is linked to insulin stimulation and antiapoptotic activity.

Ji et al. (Ji et al., 2019) reported that daphnetin at doses ranging from 4 to 16 mg/kg improved experimental colitis by reducing inflammation in the colon, improving colon integrity, and restoring metabolic and immune homeostasis. The compound was found to increase the production of short-chain fatty acids in the gut microbiota. In another study, daphnetin inhibited melanin biosynthesis in B16F10 cells by suppressing the expression of microphthalmia-associated transcription factors and melanogenic enzymes such as tyrosinase (Nam et al., 2022). The compound also inhibited the phosphorylation of kinases including mitogen and stress-activated protein kinase, PKA, cAMP response element binding protein, and ERK. The authors concluded that

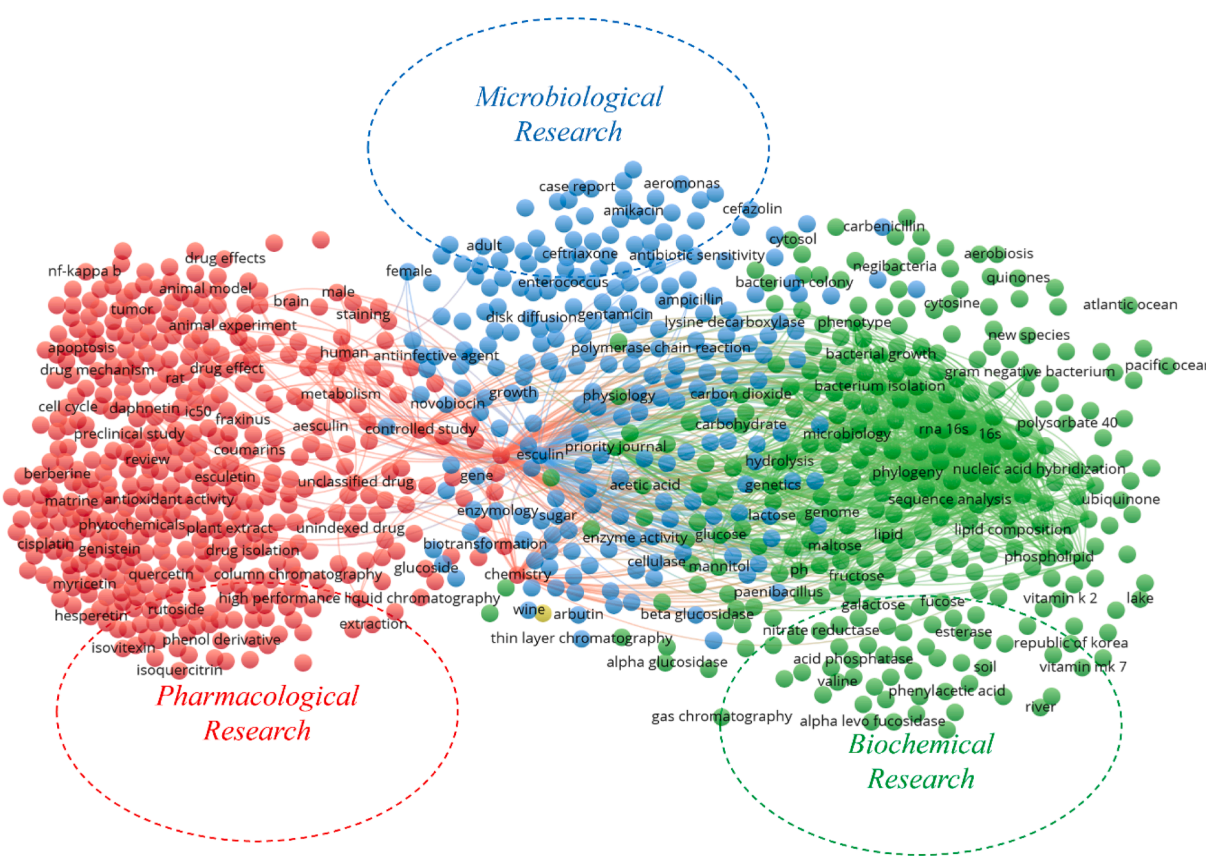

Fig. 8. Thematic literature classification of daphnetin and esculin research published in journals indexed in the Web of Science and the Scopus database from 1990 to 2022.

daphnetin exhibited anti-pigmentation effects by regulating the PKA/CREB and ERK/MSK1/CREB cascade.

Similarly, esculin exhibited antioxidant and antiradical effects by quenching superoxide radicals and reducing Fe-induced lipid peroxidation (Biljali et al., 2012). It also acted as an inhibitor of 12- and 5-lipoxygenase, inhibiting the production of hydroxyeicosatetraenoic acid and leukotrienes via the lipoxygenase cascade (Kaneko et al., 2003). Esculin protected against dopamine-stimulated cell death and caspase-3 cleavage, reduced reactive oxygen species (ROS) synthesis, preventing nucleic acid damage and defects in antioxidant proteins (Zhao et al., 2007). Additionally, it quenched hydroxyl radicals, inhibited lipid peroxidation in rat hepatocytes (Qin et al., 2003), and displayed gastroprotective action. Esculin also showed effects such as abrogation of enzymes such as collagenase and hyaluronidase, protection of capillaries, enhancement of skin vasculature, and efficacy in cellulitis management (Cadwallader et al., 2010; Venkateshwarlu et al., 2015). Furthermore, esculin demonstrated antidiabetic and diuretic activities, causing a dose-dependent decrease in blood glucose levels and increased excretion of potassium, sodium, and water in *in vivo* models (Venkateshwarlu et al., 2015).

The blue cluster (cluster 2) with keywords such as enterococcus, disc diffusion, ampicillin, gentamycin, bacterium colony, and antibiotic sensitivity represents the microbiological research thematic area. This cluster covers publications focusing on the antimicrobial activity of daphnetin and esculin. Both compounds demonstrated antimicrobial activity against bacteria and fungi, indicating their potential as natural antimicrobial agents. For example, Huang et al. (Huang et al., 2006) screened the antimalarial activities of daphnetin and its 21 derivatives against *Plasmodium falciparum* using *in vitro* culture. Daphnetin and two derivatives (DA79 and DA78) showed potent antimalarial activity against *P. falciparum*. In another study, daphnetin exerted antibacterial activity against *Helicobacter pylori* through increased DNA damage, change of membrane structure, and phosphatidylserine (PS) translocation, and decrease of *H. pylori* attachment to gastric epithelial (GES-1) cells (Wang et al., 2019). Similarly, esculin and its oligomer fractions exhibited antibacterial effects against different bacteria strains, including *Staphylococcus aureus*, *Enterococcus faecalis*, *Salmonella enteritidis* and *Salmonella typhimurium* (Mokdad-Bzeouich et al., 2015). Daphnetin and esculin act by disrupting the integrity of the bacterial cell membrane and interfering with bacterial DNA synthesis (Wang et al., 2019).

The green cluster (cluster 3) represents the biochemical research thematic area of daphnetin and esculin, exploring their interactions with biological systems and effects on various biochemical processes. This area investigates keywords such as nitrate reductase, alpha levofucosidase, hydrolysis, cytosine, esterase, galactose, and fructose. For example, Xia et al. (Xia et al., 2018) studied the structure-methylation relationship of daphnetin and its C-4 derivatives (4-methyl daphnetin, 4-phenyl daphnetin, and 4-acetic acid daphnetin) about metabolic stability, selectivity, and catalytic kinetics of human catechol-*O*-methyltransferase (COMT). They found that the C-8 hydroxyl group of daphnetin was the primary metabolic site for human COMT, while the C-7 hydroxyl group had minimal methylation. The electronic effects of the C-4 substituents on daphnetin and their coordination in the COMT active site influenced the enzyme's catalytic efficiency. The order of metabolic stability and catalytic kinetics of COMT was as follows: 4-phenyl daphnetin > 4-methyl daphnetin > 4-acetic acid daphnetin (Xia et al., 2018).

4. Conclusions and future perspectives

This review highlighted the past and current research trends of two coumaric compounds, daphnetin, and esculin. The compounds have gained significant attention in research owing to their wide and potent therapeutic potential. From 1990 to 2022, the research output of these compounds showed an annual percentage growth rate of 4.46 %, with 2172 documented publications. The number of publications increased from 18 in 1990 to over 100 in 2022.

In the previous 10 years, a total of 1183 works (54.46 %) focused on daphnetin and esculin. Most of these publications were original articles (93.92 %), with the remaining being reviews (4.60 %). This indicates a high level of research conducted on these compounds. Furthermore, there were 43 single-authored publications, indicating an increasing interest in utilizing the two compounds in research. The collaborative index (3.11) demonstrates a high rate of collaboration among authors to produce research output on these compounds. This is another indication of the increasing interest in studying daphnetin and esculin. The broad health-promoting potentials of these compounds against various diseases contribute to this trend. Based on the bibliometric data, China (576) and USA (198) are the two countries with the highest research rates on these compounds. Together, they accounted for 774 (37.9 %) of the total 2172 publications. These countries also accumulated the highest number of article citations, with China receiving 9248 and USA receiving 6996 citations. Furthermore, articles on these two compounds were primarily published in high-impact publishers, including Springer, Elsevier, American Society for Microbiology, and Microbiology Society. The Journal of Clinical Microbiology (11.67) and Food Chemistry (7.51) were the most impactful journals in terms of publications on daphnetin and esculin. The emphasis of most cited papers on these compounds revolved around their antiviral, antioxidant, anti-inflammatory, and antimicrobial properties.

The pharmacological properties of daphnetin and esculin, both in their natural and synthetic derivatives, exhibited diverse effects. For example, these compounds were effective against fungi, Gram-positive and Gram-negative bacteria that are resistant to certain antibiotics. Additionally, they demonstrated anticancer, anti-fever, neuroprotective, anti-stroke, anti-arthritic, cardioprotective, anti-ischemic, and analgesic activities.

Overall, the two coumaric compounds and their derivatives, whether synthetic or natural, possess potent health-promoting properties due to their wide pharmacological actions and structural diversity. Currently, there are no publications on these compounds from Africa based on the bibliometric analysis. Given that plants from the genus *Daphne* where the two coumaric compounds discussed in this study are also distributed in some parts of Africa, it is recommended that future research explores these medicinal plants from Africa. This could help to uncover new derivatives of daphnetin and esculin, establishing their therapeutic roles. Such findings could also offer cost-effective, readily available, and safe scaffolds for designing molecules to manage and treat various diseases. While most reported data on daphnetin and esculin are preclinical studies conducted using *in vitro* and *in vivo* models, it is necessary to conduct further toxicological studies to determine their safety. Furthermore, conducting clinical studies is essential to assess the efficacy of these compounds and their derivatives in humans.

CRediT authorship contribution statement

Tomi Lois Adetunji: Conceptualization, Writing – original draft, Writing – review & editing. **Chijioke Olisah:** Writing – original draft. **Ahmed Olatunde:** Conceptualization, Writing – original draft, Writing – review & editing. **Habibu Tijjani:** Writing – original draft. **Mohammad S. Mubarak:** Supervision, Writing – review & editing. **Abdur Rauf:** Supervision, Writing – review & editing. **Adeyemi Oladapo Aremu:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The original contributions of the study are available in the article and Supplementary Material. Additional inquiries can be directed to the corresponding authors.

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Appendix A. Supplementary material

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