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Thymoquinone-related knowledge (1915–2022): A comprehensive bibliometric analysis

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Abstract:

Nigella sativa L. and its active component, thymoquinone, attract a lot of scientific attention. However, very few review articles on this issue have been published so far, and no review relied on the method of bibliometrics, which is currently the most prominent technique for citation mapping.

This review involves a total of 2072 studies on thymoquinone reported in the Scopus database between 1915 and September 15, 2022. The data obtained were processed using the VOSviewer software, MS Excel, and Scopus Analytic. The review introduces some prospective research areas based on theme mapping, knowledge trending, bibliographic coupling, and keyword co-occurrence networks. The authors, documents, journals, institutions, and countries were ranked based on the knowledge impact and the number of publications.

The 2072 selected publications belonged to 7605 scholars, with 3.67 authors per document on average. The average number of citations per document was 68.84. The Phytotherapy Research Journal scored as the top source. M.N. Nagi proved to be the topcited author with 2076 citations, while Saudi Arabia appeared to be the most productive and cited country. The best-studied areas were represented by such topics as anti-inflammatory properties of thymoquinone, cytokine network, and arthritic disease model. Molecular-based approaches in conjunction with ethno-knowledge may be of assistance in comprehending the cellular mechanisms of thymoquinone and establishing its efficacy against a variety of diseases.

Keywords: Bibliometric analysis, thymoquinone, Nigella sativa L., performance analysis, Scopus database

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INTRODUCTION

Nigella sativa L. (*Ranunculaceae* family) is also called black caraway, black cumin, nigella, kalonji, or siyahdaneh. Its seeds are commonly known as black seeds in English and *Alhabbah Al-saudaa* in Arabic. Black seeds are a popular traditional medicine against a vast range of ailments in many regions of the world, especially in the Middle East and the Far East. *N. sativa* is cultivated in the Mediterranean region, western Asia, the Middle East, southern Europe, and northern Africa.

For centuries, N. sativa seeds have been used to treat fever, asthma, infection, inflammation, chest congestion, eczema, cough, bronchitis, flatulence, obesity, chronic headache, dysmenorrhea, diabetes, and diarrhea [1–4].

N. sativa contains some active ingredients that showed antioxidant, analgesic, anti-inflammatory, antiasthmatic, antipyretic, antibacterial, antihypertensive, and antineoplastic properties [5]. *N. sativa* is a substantial and prospective source of several bioactive compounds, including 4-terpineol, p-cymene, thymoquinone (Fig. 1), dithymoquinone, thymohydroquinone, and t-anethol. In addition, *N. sativa* contains vitamins, fatty acids, proteins, mineral elements, and vital amino acids. *N. sativa* seeds also contain nigellimine, nigellidine, saponine, nigellcine, and water-soluble triterpenes.

Thymoquinone (2-isopropyl-5-methyl-1, 4-benzoquinone) exhibits antioxidant, antihistaminic, anti-Alzheimer, anticancer, analgesic, hepatoprotective, and anti-

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Figure 1 Thymoquinone: chemical structure

ischemic properties, besides being an excellent neuroprotector, insecticide, histone protein modulator, and renoprotector [6, 7].

Thymoquinone inhibits cancer at the stages of proliferation, migration, and invasion. It also functions as an anticancer agent against various human malignancies, including breast, pancreatic, blood, oral, prostate, bone, head and neck, cervical, lung, and liver cancers [8, 9]. Thymoquinone causes apoptosis and controls pro- and anti-apoptotic gene expression [8]. It effectively facilitates miR-34a up-regulation, increases miR-34a levels via p53, and suppresses Racl expression [10]. In addition, thymoquinone diminishes the phosphorylation of NF-B and IKK, as well as the metastasis and the activity of ERK1/2 and PI3K. Thymoquinone suppresses the spread of cancer cells by activating JNK and p38 [11]. It owes its anticancer impact to its antioxidative potential and ability to reduce oxidative stress. Other scientists believe that thymoquinone induces apoptosis in cancer cells by inflicting oxidative damage [11, 12].

Thymoquinone can function as an antioxidant and a pro-oxidant in a dose-dependent way; it acts as an antioxidant at low concentrations and as a pro-oxidant at high ones. Thymoquinone showed a good potential against doxorubicin, a drug used to cause cardiotoxicity and free radicals that cause oxidative damage [13]. Thymoquinone also speeds up cell growth in rats, relieves oxidative stress caused by Fe-NTA, and works well as a chemoprotective phytochemical [14]. In recent research, thymoquinone proved to be an effective antidiabetic drug in healthy male volunteers: it lowered cholesterol and triglyceride levels while increasing highdensity lipoprotein, glucose-induced insulin secretion, and insulin sensitivity [15].

As a natural substance, thymoquinone has a considerable pharmaceutical potential. For instance, it has become subject of in-depth research that determined its ability to stop the proliferation, migration, and invasion stages of human malignancies. However, its canceractivity still remains understudied. Moreover, thymoquinone medication development requires adequate clinical studies. The most urgent task is to define the relationship between its structure and antitumor activity. Only then will scientists be able to address such issues as purification or commercial production of *N. sativa*derived substances.

In general, thymoquinone appears in hundreds of studies that focus on a wide range of aspects. This enormous amount of bibliographic data needs an effective and comprehensive review that would combine this intellectual variety from a new perspective. This goal can be achieved using the interdisciplinary method of bibliometric techniques that include mathematics, statistics, data mining, mapping, and visualization [15]. Bibliometric methods involve performance analysis, keyword co-occurrence, co-authorship mapping, cocitation, and bibliographic coupling. All these techniques combined can reveal the knowledge structure, hotspots, international collaboration, trending, and roadmapping for future research [16, 17]. The current study was designed to analyze and visualize thymoquinonerelated publications using the VOSviewer software, where the abbreviation stands for visualizing scientific landscapes.

STUDY OBJECTS AND METHODS

Selecting the database and keywords. Bibliometric analyses reflect the coverage of their underlying databases in the sense that the coverage essentially specifies what is included in the analysis. The bibliometric assessment contextualizes these publications against the database, which is likewise reliant on the coverage. Scopus was founded in 2004 by Elsevier, which claims it to be the most complete overview of the world's research outputs, monitored by a team of subject matter experts. Scopus's goal is to create the largest possible database of high-quality research publications. Scopus differs from Web of Science (WoS) in that WoS promotes quantity above quality, while Scopus attempts to balance between the two. Both Elsevier and Clarivate Analytics provide subscriptionbased databases, but we chose to use the Scopus database for our research objective.

Selecting the keywords is one of the fundamentals of bibliometric research. More data can be gathered and evaluated to yield findings that can be expanded upon in understanding performance, knowledge structure, hot spots, and other indicators of the bibliometric analysis. The bifurcation that accompanies all scientific research related to thymoquinone means that databases require several keywords since the research conducted on this natural compound included agriculture, chemistry, traditional and prophetic medicine, pharmacology, and computational biology. In this study, we chose the word *thymoquinone* as the keyword to search in the Scopus database. Thus, the search results are comprehensive for all types of related studies.

Sample size. The method of bibliometric analysis is applied when the number of bibliometric data is considerable, and the literature review is too broad for a manual examination. As a rule, bibliometric analysis is recommended in cases when the number of references exceeds 200 [18]. The average category of normalized citation impacts of bibliometric studies with smaller



Figure 2 Search strategy, sampling criteria, and exportation of bibliographic data: ar - article; cp - conference paper

sample sizes (< 200 documents) varies greatly, making this method unreliable. The present research included trial-and-error approaches and keyword filtering, and the sample size was enough to apply the method of bibliometric analysis.

Search results. We checked some article titles in the Scopus database for the keywords to confirm that the bibliographic data were relevant to the study subject. The preliminary findings (n = 2778) included articles, reviews, letters, notes, editorials, errata, conference papers, short surveys, book chapters, conference reviews, data papers, and retractions (1915–2022). In addition, we collected bibliographic data for original research published in English, i.e., journal articles and conference papers (Fig. 2). This step made it possible to refine the conclusions. Finally, we downloaded the data on 2072 articles published in 1915–2022 into a CSV spreadsheet using Microsoft Excel.

Performance analysis and bibliographic mapping. The integrated Scopus analyzer helped us determine the volume of annual research and their citations, as well as the performance of the thymoquinone-related research. We used the method of regression analysis to define the incremental annual increase. Bibliographic mapping was performed using the VOSviewer platform. VOSviewer is a program for creating and displaying bibliometric networks. These networks may be built via citation, bibliographic coupling, co-citation, or co-authorship relationships and can comprise journals, researchers, or individual articles. VOSviewer also has text-mining tools for creating and visualizing co-occurrence networks of key phrases collected from the scientific literature.

RESULTS AND DISCUSSION

Overview. We identified 7605 scholars for 2072 sources with 3.67 as the average number of authors per document. The average number of citations per document was 68.84, which means that thymoquinone research is well-regarded in the academic community. The interdisciplinary character of the subject indicated a collaboration among specialists from many fields. Table 1 covers the general information regarding the documents utilized for this study. The most productive

Table 1 Main bibliographic data*

Results						
1915-2022						
949						
2072						
2.18						
68.84						
1333.1						
2072						
1117						
21						
17 136						
4531						
14 402						
Authors						
7605						
3.67						

* The average number of citations per year was calculated by dividing the total number of citations by the number of years for all the documents source, institution, and country proved to be *The Biomedical Sciences Instrumentation*, King Saud University (Saudi Arabia), and Saudi Arabia, respectively. The highest number of published articles belonged to such subject areas as *Biochemistry* and *Genetics and Molecular Biology*. H. Benghuzzi, affiliated with Global Training Institute, Flowood, United States, appeared to be the most productive author (n = 43). H. Benghuzzi's research focused on the effect of thymoquinone on cardiomyocyte, SiHa, and SH-SY5Y cell lines [19–21].

Performance analysis. Over the last eleven decades (1915–2022), the number of publications increased at an average yearly rate of 19.38%. The last ten years saw 75.2% of the total research production. According to the Scopus database, the first article on thymoquinone belonged to McPherson and Stratton [22]. They described the action of α -benzoyl-p-tolylhydrazine upon thymoquinone. They referred to thymoquinone as a previously identified chemical [22]. This indicates that thymoquinone had been discovered before 1915; however, the Scopus database has no information on the discovery.

Figure 3 shows the annual escalation of publications. The upward trend was fitted using a polynomial trendline (order 6; R-squared = 0.9676). When data vary, a polynomial trendline is represented as a curved line. The number of data fluctuations or bends in the curve establish the polynomial order. After the commencement, the number of publications began to climb drastically in 2000 and accounted for 15 scientific articles before reaching 259 in the year of 2021. This was before the number of publications reached 259 in 2021. The obtained results mean that thymoquinone attracts the attention of the global scientific community, and such a significant number of studies indicates its significance [5].

Research impact: citation networking. Scientific impact can be described using different scales, ranging from high to low for researchers and papers to national and institutional dimensions. Numerous studies concentrate on scientific achievement, scholarly network analysis, and scientific impact metrics. We are currently

witnessing a dramatic rise in publications that feature the issue of scientific impact and how it has changed through time in the *science of science*. However, many of these studies focus on a certain historical period. Citation networks are a common tool for measuring scientific impact, although heterogeneous scholarly networks have lately drawn more attention. The structural measure, citation analysis, and behavioral complexity are all important factors in quantifying scientific effects in the diverse scholarly network [23, 24].

This section of our research highlights the most important and relevant sources on thymoquinone. According to the Scopus dataset, the 2072 papers we selected came from 949 sources. Table 2 shows the distribution of the top ten most pertinent sources. According to the number of publications, *Molecules* (25), *Phytotherapy Research* (22), and *PLoS ONE* (18) proved to be the top-publishing sources. The *Phytotherapy* research journal scored as the top source based on all the bibliometric metrics, e.g., the number of publications, total citations, average citation, *h*-index, and CiteScore (Table 2). As for the *h*-index, all the articles published in *The Journal of Ethnopharmacology, Planta Medica*, and *Anticancer Research* have been cited.

Analyzing bibliometric citations is a useful method for judging authors' output in scientific literature and knowledge generation [27]. Figure 4 shows the top scholars who have engaged in thymoquinone research throughout the years. These top prolific 40 authors were mapped using VOSviewer's density visualization out of 7605. Density visualizations provide a quick overview of the main authors in a bibliometric citation. For each of the 40 authors, we calculated the total strength of the citation links with other authors and selected the authors with the greatest total link strength. Nagi proved to be the top-cited author with 2076 citations, followed by Badary (n = 1793), Al-Shabanah (n = 1247), and Al-Bekairi (n = 1050). Nagi (Saudi Arabia) has worked on the antioxidant mechanisms of this natural compound on chemically induced disease models of liver, heart, lung, and kidney. The team used thymoquinone to eliminate experimental carcinogenicity in the liver [28-33]. Nagi's citation effect reflects extensive work on the



Figure 3 Annual escalation of documents. The incremental trend was fitted using a polynomial trendline (order 6; $R^2 = 0.9676$)

Table 2 Top-cited sources

Source	Documents	Citations	CA	<i>h</i> -index	CS 2021	Total link strength
Phytotherapy research	22	2315	105.22	13	9.3	214
Life Sciences	16	1109	69.31	12	8.0	109
Planta Medica	8	1088	136.00	8	6.2	141
Plos One	18	959	53.27	16	5.6	75
International Immunopharmacology	11	749	68.09	11	7.0	150
Food Chemistry	10	636	63.60	9	10.0	47
Anticancer Research	5	602	120.40	5	4.1	87
Journal of Ethnopharmacology	7	592	84.57	7	6.9	91
Chemico-Biological Interactions	15	575	38.33	11	9.0	113
Molecules	25	437	17.48	15	5.9	132

CA – citation average; *h*-index – the maximal value of *h* means that the given author/journal has published at least *h* papers that have each been cited at least *h* times [25]; CS – CiteScore, a metric that reflects the average annual number of citations to recent papers published in that journal [26]



Figure 4 Overlay visualization of the top-cited authors and their distribution over time (2000–2022). This range of years was automatically selected by the software

antioxidant properties of thymoquinone. Badary (Egypt) has worked on the anticlastogenic and superoxide anion scavenging activities of thymoquinone. They also demonstrated the protective properties of thymoquinone on benzo(a)pyrene-induced forestomach carcinogenesis, doxorubicin-triggered hyperlipidemic nephropathy, galactose- and aluminum chloride-induced neuroto-xicity in rats, ifosfamide-induced Fanconi syndrome, 20-methylcholanthrene-induced fibrosarcoma tumorigenesis, etc. Figure 4 visualizes the research dynamics. The multicolored frames indicate the dynamics of the knowledge structure. The authors in the yellow frames started their research after 2018.

Citation counts assess the scientific effect of the particular publication on the assumption that a higher number of citations indicates a more widely endorsed publication. Document analysis identifies the intellectual structure of a topic of knowledge by determining the quantity and authority of cited literature. Table 3 displays the top ten most-cited papers according to the Scopus citation data, with worldwide citations ranging from 184 to 1411. In particular, Burits and Bucar, Houghton et al., Badary et al., and Worthen received 1411, 692, 330, and 327 citations, respectively, and were ranked as the top four most-cited publications [34–37]. Burits and Bucar investigated the antioxidant properties of thymoquinone using two thin-payer chromatography screening methods, a diphenylpicrylhydracyl assay, a non-enzymatic lipid peroxidation in liposomes, and a deoxyribose degradation assay. They proved that thymoquinone is an effective OH radical scavenging agent. Houghton et al. studied the inhibition of eicosanoid generation in leukocytes and membrane lipid peroxidation by the pre-administration of fixed oil of N. sativa and thymoquinone [35]. They demonstrated that thymoquinone was very potent against

Document	DOI or Pubmed link	Citation	Reference
Burits and Bucar	10.1002/1099-1573(200008)14:5<323::AID-PTR621>3.0.CO;2-Q	1411	[34]
Houghton et al.	10.1055/s-2006-957994	692	[35]
Badary et al.	10.1081/DCT-120020404	330	[36]
Worthen	https://pubmed.ncbi.nlm.nih.gov/9673365	327	[37]
Yi et al.	10.1158/1535-7163.MCT-08-0124	276	[39]
Gali-Muhtasib et al.	https://pubmed.ncbi.nlm.nih.gov/15375533	276	[40]
Sethi et al.	10.1158/1541-7786.MCR-07-2088	264	[41]
Ghosheh et al.	10.1016/S0731-7085(98)00300-8.	264	[42]
Nagi et al.	10.1006/phrs.1999.0585	258	[33]
Mansour et al.	10.1002/cbf.968	249	[28]

Table 3 Top-cited documents



Figure 5 Density visualization of the most bibliographically coupled documents. Circles represent the total link strength for each document. Of the 2072 documents, 82 meet the threshold of citation (120). For each of the 82 documents, we calculated the total strength of the bibliographic coupling links with other documents

5-lipoxygenase and cyclo-oxygenase. Their pharmacological results on oil provided credence to the longstanding usage of *N. sativa* and its products as a remedy for rheumatism and other similar inflammatory conditions. Badary et al. also confirmed the superoxide anion scavenging properties on an iron-dependent micsomal lipid peroxidation assay [36]. The antioxirodant properties of thymoquinone are still under investigation and have not yet been determined as a result of its distinctive chemical composition and the multiplicity of mechanisms for antioxidants. Many theories have been proposed to explain this property. Some scientists believe that it is the mitochondrial respiratory chain that triggers thymoquinone antioxidant activities in the cell because it converts the supplied thymoquinone to its hydroquinone form [38].

Bibliometric coupling. Bibliometric coupling evaluates previous articles on a particular topic, identifies major researchers, and elucidates the nature of scholarly talks on the subject. Of the 2072 documents, 82 meet the threshold of citation, which was 120. For each of the 82 documents, we calculated the total strength of the bibliographic coupling links with other documents and selected the documents with the greatest total link strength.

Figure 5 illustrates a scientific mapping, which uses the full counting method to reveal the most bibliographically coupled essential documents and how they are related. The number of local citations was used to assess the scientific impact of each document. Based on the total link strength and subject effect, we found five clusters, each in a distinct hue of red, purple, green, yellow, and blue. These five clusters had the total link strength and links of 2746 and 202, respectively. The red cluster was anchored by Burits with citation, total link strength, and links of 1406, 48, and 31, respectively [34]. It was followed by Badary and Worthen [36, 37]. They examined the role of the antioxidant capacity of thymoquinone in suppressing chemically induced oxidative injuries. The green cluster was headed by El-Mahdy et al., Sethi et al., Khan et al., and Woo et al. [41, 44, 43, 45]. This cluster's documents focused on the anticancer activity of thymoquinone in various in vivo and in vitro models. These authors proposed possible involvement of the PPAR- γ pathway and nuclear factor-kB activation and inhibition of antiapoptotic gene products as mechanisms [43-45]. Ramadan and Hossienzadeh headed the blue cluster: their research was on the neutraceutical applications of thymoquinone [46, 47]. The yellow cluster contained three publications that supported the research publi-



Figure 6 Density (a) and overlay (b) visualization for the most frequent keywords. Circles represent the number of occurrences. Different colors of the frames define the trending knowledge in each cluster

shed by El-Mahmoudy in 2022. It demonstrated that thymoquinone inhibited the expression of inducible nitric oxide synthase in rat macrophages [48]. We obtained only two documents in the fifth cluster. This violet cluster documents the effect of thymoquinone on inflammation, cytokine network, and arthritic disease model [49, 50].

Lexical analysis: keyword co-occurrence. Thematic evolution is a crucial bibliometric method: it is a primary technique that gives a historical perspective on research and offers a science-based model concentrating on future research directions. It highlights the most important research topics and demonstrates how they have developed over time, offering insights into the future direction that research should follow [51, 52]. The authors used 4531 keywords in thymoquinonerelated research. We selected only 248 keywords. For every keyword, we calculated the total strength of the co-occurrence links with other keywords using VOSviewer and clustered them into four categories marked as red, green, blue, and yellow. Figure 6a shows the keywords with the greatest total link strength. Cluster one (red) included 37 keywords. Its most frequent keywords were *apoptosis* and *oxidative stress*. Reactive oxygen species (ROS) and the oxidative stress they cause play a significant part in the process of apoptosis. Apoptosis may be prevented or delayed by antioxidants and thiol reductants [53]. The green cluster (n = 70) was led by *inflammation, antioxidant*, *cytotoxicity, doxorubicin*, and *breast cancer*. Extensive



Figure 7 Mapping of co-authorship

 Table 4 International collaboration as measured by co-authorship

Country	Documents	Citations	Total link strength
Saudi Arabia	342	9766	297
Egypt	275	8131	227
India	267	6119	124
Turkey	267	3886	53
United States	248	9346	166
Iran	183	3724	24
China	141	3270	58
Malaysia	92	1615	61
Germany	66	2799	38
Pakistan	62	953	42
France	45	1292	49
Japan	43	1260	35
South Korea	39	1598	31
Indonesia	37	110	7
Canada	36	1024	28
Jordan	33	635	31
Lebanon	32	1591	28
Italy	31	1082	19
United Kingdom	28	1182	32
Iraq	25	409	19

research conducted over the last two decades has uncovered the mechanism by which persistent oxidative stress may rise to chronic inflammation, which may, in turn, mediate most chronic illnesses, including cancer [54]. Keywords related to the chemical composition, antibacterial, and antimicrobial properties of the *N. sativa* essential oil dominated the third cluster (blue, n = 77). Cluster four (yellow) with 66 words involved *antioxidant, molecular docking*, and COVID-19. VOSviewer generated an automatically-determined time limit for the overlay visualization (Fig. 6b). The time frame was from 2012 to 2018. This knowledge structure aligns with the scientific productivity that began in the past two decades. The yellow frames display the most popular terms, which in turn reflect the most cutting-edge research and knowledge.

Geographical and authorship mapping. Understanding the trajectory of research across a wide variety of study fields requires a solid grasp of the author cooperation network. This partnership frequently results in establishing academic hubs that enhance the growth and future expansion in that study area. Figure 7 presents a co-author network that depicts the intellectual relationships between scholars on a country-by-country basis. Based on co-authorship, Fig. 7 identifies the nation that has contributed the most publications. Of 100 different countries, 42 countries with four clusters, 254 links, and a total link strength of 811 met the cut-off point, with the minimal number of papers being ten and its minimal number of citations being five. The diameter of the circle represents the total number of publications per country. Line thickness and circle spacing are used to gauge the level of collaboration. The total strength of a country's relations is determined by the number of documents published by authors from two or more different nations. Four main networks emerged: Saudi Arabia (red), Malaysia (green), France (blue), and Turkey (yellow). However, Saudi Arabia, Egypt, India, Turkey, and United States proved to be the leading countries (Table 4).

CONCLUSION

This research results have a considerable theoretical and practical significance. The publication introduces a comprehensive historical overview of scientific literature during the past eleven decades. First, it highlights the most influential and productive authors,

publications, and nations. Second, scientists that work with thymoguinone can use this article to determine prospective co-authors and journals where to publish their findings. Third, our article gives academics a chance to concentrate their attention on the most relevant, prominent, and recent papers. Fourth, the results of this study may be used by researchers who employ neural networks and data scientists to choose the research topics we identified as gaps. For instance, more study is required to evaluate the precise mechanism of thymoquinone in the mitochondrial oxidation system. Thymoquinone is a well-known antioxidant supplement that promotes health. However, it can potentially be harmful to cells and organs due to its propensity to encourage the oxidation of biomolecules under certain circumstances. Furthermore, the reduced metabolite thymohydroquinone may be more effective than thymoquinone since hydroquinones have been discovered to display higher antioxidant and prooxidant activity than their parent quinones.

However, this study relied entirely on the Scopus database for pertinent papers. We had to leave few documents out because they lacked the necessary details. Future research projects may employ other databases, such as Web of Science (WoS) and Google Scholar, to use a variety of review approaches and give a more detailed quantitative and qualitative summary. The shortcomings of the methodologies in terms of in-depth study balance out their benefits in terms of a wider scope. We failed to investigate the approaches and models to perform a more critical analysis of the research issue, but this is a fundamental flaw in all bibliometric approaches since they frequently focus more on the outputs than on the actual subject matter.

CONTRIBUTION

S.I. Abdelwahab and M.M.E. Taha conceived and designed the manuscript, contributed data and analysis tools, and performed the analysis. S.I. Abdelwahab and A.A. Mariod collected the data and wrote the paper.

CONFLICT OF INTEREST

Authors declare no conflict of interests regarding the publication of this article.

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