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Review Article

Bibliometric analysis and review of research frontiers on Transient Receptor Potential Vanilloid 4 channels

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ABSTRACT

The transient receptor potential vanilloid 4 (TRPV4) channel is a member of the TRP vanilloid subfamily in the TRP superfamily of ion channels. This study aimed to provide an overview of the research progression on TRPV4 channels, from initial discovery to present, using bibliometric methods. TRPV4 channel-related articles published from 2000 onwards were retrieved from the Scopus database. Microsoft Excel and Harzing's Publish or Perish were used for the quantitative analysis of several characteristics of the retrieved articles. VOSviewer was used to construct networks based on the co-occurrence of author keywords. From 2000 onwards, 877 TRPV4 channel-related English language articles written were published and included in the final bibliometric analysis. The number of publications appeared to fluctuate over the years; however, the number is predicted to increase over time. The Journal of Biological Chemistry ranked top for publishing 46 papers. Our co-occurrence analysis of author keywords revealed four main clusters: ``Cardiovascular-related,'' ``Channelopathies,'' ``Tumorigenesis,'' and ``Smooth muscle regulation.'' Our study also highlighted four main research frontiers of TRPV4: glaucoma, mitochondria, inflammation, and cell signaling. This is the first study to examine and demonstrate the trends and outlook for TRPV4 channel research using bibliometrics.

Key words: Bibliometric analysis, Co-occurrence analysis, Harzing's Publish or Perish, TRPV4 channel, VOSviewer

INTRODUCTION

The mammalian transient receptor potential (TRP) superfamily is a diverse family of ion channels that is further subdivided into six subfamilies: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystic), and TRPV (vanilloid)[1]. The TRPV channels have six members (TRPV1-6) and were named due to the activation of the first member by capsaicin, a vanilloid-like molecule[1]. The TRPV4 channel is a calcium-permeable nonselective cation channel ubiquitously expressed in a variety of tissues, including the brain, eyes, kidney, skin, gastrointestinal tract, and urinary bladder[2]. It is also polymodally activated by a wide range of stimuli, including physical (*i.e.*, cell swelling, heat, and mechanical stimulation) and chemical stimuli (*i.e.*, endocannabinoids, arachidonic acid, and 4alpha-phorbol esters)[2,3]. Since its discovery as an osmosensitive calcium-permeable cation channel in 2000[4], TRPV4 has gained considerable attention in multidisciplinary research. Studies have assessed its physiological and pathophysiological significance[5], pharmacological modulators[6,7], and therapeutic potential in a variety of human diseases[8,9].

Bibliometric analysis is a scientific method that enables the quantitative and qualitative analysis of massive bibliometric data to provide information on essential research constituents, including authors, countries, journals, and emerging trends[10]. Unlike other frequently used review methods, such as systematic reviews, which are confined to specific and limited aspects of a research question, bibliometric analysis provides an objective and comprehensive overview of the literature on a particular research area to illustrate overall research trends and reveal future directions. It can accommodate large datasets and is better suited for broad study scopes[10–12]. In recent years, bibliometric analysis has been used in various areas of research, including melatonin[13], neurodegenerative diseases[14], and ion channels[15,16]. Although a recent bibliometric analysis has been conducted on TRP ion channels[15], no prior bibliometric studies have been conducted specifically on TRPV4 channels, which belong to the TRPV subfamily of TRP channels. Moreover, unlike the previous bibliometric analysis on TRP channels, which utilized the Web of Science database[15], we used the Scopus database and demonstrated the trends and future development in TRPV4-related research from 2000 to now.

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MATERIALS AND METHODS

The online literature search was performed on July 27th, 2022, using the Scopus database. The search query was determined after an exhaustive review of the literature for terms relevant to the research question. The National Center for Biotechnology Information's Gene database was used to look for TRPV4 aliases (https://www.ncbi.nlm.nih.gov/gene/59341). Following this, [TS = trpv4 OR "transient receptor potential vanilloid 4 channel" OR "OTRPC4" OR "VROAC"] was used as the search strategy. The use of these search queries within article titles facilitated the retrieval of the maximum number of documents while minimizing the presence of extraneous outcomes. Only articles and reviews written in English and published from 2000 onwards were included in the analysis. Other document types, such as notes, errata, book chapters, editorial materials, conference papers, letters, short surveys, and non-English publications, were excluded. In total, 877 documents were included for further bibliometric analysis (**Figure 1**). Descriptive statistics were analyzed using Microsoft Excel, citation analysis was performed using Harzing's Publish or Perish version 8.2.3944, and the VOSviewer version 1.6.18 software tool was used for network visualization of the author keyword co-occurrence map.

RESULTS

The trends in global publications

A total of 877 articles met the search criteria from 2000 to the present and were retrieved from the Scopus database (**Figure 1**). Since the publication of the first paper on TRPV4 channels (initially referred to as TRP [transient receptor potential]-like channel protein, OTRPC4) in 2000[4], the number of publications has fluctuated over time, reaching a peak in 2020 (**Figure 2**). However, the overall publication output regarding TRPV4 research has been on an upward trend, and it is predicted that the number of pertinent articles in 2022 will continue to rise based on this trend.

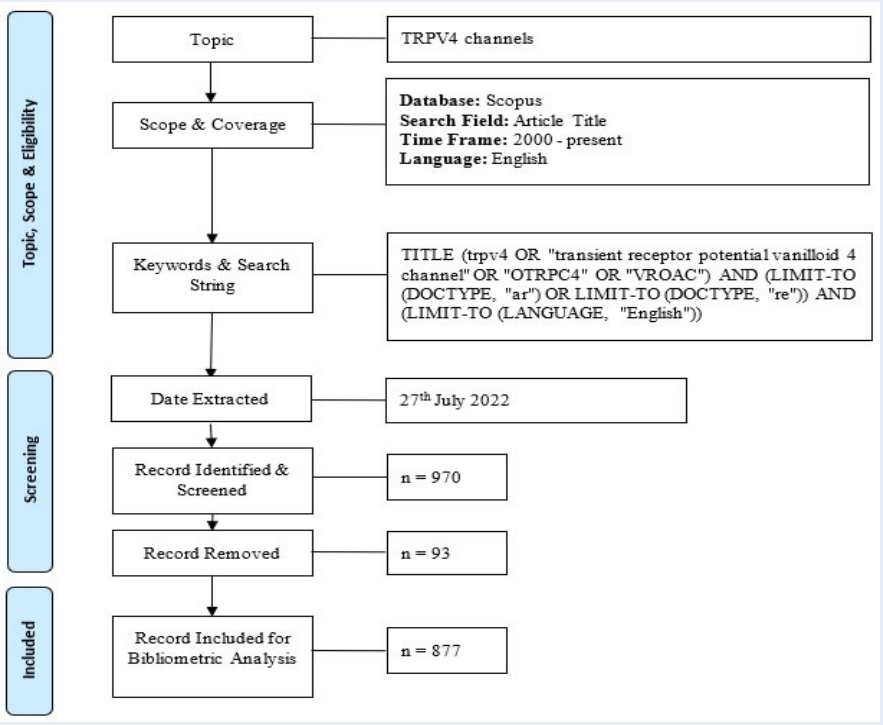

Figure 1: **PRISMA flow chart of data inclusion and exclusion [17].**

Table 1: Top 10 Most Productive Journals

Source Title	TP	TC	Publisher	Cite Score (2021)	SJR (2021)	SNIP (2021)
Journal of Biological Chemistry	46	5937	Elsevier	8.8	1.871	1.239
Pflugers Archiv European Journal of Physiology	25	913	Springer Nature	6.6	1.133	1.075
PLoS One	22	1024	Public Library of Science	5.6	0.852	1.368
Proceedings of the National Academy of Sciences of the United States of America	22	3281	National Academy of Sciences	18.1	4.184	3.063
Scientific Reports	20	628	Springer Nature	6.9	1.005	1.389
British Journal of Pharmacology	17	464	Wiley-Blackwell	13.6	1.993	1.871
American Journal of Physiology - Lung Cellular and Molecular Physiology	16	1076	American Physiological Society	8.8	1.639	1.271
American Journal of Physiology - Renal Physiology	15	645	American Physiological Society	6.6	1.224	1.026
Biochemical and Biophysical Research Communications	14	348	Elsevier	6.5	0.805	0.723
International Journal of Molecular Sciences	13	86	Multidisciplinary Digital Publishing Institute (MDPI)	6.9	1.176	1.401

Abbreviations: **TP**: total number of publications; **TC**: total citations

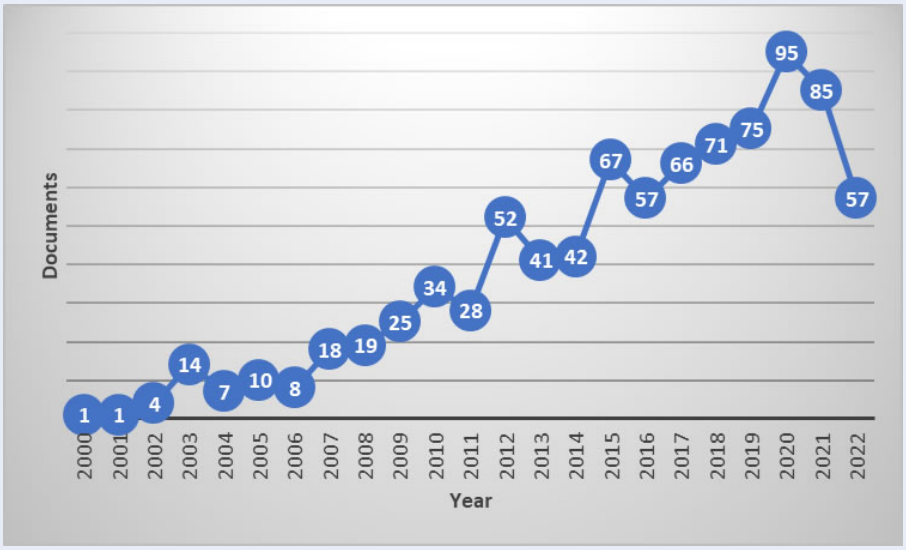

Figure 2: **Publication outputs on TRPV4-related research**.

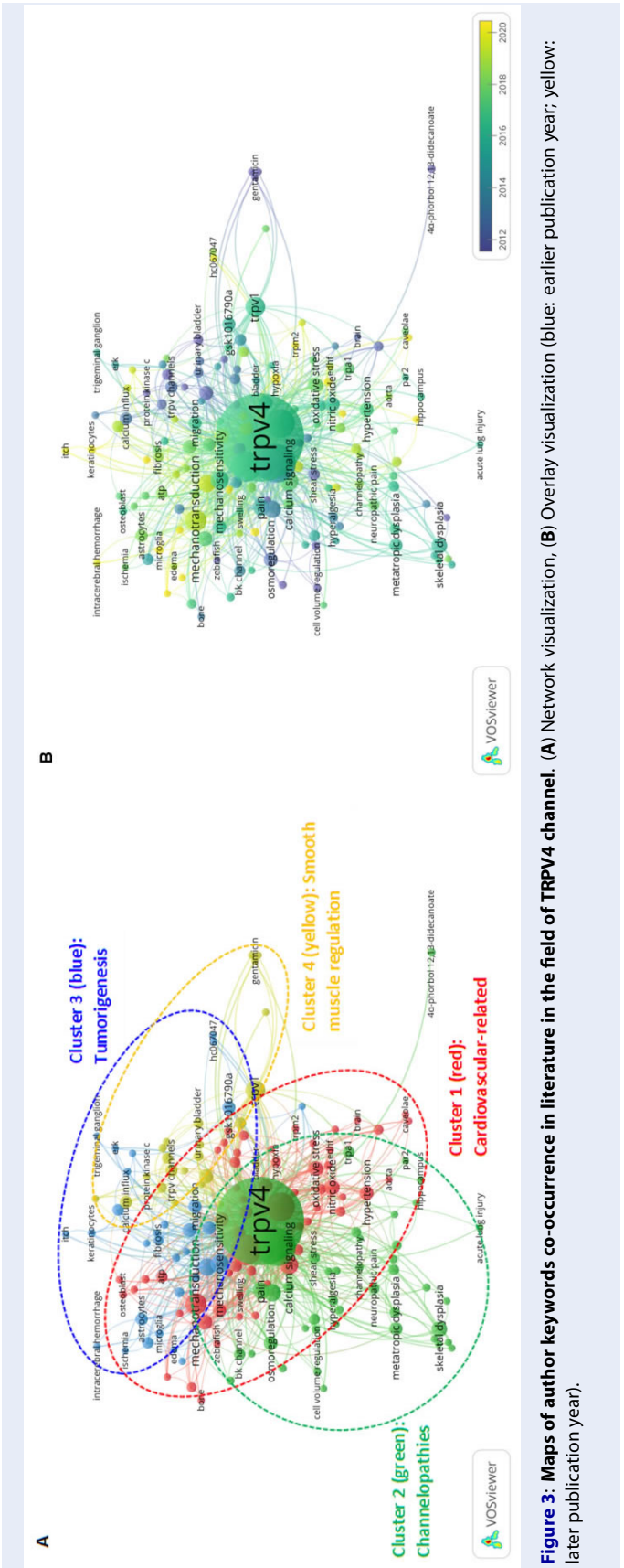

Figure 3: **Maps of author keywords co-occurrence in literature in the field of TRPV4 channel**. (**A**) Network visualization, (**B**) Overlay visualization (blue: earlier publication year; yellow: later publication year).

Top 10 productive journals publishing articles on TRPV4 channels

The top 10 journals that published articles on TRPV4 channels are shown in **Table 1**. The Journal of Biological Chemistry (Cite Score = 8.8, 2021) had the highest number of publications, with 46 articles. The Pflugers Archiv European Journal of Physiology (Cite Score = 6.6, 2021) ranked second with 25 articles, followed by the PLoS One (Cite Score = 5.6, 2021) and the Proceedings of the National Academy of Sciences of the United States of America (Cite Score = 18.1, 2021), with 22 articles each.

Co-occurrence analysis of keywords

The author keywords of the 877 original articles and reviews were analyzed using VOSviewer. As shown in Fig. 3, 159 out of 1758 keywords met the threshold (defined as being used more than three times in all the articles and with a minimum cluster size of 21). Overall, 751 links were classified into four clusters: "Cardiovascular-related" (in red), "channelopathies" (in green), "tumorigenesis" (in blue), and "smooth muscle regulation" (in yellow). The "cardiovascular-related" cluster was the largest, with 59 items. Among the keywords related to this cluster were "calcium" (49 occurrences), "endothelium" (44 occurrences), "nitric oxide" (12 occurrences), "hypertension" (10 occurrences), and "vasodilation" (10 occurrences). For the "channelopathies" cluster, 46 items were identified with the primary keywords including "trpv4" (401 occurrences), "ion channels" (18 occurrences), "pain" (15 occurrences), "skeletal dysplasia" (13 occurrences), and "neuropathic pain" (6 occurrences). The "tumorigenesis" cluster comprised 31 items with primary keywords like "mechanosensitivity" (18 occurrences), "inflammation" (16 occurrences), "apoptosis" (10 occurrences), "proliferation" (9 occurrences), and "migration" (9 occurrences). For the "smooth muscle regulation" cluster, 23 items were identified, and the primary keywords included "trpv1" (20 occurrences), "vascular smooth muscle cells" (10 occurrences), "calcium influx" (8 occurrences), and "urothelium" (7 occurrences).

Research frontiers of TRPV4 channels

The research frontiers of TRPV4 channels were predicted based on the occurrences of the 159 keywords that met the threshold for the past three years (2019–2022), as analyzed by the VOSviewer software tool. Out of the 159 items, 30 were identified as the frontiers of TRPV4 research. Fifteen items were identified from Cluster 1, including "glaucoma" (10 occurrences; average publication year: 2020.40) and "angiogenesis" (9 occurrences; average publication year: 2019.33). For Cluster 2, two items were identified as research frontiers: "stroke" (3 occurrences; average publication year: 2021.33) and "mitochondria" (4 occurrences; average publication year: 2019.25). In Cluster 3, 12 items were identified: "inflammation" (16 occurrences; average publication year: 2019.25), "microglia" (4 occurrences; average publication year: 2020), "keratinocytes" (4 occurrences; average publication year: 2019.75), and "metastasis" (4 occurrences; average publication year: 2019). For Cluster 4, "cell signaling" (3 occurrences; average publication year: 2019) was the only keyword identified as a research frontier.

DISCUSSION

This bibliometric analysis identified 877 Scopus-indexed articles related to TRPV4 channels published from 2000 to the present. Based on our data, the number of global publications on TRPV4 channels has fluctuated over this time, reaching a peak in 2020. A downward trend in global publication outputs was seen in 2021, most likely due to the COVID-19 pandemic, as this resulted in a significant realignment of priorities and research efforts, causing a decline in overall publishing rates and funding for other biomedical research areas unrelated to COVID-19 [18]. Although there was a slight decrease in the number of publications in 2022, this was somewhat expected given that it was still within the update period when the literature search was conducted. The inclusion of the year 2022 was to allow for the analysis of the emerging trends in TRPV4 channel research. Taken together, based on the recent trends, we anticipated that the annual number of published documents on the TRPV4 channel would continue to rise in 2022, indicating that TRPV4 channel research is gaining greater attention. Similar publication trends were observed in studies of other channels [15,19,20].

Concerning the active journals publishing TRPV4-related articles, the Journal of Biological Chemistry (a journal from the United States of America) was the leading journal, with 46 articles published and a total citation number of 5937, followed by Pflugers Archiv European Journal of Physiology, PLoS One and the Proceedings of the National Academy of Sciences of the United States of America. Interestingly, the majority of these journals have been listed among the top 10 journals for articles published on TRP channels [15], indicating that these are some of the most favorable journals for publishing research on the TRP superfamily of cation channels, including TRPV4. These highly influential academic journals are expected to

be among the major sources of future articles related to the TRPV4 channel.

Term clustering from our network analysis revealed four main clusters. The first and the biggest cluster, the "cardiovascular-related" cluster, had 59 items, indicating that it is currently the most popular area of research involving TRPV4 channels. The core keywords in this cluster were "calcium," "endothelium," "nitric oxide," "hypertension," and "vasodilation." A growing number of studies have reported the physiological and pathological role of TRPV4 in the cardiovascular system[21]. For instance, using *in vivo* and *in vitro* study models, Zou *et al.*[22] demonstrated that TRPV4 activation contributes to pressure overload-induced cardiac hypertrophy and heart failure. Therefore, TRPV4 antagonism may confer a therapeutic advantage for this pathological condition.

The second cluster identified was "channelopathies". This cluster contained 46 items, with the primary keywords being "trpv4," "ion channels," "pain," "skeletal dysplasia," and "neuropathic pain." TRPV4 channelopathies are mutations in the *TRPV4* gene that alter channel function, leading to several phenotypically distinct diseases that can be classified into two groups: skeletal dysplasias and neuropathies[23]. TRPV4-associated skeletal dysplasias encompass a heterogeneous group of skeletal diseases commonly characterized by a shortening of the trunk, while TRPV4-mediated neuropathies include a spectrum of hereditary neuropathies which can present with primarily motor axonal peripheral neuropathy or are associated with sensory involvement[23].

The third cluster, "tumorigenesis," had 31 items. This cluster was represented by keywords such as "mechanosensitivity," "inflammation," "apoptosis," "proliferation," and "migration." These keywords illuminate the increasingly recognized role of TRPV4 in cancer hallmarks, including apoptosis, proliferation, migration, and metastasis[24–27]. Therefore, TRPV4 is a viable target for cancer treatment[28]. The role of the mechanosensitive TRPV4 ion channel in inflammation has also been elucidated[29]. TRPV4 has been implicated in the inflammatory response, whereby stretch-induced TRPV4 activation causes the release of the pro-inflammatory cytokines IL-6 and IL-8 in human lung epithelial cells[30]. TRPV4 has also been identified as a regulator of neutrophil activation, as TRPV4 deficiency prevents neutrophil response to pro-inflammatory stimuli in acute lung injuries[31].

The fourth cluster, "smooth muscle regulation," was represented by "trpv1," "vascular smooth muscle cells," "calcium influx," and "urothelium." TRPV1, which is a close relative of TRPV4, is a receptor for capsaicin (an active component of chili peppers)[32]. Similar to the polymodal TRPV4 ion channel, TRPV1 is a nonselective cation channel activated by noxious heat (greater than 42°C), acidosis (pH < 6), and several endogenous agonists, including endocannabinoids, anandamide, and arachidonic acid-derived metabolites[33]. TRPV1 is involved in several processes, including thermoregulation, nociception, and inflammation[33,34]. TRPV4 expression has been documented in vascular smooth muscle cells, such as the smooth muscle cells of rat cerebral arteries[35], rat pulmonary arterial smooth muscle cells[36], and human and rat smooth muscle extra-alveolar vessels[37]. Increasing evidence has documented the role of TRPV4 channels in vascular function regulation, including in vascular dilation and constriction, permeability, remodeling, and damage[38].

The four main research frontiers of TRPV4 identified from our analysis were glaucoma, mitochondria, inflammation, and cell signaling. We have further enumerated these research frontiers below.

TRPV4 and glaucoma

The potential role of the TRPV4 channel has been investigated in several ocular diseases, including glaucoma[39]. Glaucoma is a group of eye diseases characterized by progressive degeneration of retinal ganglion cells that can result in subsequent loss of vision and blindness, typically due to increased intraocular pressure (IOP)[40]. Dysfunction of the trabecular meshwork is associated with elevated IOP in glaucoma; recent findings have provided evidence regarding the involvement of TRPV4 channels in IOP regulation[41]. Patel *et al.*[41] found that glaucomatous primary human trabecular meshwork cells showed impaired TRPV4 channel activity, reduced endothelial nitric oxide synthase (eNOS) signaling, and a subsequent reduction in nitric oxide production and elevated IOP, further implicating TRPV4-eNOS signaling in glaucoma pathogenesis. Further mechanistic studies on TRPV4's role in glaucomatous eyes may illuminate the potential of TRPV4 as a therapeutic target for glaucoma.

TRPV4 and mitochondria

Previous studies have reported that TRPV4 is endogenously expressed in mitochondria and involved in the regulation of mitochondrial calcium homeostasis, temperature, and metabolism[42]. TRPV4 has also been implicated in the regulation of mitochondrial morphology, smoothness, and fusion-fission events, further highlighting the interplay between TRPV4

and mitochondria[42]. Zhang *et al.*[43] recently provided evidence on the new role of mitochondria in shaping TRPV4-mediated calcium signaling by facilitating adenosine triphosphate (ATP) release. Investigating the molecular mechanisms that link TRPV4 to mitochondria is worthy of further investigation to improve the understanding of TRPV4's involvement in the regulation of mitochondrial function and its potential role in mitochondria-mediated diseases.

TRPV4 and inflammation

A growing body of evidence suggests TRP channels play a role in the physiology and pathophysiology of inflammation and the immune system[44]. Early evidence regarding the role of TRPV4 in inflammation has been demonstrated by Yin *et al.*[31], who reported that genetic deficiency or pharmacological inhibition of TRPV4 attenuated the functional, histological, and inflammatory characteristics of acute lung injury in a murine model of acid-induced acute lung injury. Considering the importance of TRPV4 channels in various inflammatory conditions, such as chronic lung disease[45] and osteoarthritis[46], TRPV4 is subject to ongoing research to gain further insights into the precise molecular mechanisms underlying TRPV4-mediated inflammation. Such interest could result in the discovery of new therapies for these inflammatory conditions.

TRPV4 and cell signaling

Cell signaling refers to the fundamental, ubiquitous process that living systems utilize to respond to the environment. It provides the coordination required for multicellular organisms to function properly[47]. Compelling evidence has implicated some components of the calcium signaling machinery, such as TRP channels, in the development and progression of cancer. Therefore, these components may be plausible drug targets for cancer therapy[48]. Increasing evidence has begun to demonstrate the functional importance of TRPV4-mediated calcium signaling in several aspects of tumorigenesis, including angiogenesis, metastasis, and apoptosis, in various cancer types[26,27,49–52]. Delineating the key signaling pathways involved in TRPV4-mediated oncogenesis could pave the way for the development of novel, targeted cancer therapies.

Strengths and Limitations

To the best of our knowledge, this study is the first bibliometric analysis to specifically address TRPV4 channels. Our data analysis was objective and clearly demonstrated the general global trends in research pertaining to TRPV4 channels, as well as the research frontiers, which could serve as a reference for researchers interested in conducting more in-depth studies in this field. However, since our study collected the articles from a single database only (*i.e.*, the Scopus database) and was limited to original articles and reviews, we might have missed other relevant articles in the literature. We decided to retrieve articles from the Scopus database as it is a leading global academic database and covers a wider spectrum of journals than other databases, such as PubMed, Web of Science, and Google Scholar[53]. Additionally, the Scopus database is a single database with no further restrictions on content accessibility, making it an ideal data source for bibliometric applications[54]. Nevertheless, given that our study encompasses most articles published from 2000 to the present, the most recent publications would not have a significant impact on the results presented in this study.

CONCLUSIONS

This is the first bibliometric study demonstrating the global trends and future developments in TRPV4 channel research. Our results indicate that TRPV4 research will remain an important and emerging field of study, with an expected rise in publication output. A considerable number of papers related to TRPV4 channels have been published in highly influential journals. Four clusters, "cardiovascular-related," "channelopathies," "tumorigenesis," and "smooth muscle regulation," were identified from the author keyword co-occurrence analysis of TRPV4-related publications. Our study highlighted several research frontiers of TRPV4 channels, which will likely expand soon. TRPV4 is a subject of growing interest. Future studies could further define the pathophysiological role of TRPV4 and unveil its therapeutic potential in several human diseases.

ABBREVIATIONS

ATP: adenosine triphosphate, **eNOS:** endothelial nitric oxide synthase, **IOP:** intraocular pressure, **TRP:** transient receptor potential, **TRPA:** transient receptor potential ankyrin, **TRPC:** transient receptor potential canonical, **TRPM:** transient receptor potential melastatin, **TRPML:** transient receptor potential mucolipin, **TRPP:** transient receptor potential polycystic, **TRPV:** transient receptor potential vanilloid, **TRPV1:** transient receptor potential vanilloid 1, **TRPV4:** transient receptor potential vanilloid 4

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AUTHOR'S CONTRIBUTIONS

Conceptualization, S.Y.N.J., A.H.J. and R.Z.; methodology, R.Z.; data analysis, S.Y.N.J., A.H.J. and R.Z.; writing - original draft preparation, S.Y.N.J.; writing - review and editing, S.Y.N.J., A.H.J. and R.Z. All authors have read and agreed to the published version of the manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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