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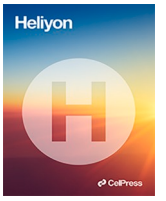

Research article

Visual analysis of global research on the transient receptor potential ankyrin 1 channel: A literature review from 2002 to 2022

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ABSTRACT

Background and aims: The transient receptor potential ankyrin 1 (TRPA1) channel has become a focus in pain research. However, there are no bibliometric studies that systematically analyze the existing research in this area. This study aimed to provide a systematic review of the existing literature on TRPA1 using a bibliometric analysis.
Methods: Published literature in the field of TRPA1 was collected from the Web of Science Core Collection database. Quantitative and qualitative analyses of publications, countries, institutions, authors, journals, and other entries were conducted using Excel, VOSview, and Citespace software to provide insight into global research hotspots and trends in the TRPA1 field.
Results: This study included 1189 scientific products published in 398 journals from 52 countries. The United States of America (n = 367) had the most publications, ahead of Japan (n = 212) and China (n = 199). The University of Florence (n = 55) was the most productive institution and Pierangelo Geppetti (n = 46) was the most productive author. *PLoS One* (n = 40) published the most articles on TRPA1. Pain, cold, inflammation, covalent modification, hyperalgesia, and oxidative stress were the most common keywords used in the studies.
Conclusion: This study provides the first bibliometric analysis of TRPA1 publications. The physiological functions of TRPA1, TRPA1, and neuropathic pain, TRPA1 as a therapeutic target, and agonists of TRPA1 are trending in TRPA1 research. Neuropathic pain, apoptosis, and sensitization could be focus areas of future research. This study provides important insight in the field of TRPA1 research.

1. Introduction

The transient receptor potential (TRP) channel is a transmembrane protein that forms non-selective cation channels [1]. TRP channels have attracted a great deal of attention among researchers, clinicians, and drug developers as molecular sensors for a variety

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Abbreviations

ADH	alcohol dehydrogenase
ANKTM1	ankyrin-like protein with transmembrane domains protein 1
ARD	ankyrin repeat domain
BTZ	bortezomib
CCI	chronic constriction injury
CGRP	calcitonin gene-related peptide
CPP	average number of citations per publication
cryo-EM	cryo-electron microscope
CS	cigarette smoke
DADS	allicin and diallyl disulfide
DEP	diesel exhaust particles
DRG	dorsal root ganglion
H2O2	hydrogen peroxide
I/R	ischemia and reperfusion
IASP	international association for the study of pain
IF	impact factor
KCNMA1	calcium-activated potassium channel subunit α-1
miR	microRNAs
MRC	mitochondrial respiratory chain
mTRPA1	mouse TRPA1
NOX	NADPH oxidase
NOX1-dependent	NADPH oxidase-1-dependent
NP	neuropathic pain
PaI	participation index
PAR2	proteinase-activated receptor 2
PMs	particulate matter
PN	peripheral neuropathy
ROS	reactive oxygen species
TC	total citations
tMD	transmembrane domain
TP	total publications
TPTE	transmembrane phosphatase with tension homology
TRP	transient receptor potential channel
TRPA	ankyrin
TRPC	canonical
TRPM	melastatin
TRPML	mucolipin
TRPP	polycystin
TRPV	vanilloid
WOSCC	Web of Science Core Collection
4-HNE	4-hydroxynonenal

of physical and chemical stimuli [2]. The TRP family consists of 28 different members [3] and is divided into six main sub-families: vanilloid (TRPV), ankyrin (TRPA), melastatin, canonical, polycystin, and mucolipin [4]. Although these six subtypes are structurally similar, their physiological functions are different and distinctive [5]. TRPA1 is a member of the TRP family. As a multimodal cell membrane receptor [6], TRPA1 can be activated by irritant compounds in garlic, mustard, and cinnamon, as well as by reactive oxygen species produced during tissue stress [7,8]. TRPA1 can be simultaneously regulated by Ca^{2+}, trace metal, pH, and many other substances [9]. TRPA1 is mainly involved in the expression of primary sensory neurons and the dorsal root ganglion (DRG) [10]. As such, TRPA1 has promising research potential in pain-related and respiratory diseases [11] and is currently being investigated as a therapeutic target because of its anti-oxidant, anti-apoptotic, and anti-inflammatory mechanisms. Emerging disciplines such as chemical optogenetics [12] and sequence analysis [13] are now being carried out, further enriching the research field of TRPA1.

TRPA1 channels are tetrameric proteins consisting of four subunits (1119 amino acids in humans) [14]. The overall structure can be divided into three layers: the top transmembrane domain, the middle coupling domain, and the bottom ankyrin repeat domain (ARD) [15]. The structure of TRPA1 is similar to TRPV1, in that it consists of six transmembrane α-helices (S1–S6) coupled with a pore loop between S5 and S6[16]. Moreover, TRPA1 has distinct NH_2 and COOH termini in the cell, which together account for about 80 % of its molecular mass [16]. The NH_2 end contains 16 anchor protein repetitive sequences (AR1-AR16) that are arranged in tandem to form an elongated ARD. Upon activation of TRPA1 by stimulatory compounds, ion channels open and the central pore expands, allowing

calcium to flow into the cytosol to induce signal transduction pathways [17].

Bibliometric analysis is a research method used for the quantitative and qualitative analysis of publications in a specific field of study [18]. This method helps elucidate publications characteristics, including countries, institutions, authors, journals, and the evolution and development of a particular research field [19]. To date, no bibliometric analysis of TRPA1 has been published. In this study, we aimed to analyze the historical evolution pattern of the TRPA1 field, summarize the research trends, and predict future research directions.

2. Materials and methods

2.1. Data sources and search strategies

The literature search was conducted using the Web of Science Core Collection (WoSCC), and the search terms for this study were identified in the Medical Subject Headings (MeSH) database (https://www.ncbi.nlm.nih.gov/MeSH). The retrieval strategy was as follows: TI=(TRPA1) OR TI=(Transient Receptor Potential Ankyrin-1) OR TI=(ankyrin-like protein with transmembrane domains protein 1) OR TI=(anktm1). Non-English or non-article publications were excluded. Two authors (NG, ML) conducted the literature search and screening independently. In case of disagreement, a third author (WMW) was engaged in discussion.

2.2. Data collection

Seventy-two categories of data including author, article title, source title, abstract, address, times cited, and publication year, among others, were collected from the WoSCC database and were downloaded as ".txt ", ".xls" format to allow for further analysis. A journal's impact factor (IF) was determined using https://JCR.Clarivate.com/in this study. The H-index of high-yielding authors and the Journal Citation Report category quartile were obtained through the WoS database. To avoid bias caused by frequent database updates, all literature searches and data extraction were completed on the same day (December 13, 2022).

2.3. Bibliometric indicator

The following indicators were used in this study: (i) Price's law: to analyze the annual distribution of publications; (ii) Bradford's law: to identify core journals in the TRPA1 field; (iii) Participation Index (PaI): to evaluate the literature output of different countries; (iv) Total publications (TP): total number of publications during the observation period; (v) Total citations (TC): total citations of publications; (vi) CPP (TC/TP): average number of citations per publication.

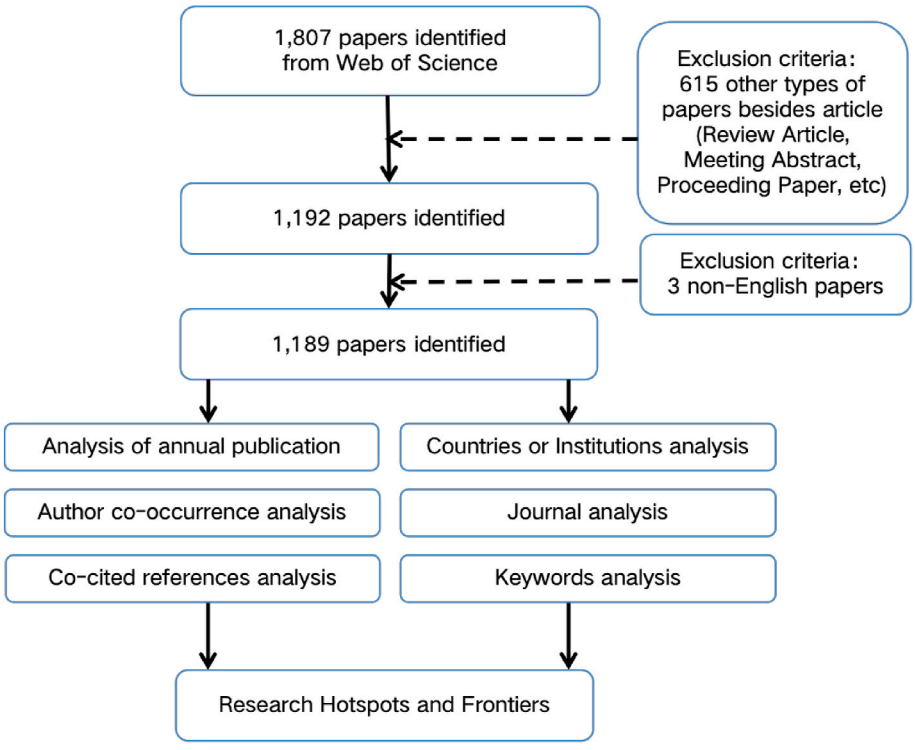

Fig. 1. Flow chart of literature screening.

2.4. Statistical software and analysis

The following software systems were used for data analysis in this study: (i) Microsoft Excel (version.2019; Microsoft Corporation; United States): used to manage data by category and draw statistical charts; (ii) VOSviewer (version.1.6.18; The Center for Science and Technology Studies. Netherlands): used to analyze the number of publications by authors, countries, and institutions, to construct collaborative networks, and to analyze keywords by clustering. We also performed manual verification to correct incorrect values; and (iii) Citespace (version.V; Drexel University; United States): used to organize the historical evolution of research topics.

3. Results

3.1. Publication outputs

By searching the WoSCC database, we retrieved 1189 publications related to TRPA1 between 2002 and 2022, including 1125 articles and 64 reviews. The detailed literature screening process for this study is shown in Fig. 1. The first article in the TRPA1 field was published in 2004, and the annual number of publications until 2010 was less than 50. The number of publications increased rapidly after 2010, with the highest quantity of 113 publications in 2020. To determine whether the growth in study output followed Price's law, we linearly adjusted the data using the equation y = 5.5737x – 11157, and 19.68 % of the variance was not explained by the model fit (R^2 = 0.8032) (Fig. 2). The data can be better fitted linearly compared to an exponential fit. Consequently, it can be expected that publications in the field of TRPA1 will continue to grow, with the number of annual publications expected to increase to 158 by the year 2030.

3.2. Contributions of countries

Over the last approximately 20 years, 52 countries have participated in research in the TRPA1 field, and the specific distribution of country contributions is shown in Fig. 3A. Table 1 presents the top 10 countries in terms of contribution, with the United States of America (USA) publishing the most articles (PaI = 30.03), followed by Japan (PaI = 17.83) and China (PaI = 16.74). Fig. 3B shows the annual trend of publications in these three countries, with the USA and Japan initiating research in the field of TRPA1 earlier, peaking in 2016 (n = 36) and 2012 (n = 22) in terms of publications, respectively. Research in the TRPA1 field began late in China but developed rapidly, surpassing Japan and the USA in 2016 (n = 23) and 2021 (n = 31) respectively. In addition, Jordan and New Zealand have recently emerged in the field of TRPA1 (Fig. 3C).

3.3. Contributions of institutions

Table 2 shows the top 10 institutions in terms of contribution to the TRPA1 field, with the University of Florence having the highest number of publications (TP = 55), followed by the National Institutes of Natural Sciences in Japan (TP = 41) and King's College London (TP = 39). The threshold was set to six to construct the institutional cooperation network (Fig. 4), which shows the cooperation relationship among 90 institutions. The analysis shows that the cooperation between institutions is relatively close, which has likely contributed to the communication and cooperation among academic institutions.

3.4. Journal analysis

Publications in the TRPA1 field were published in a total of 398 journals (Table 3), and we included these journals in Bradford's five

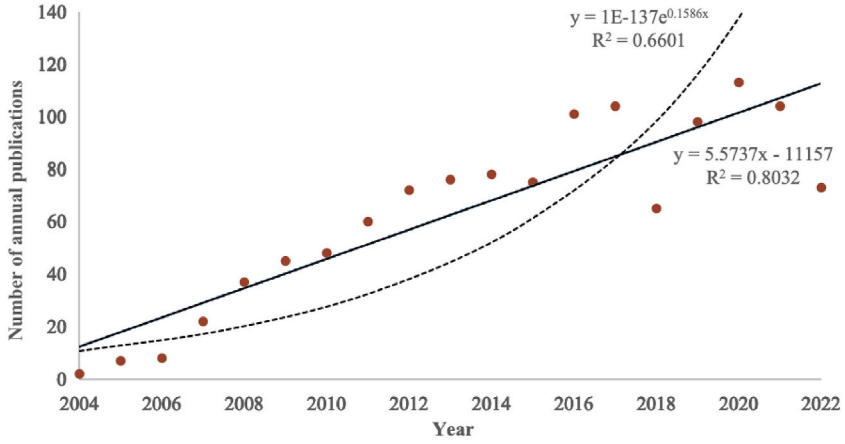

Fig. 2. Annual number of publications in TRPA1 research.

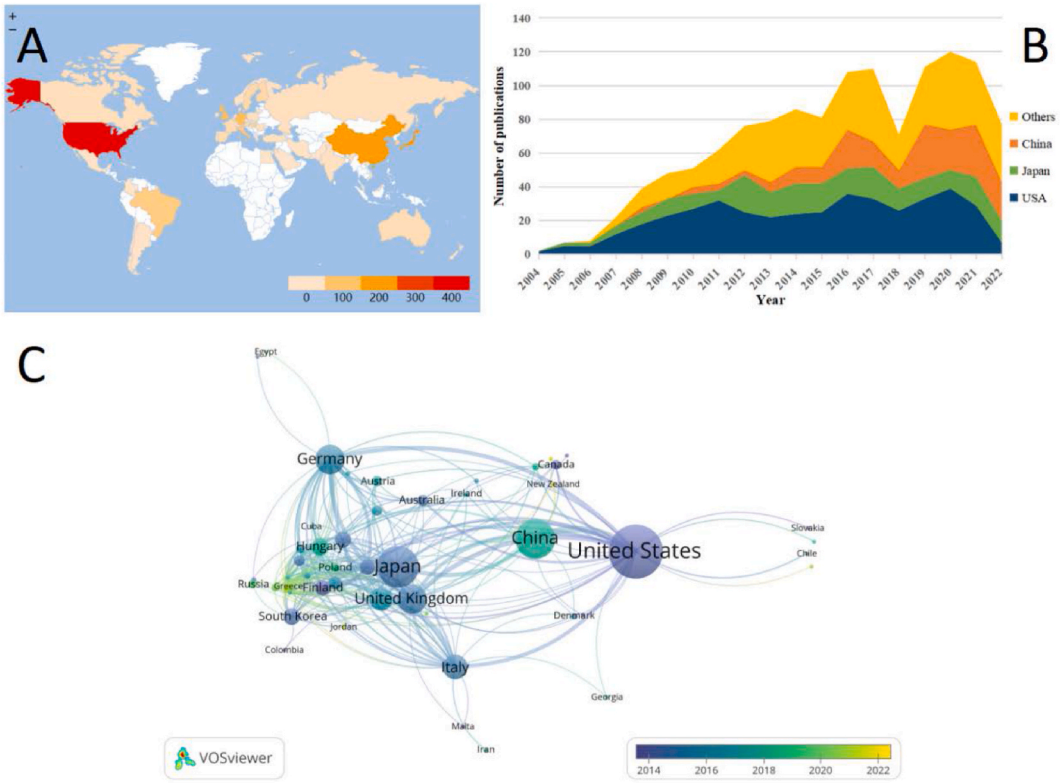

Fig. 3. The distribution of countries in TRPA1 research.

Table 1
The top 10 most productive countries in TRPA1 research.

Rank	Country	TP	PaI	TC	CPP
1	USA	357	30.03	28,793	80.65
2	Japan	212	17.83	7700	36.32
3	China	199	16.74	3050	15.33
4	Germany	115	9.67	4752	41.32
5	UK	113	9.50	5291	46.82
6	Italy	82	6.90	4601	56.11
7	Brazil	74	6.22	2263	30.58
8	Hungary	45	3.78	1103	24.51
9	South Korea	40	3.36	2110	52.75
10	Belgium	37	3.11	3195	86.35

Abbreviations: TP, total publications; PaI, participation index; TC, total citations; CPP, average number of citations per publication.

Table 2
The top 10 most productive institutions in TRPA1 research.

Rank	Institution	Country	TP	TC	CPP
1	University of Florence	Italy	55	3742	68.04
2	National Institutes of Natural Sciences	Japan	41	1912	46.63
3	King's College London	UK	39	2658	68.15
4	University of Pécs	Hungary	37	660	17.84
5	University of Erlangen-Nurnberg	Germany	32	2195	68.59
6	Kyoto University	Japan	24	1312	54.67
7	Federal University of Santa Catarina	Brazil	23	1064	46.26
8	Duke University	USA	21	1511	71.95
9	Hannover Medical School	Germany	20	1071	53.55
10	Katholieke Universiteit Leuven	Belgium	20	2077	103.85

Abbreviations: TP, total publications; TC, total citations; CPP, average number of citations per publication.

zones, each containing an average of 238 publications as follows: Core Zone; Zone 1; Zone 2; Zone 3 ≈ 1: 2: 2^2: 2^3, which is in accordance with Bradford's Law. Table 4 lists the eight journals in the Core Zone, which contains 239 publications, accounting for 20.10 % of the total number of publications in the Core Journals in the field of TRPA1. *PLOS One* had the highest number of publications with 40 articles, followed by *Sci Rep* (TP = 35), *Int J Mol Sci* (TP = 34), and *Mol Pain* (TP = 32). *Br J Pharmacol* had the highest IF (IF = 9.47), and more than half of the journals belonged to Q1 or Q2 divisions, indicating that the overall research in the field of TRPA1 is of high-quality and has received attention and recognition from high-level journals.

3.5. Contributions of authors

Table 5 shows the 10 most productive authors in the TRPA1 field, with the highest contribution from Pierangelo Geppetti (TP = 46), followed by Romina Nassini (TP = 44), Makoto Tominaga (TP = 37), and Serena Materazzi (TP = 32). Serena Materazzi had the highest CCP value (102.59), indicating their prominence in the field. In terms of author collaborations (Fig. 5), the authors in this field are closely linked and have formed numerous tight-knit research teams represented by Romina Nassini, Pierangelo Geppetti, and Juliano Ferreira.

3.6. Most cited publications

The number of highly cited papers indicates a significant influence [20] and reflects the trends and depth of research in the field [21]. Table 6 shows the 10 most cited articles. The most cited article (TC = 1366) was "TRPA1 mediates the inflammatory actions of environmental irritants and pro-algesic agents", published by Bautista et al., in 2006. This was followed by "Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin" published in *Neuron* in 2004 (TC = 1335).

3.7. Keywords analysis

3.7.1. Co-occurrence analysis of keywords

Table 7 lists the top 20 high-frequency keywords in the field of TRPA1. In addition to "trpa1" and "transient receptor potential channel", keywords such as pain, cold, inflammation, covalent modification, hyperalgesia, and oxidative stress appeared more frequently.

3.7.2. Clustering analysis of keywords

The threshold of the number of publications was set to 20, and the co-occurrence network visualization map of keywords was generated (Fig. 6), containing 66 keywords. According to the node color, the keywords can be divided into five clusters: (i) Cluster 1 (red): the physiological functions of TRPA1 channels, including pain, cold, ion channel, neurons, sensation, and another 19 keywords; (ii) Cluster 2 (green): TRPA1 and neuropathic pain, including mechanical hypersensitivity, inflammatory pain, allodynia, mechanical hyperalgesia, and another 18 keywords; (iii) Cluster 3 (blue): TRPA1 as a therapeutic target, including inflammation, apoptosis, asthma, itch, agonist, and another 15 keywords; (iv) Cluster 4 (yellow) and (v) Cluster 5 (purple): TRPA1 agonists, including hydrogen peroxide, cigarette-smoke, cinnamaldehyde, allyl isothiocyanate, and another 14 keywords.

3.7.3. Keyword burst analysis

Fig. 7 shows the 25 keywords with the strongest citation bursts in the TRPA1 research field. The strongest keyword was "covalent

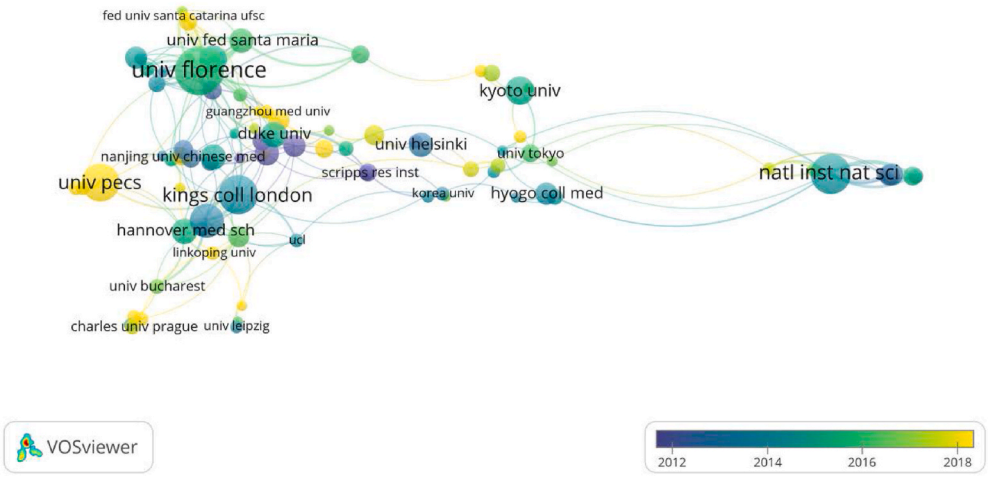

Fig. 4. Overlay visualization map of co-authorship among institutions.

Table 3
Distribution of the journals in Bradford's zones.

	No. of journals	% of journals	No. of articles	% of articles	Bradford multiplier
Core	8	2.01	239	20.10	
Zone 1	20	5.03	235	19.76	2.50
Zone 2	44	11.06	239	20.10	2.20
Zone 3	96	24.12	238	20.02	2.18
Zone 4	230	57.79	238	20.02	2.40
Total	398	100.00	1189	100.00	2.32

Table 4
Top 8 core journals in TRPA1 research.

Rank	Journal	TP	TC	CPP	JCR	IF
1	PLoS One	40	1819	45.48	Q3	3.75
2	Sci Rep	35	816	23.31	Q3	5.00
3	Int J Mol Sci	34	185	5.44	Q2	6.21
4	Mol Pain	32	2244	70.13	Q3	3.37
5	Pain	31	1654	53.35	Q1	7.93
6	J Biol Chem	23	1341	58.30	Q2	5.49
7	Journal of Neuroscience	23	3148	136.87	Q1	6.71
8	Br J Pharmacol	21	1186	56.48	Q2	9.47

Abbreviations: TP, total publications; TC, total citations; CPP, average number of citations per publication; IF, impact factor.

Table 5
The top 10 authors in TRPA1 research.

Rank	Author	TP	TC	CPP
1	Pierangelo Geppetti	46	3553	77.24
2	Romina Nassini	44	3200	72.73
3	Makoto Tominaga	37	1471	39.76
4	Serena Materazzi	32	3283	102.59
5	Gabriela Trevisan	29	983	33.90
6	Francesco De Logu	27	743	27.52
7	Erika Pinter	24	479	19.96
8	Zsuzsanna Helyes	22	431	19.59
9	Peter W Reeh	22	1033	46.95
10	Juliano Ferreira	21	777	37.00

Abbreviations: TP, total publications; TC, total citations; CPP, average number of citations per publication.

modification" (13.44) and the longest bursts were "anktm 1" (2005–2012), "primary afferent neuron" (2006–2013), and "mechanical hypersensitivity" (2010–2017). The intensity and duration of the various keyword bursts reflect the evolving direction of TRPA1 research. The keywords that continue to burst were neuropathic pain, apoptosis, and sensitization, representing cutting-edge trends in the field of TRPA1 research.

4. Discussion

4.1. General information

This study provides a bibliometric analysis of publications related to TRPA1 over the past 20 years. In 2004 Bandell et al. [22] reported that natural compounds of cinnamon oil, wintergreen oil, clove oil, mustard oil, and ginger species could activate TRPA1. This became the first article in the field. Since then, there has been a gradual increase in attention to TRPA1, with the highest number of articles (n = 113) published in 2020. The emergence of some highly cited articles has played an important role in the development of the TRPA1 field. For example, Bautista et al. [23] initially identified TRPA1 as an important component in the pathway of action of environmental stimulants and endogenous analgesics associated with inflammatory pain. Although further studies revealed that TRPA1 is not required for hair-cell transduction, it was shown that TRPA1 can facilitate transduction of mechanical, cold, and chemical stimuli in sensory neurons and nociceptors [24]. Additional associations of TRPA1 have been identified with the formalin-constructed pain hypersensitive model [25], allicin and diallyl disulfide (DADS) in garlic [26], and 4-Hydroxynonenal [27]. TRPA1 was later shown to facilitate cysteine covalent modifications that cause channel activation, characterizing the TRPA1 activation pathway [28].

Our analysis showed that the most prolific author in the TRPA1 field was Pierangelo Geppetti, Professor of Clinical Pharmacology at the University of Florence and Director of the Headache Center of the University Hospital of Carreggi. Dr. Geppetti postulated that TRPA1 may be a new direction for research and a potential treatment in migraine pathophysiology [29]. Mechanistic studies of

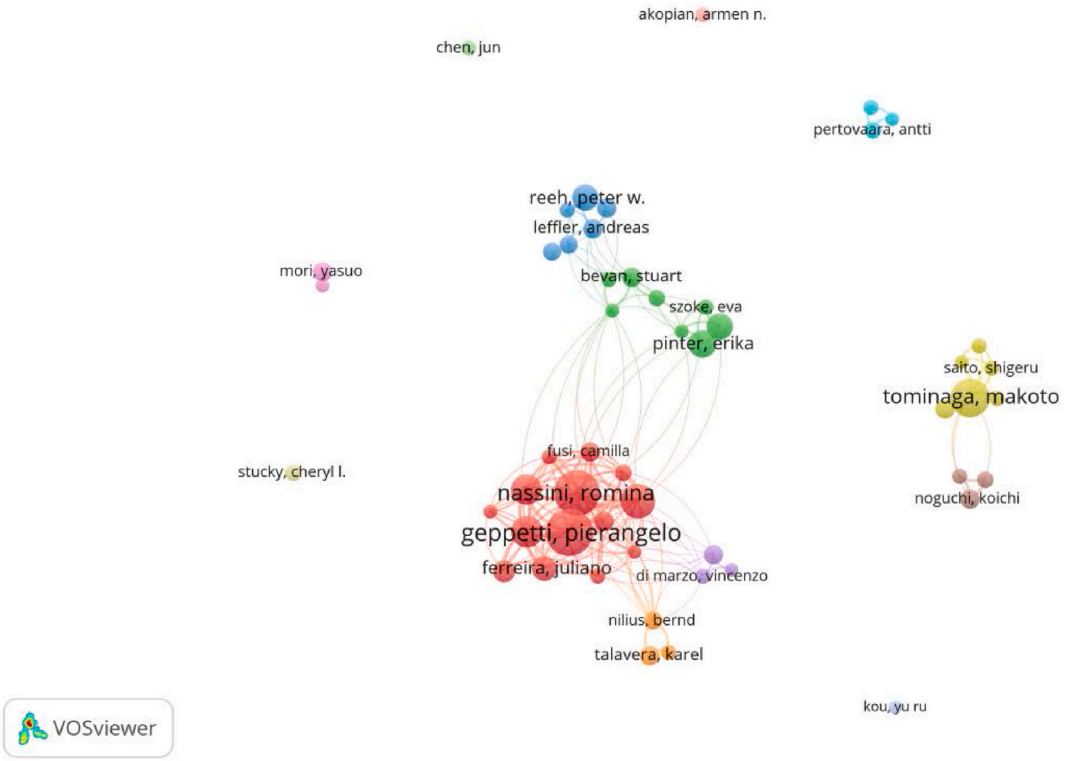

Fig. 5. Network visualization map of authors.

Table 6
Top 10 most cited publications in TRPA1 research.

Rank	Title	First author	Source	Publication year	TC
1	TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents	Bautista DM	Cell	2006	1366
2	Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin	Bandell M	Neuron	2004	1335
3	TRPA1 contributes to cold, mechanical, and chemical nociception but is not essential for hair-cell transduction	Kwan KY	Neuron	2006	938
4	TRPA1 mediates formalin-induced pain	McNamara CR	Proc Natl Acad Sci U S A	2007	908
5	Noxious compounds activate TRPA1 ion channels through covalent modification of cysteines	Macpherson LJ	Nature	2007	857
6	Pungent products from garlic activate the sensory ion channel TRPA1	Bautista DM	Proc Natl Acad Sci U S A	2005	613
7	Distinct expression of TRPM8, TRPA1, and TRPV1 mRNAs in rat primary afferent neurons with adelta/c-fibers and colocalization with trk receptors	Kobayashi K	J Comp Neurol	2005	563
8	4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1	Trevisani M	Proc Natl Acad Sci U S A	2007	555
9	TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells	Corey DP	Nature	2004	497
10	Nociceptor and hair cell transducer properties of TRPA1, a channel for pain and hearing	Nagata K	J Neurosci	2005	472

Abbreviations: TC, total citations.

monoterpene ketone umbellulone [30] and parthenolide [31] related to pain-causing and analgesia revealed that TRPA1 can be activated by a range of exogenous and endogenous drugs to further release the pro-migraine peptide, calcitonin gene-related peptide (CGRP) [32]. It has been shown that activation of TRPA1 in dural afferent nerves contributes to the induction of spontaneous behaviors associated with headache, as well as the emergence of evoked behaviors that may reflect central sensitization [33]. It was also proposed that the autocrine pathway maintained by TRPA1 and NADPH oxidase 1/2 is involved in the sensitization process of nociceptor and trigeminal neurons in nitroglycerin-induced meninges, providing a scientific explanation for the delayed headache symptoms observed in migraine patients [34].

Table 7
The top 20 keywords in TRPA1 research.

Rank	Keyword	TP	Rank	Keyword	TP
1	trpa1	650	11	transient receptor potential channel	136
2	activation	376	12	mechanism	130
3	pain	333	13	rat	119
4	ion channel	266	14	covalent modification	112
5	trpv1	222	15	neurogenic inflammation	107
6	sensory neuron	208	16	hyperalgesia	98
7	cold	187	17	oxidative stress	93
8	inflammation	166	18	calcium-channels	76
9	capsaicin receptor	165	19	neuropathic pain	76
10	neurons	140	20	nociception	70

Abbreviations: TP, total publications.

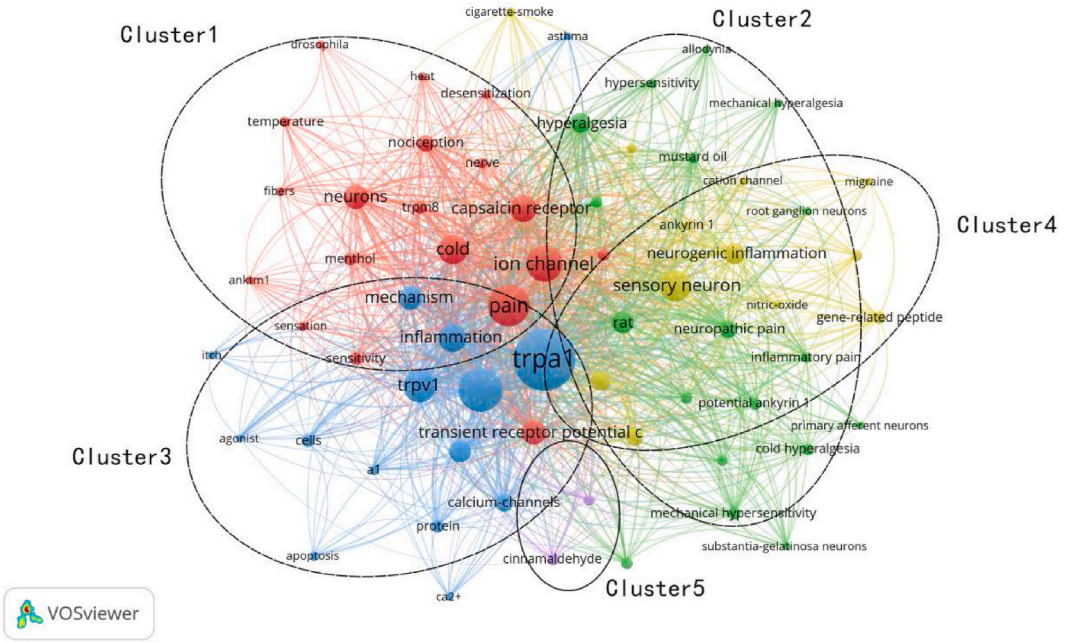

Fig. 6. Co-occurrence network visualization map of keywords.

4.2. Physiological function

The TRPA1 channel was first identified in lung fibroblasts in 1999 and was named "ankyrin-like protein with transmembrane domains protein 1" [35]. It was not until the further discovery of homology with other members of the TRP family that the name was further changed to TRPA1 [36]. TRPA1 acts as a nociceptive cationic channel involved in the sensory transduction of temperature stimuli [37]. In the nervous system, TRPA1 is expressed on injured sensory neurons [38], astrocytes [39], and oligodendrocytes [40]. Thus, TRPA1 is involved in mediating pain and neurogenic inflammation [41] and is activated by a variety of chemical and mechanical stimuli, such as mustard oils [42], allicin [43], eugenol [44], cannabinoids [45], and others.

TRPA1 is the only member of the TRPA subfamily of mammalian TRP channels [46]. However, differences in the structure of TRPA1 have been verified between species, with mammals expressing only one functional TRPA1, while four functional TRPA1s have been identified in drosophila [47]. This leads to some differences in the physiological functions of TRPA1 among different species. In rodents, for example, TRPA1 acts as a cold sensor [48,49] for temperature stimulation; however, the role is reversed in invertebrates, such as drosophila [50] and silkworm [51]. Menthol has a bimodal effect on mouse TRPA1 (mTRPA1), activating mTRPA1 at low concentrations and inhibiting mTRPA1 [52] at high concentrations, but showing activation only in the case of human TRPA1 [53].

TRPA1 expression is not only confined to neuronal cells but also exists in non-neuronal cells [54], which contributes to the complexity of the relationship between TRPA1 and chronic pain [55]. De Logu et al. [56] found that TRPA1 expression in Schwann cells generates a spatially restricted gradient of oxidative stress, maintains macrophage infiltration of injured nerves, and sends paracrine signals to activate TRPA1 in sheath nociceptors to maintain mechanical hyperalgesia. Further research found that repeated administration of a TRPA1 antagonist 1 h before ischemia and reperfusion (I/R) and three days after I/R protected against chronic post-ischemia pain from neuroinflammation and allodynia in mice [57]. Regarding the relationship between TRPA1 in neurons and

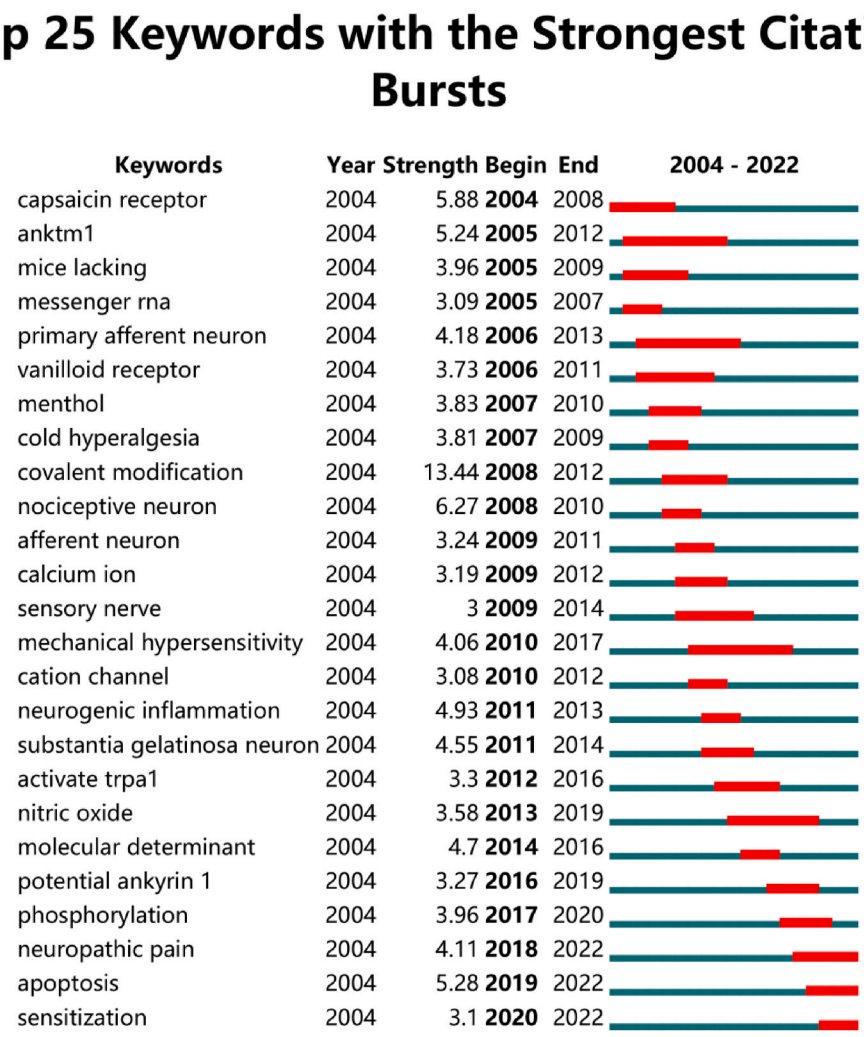

Fig. 7. Top 25 keywords with the strongest citation bursts.

non-neurons, De Logu et al. suggested that although TRPA1 is the final target of the pro-algesic signaling, feed-forward mechanisms of TRPA1 in non-neurons, such as Schwann cells, are required to maintain long-term spontaneous nociception [58]. In addition, TRPA1 in non-neuronal cells is involved in skin keratinocyte differentiation, insulin release, and gastrointestinal function regulation, among other physiological functions [59–66] (Table 8).

4.3. Therapeutic target

There is growing evidence for TRPA1 as an important regulator of inflammation [37]. For example, TRPA1 is recognized as a particularly important chemical sensor in the respiratory system, with a role in physiological reflexes such as coughing and in pathological states such as airway inflammation [67,68]. Environmental irritants emitted during industrial processes such as diesel exhaust particles, ozone, cigarette smoke (CS), and particulate matter were found to activate TRPA1 [69,70]. Acrolein and crotonaldehyde are common components of CS that directly activate TRPA1, stimulate vagal neurons, promote the release of CGRP and substance P in the airway, and induce plasma extravasation [71], thereby contributing to the development of airway inflammation [72]. Ozone is a secondary air pollutant, acting as a strong oxidant [73]. TRPA1 participates in airway inflammation induced by acute ozone exposure by affecting oxidative stress, mitochondrial quality control, and mitochondrial respiratory chain activity, which may be a potential target for clinical treatment of respiratory diseases [74]. TRPA1 is also involved in histamine non-dependent pruritus [75], airway hypersensitivity [76], and anti-apoptotic pathways [77], making TRPA1 an essential therapeutic target [78]. To date, many TRPA1 antagonists have been developed and entered preclinical trials. While TRPA1 inhibition can result in multisystemic side effects of primary concern [79], some studies have reported that local or systemic administration of TRPA1 antagonists did not result in hearing impairment or thermoregulation [80,81]. HC-030031, the first selective TRPA1 antagonist, eliminates formalin response *in vivo* with pain-related flinching by reversibly blocking TRPA1 currents [82]. Unfortunately, significant differences between human and

Table 8
TRPA1 expression on non-neuronal cells.

Tissue	Non-neuronal cells	Testing technology	Conclusion	References
skin	keratinocytes, fibroblasts, and melanocytes cells	[a], [b], [c]	TRPA1 is broadly expressed in the skin and may directly be involved in the regulation of keratinocyte differentiation as well as of inflammatory responses.	Atoyan 2009 [59]
airway	fibroblasts, epithelial and smooth muscle cells	[a], [d], [e],	Non-neuronal TRPA1 in the airways is functional and potentially capable of contributing to inflammatory airway diseases.	Nassini 2012 [60]
pancreatic	beta cells	[a], [b], [d], [e], [f], [g]	TRPA1-mediated depolarization acts synergistically with KATP channel blockade to facilitate insulin release.	Cao 2012 [61]
dental pulp	fibroblasts	[a], [b], [d], [e]	Human dental pulp fibroblasts express TRPA1 and TRPM8 at the molecular, protein, and functional levels, indicating a possible role for fibroblasts in mediating cold responses in human teeth.	El Karim 2011 [62]
gastrointestinal tract	enterochromaffin cells	[a], [d], [e]	TRPA1 acts as a sensor molecule for enterochromaffin cells and may regulate gastrointestinal function.	Nozawa 2009 [63]
sciatic nerve	Schwann cell	[a], [b], [c], [e]	Schwann cell TRPA1 generates a spatially constrained gradient of oxidative stress, which maintains macrophage infiltration to the injured nerve, and sends paracrine signals to activate TRPA1 of ensheathed nociceptors to sustain mechanical allodynia.	De Logu 2017 [64]
cerebral arteries	endothelial cell	[a], [c], [e]	Ca^{2+} influx via endothelial TRPA1 channels elicits vasodilation of cerebral arteries by a mechanism involving endothelial cell Ca^{2+}-activated K^+ channels and K_{IR} channels in arterial myocytes	Earley 2009 [65]
muscle	skeletal muscle cells	[a], [e]	mRNA of TRPA1, TRPM8 and TRPV1 are expressed in rat skeletal muscle and human skeletal muscle cells	Skagen 2023 [66]

[a] Real-time PCR.
[b] Western blot.
[c] Immunofluorescence.
[d] Immunohistochemistry.
[e] Calcium imaging.
[f] Electrophysiology.
[g] ELISA.

rodent TRPA1 homologs complicate the investigation of TRPA1-targeted drugs [83]. For example, caffeine 3 is an agonist of TRPA1 in mice, while it is an antagonist of the human channel [84].

4.4. TRPA1 and neuropathic pain

Neuropathic pain (NP) is not a disease entity, but a group of diseases with similar signs and symptoms [85]. NP is defined by the International Association for the Study of Pain as "pain caused by a lesion or disease of the somatosensory nervous system" [86]. There is growing evidence that TRPA1 plays an important role in different patterns of NP progression, such as traumatic NP [87], chemotherapeutic-induced NP [88], and diabetic NP [89]. MicroRNAs (miRs) are small non-coding endogenous RNA molecules that inhibit their target mRNAs by binding complementarily in the informative 3′-UTR [90]. Research has shown that NP was associated with the expression profile of miRNAs in DRG [91]. MiR-217 expression was significantly downregulated in the DRG of a sciatic nerve chronic constriction injury (CCI) rat model. Overexpression of miR-217, in turn, inhibited toll-like receptors, which attenuated CCI-induced NP [92]. miR-449a may improve NP by decreasing the activity of TRPA1 and the calcium-activated potassium channel subunit α-1 and by increasing the level of transmembrane phosphatase with tension homology [93]. Significant downregulation of miR-141-5p and upregulation of TRPA1 were similarly seen in the DRG of NP model rats, and intrathecal injection of miR-141-5p analogs alleviated the symptoms of NP and reduced the expression of TRPA1 [94]. Peripheral neuropathy (PN) has become a well-known side effect of chemotherapy [95]. Symptoms of PN have been reported to be present from the start of chemotherapy until a few days after therapy has been stopped [96,97]. NP can affect the physical, emotional, and cognitive functioning of cancer patients, thus affecting their quality of life [98]. Further research during patient follow-up after chemotherapy found that patients treated with docetaxel reported significantly less pain, tingling, and numbness than those treated with oxaliplatin [99]. Bortezomib (BTZ), mainly used as a treatment for multi-myeloma, is a reversible inhibitor of the proteasome compound [100]. BTZ amplifies TRPA1 expression by activating TNF-α signaling and subsequently utilizing intracellular p38-MAPK and JNK signaling, resulting in mechanical hyperalgesia and cold hypersensitivity [101]. Mitochondrial-mediated dysregulation of calcium homeostasis, neurotrophin dysregulation [102], and pro-inflammatory cytokines [103] may also be involved in this process. Further studies revealed that blocking proteinase-activated receptor 2 and TRPA1 signaling reduced the discomfort in BTZ rats [104]. In addition to BTZ, TRPA1 was also associated with NP caused by docetaxel [105], oxaliplatin [106], and paclitaxel [107]. In addition, in ethanol-induced NP patients, Schwann cells express alcohol dehydrogenase and convert ethanol to acetaldehyde, triggering NADPH oxidase-1-dependent to generate hydrogen peroxide and 4-hydroxynonenal, which act through paracrine targeting of TRPA1 to maintain abnormal pain [108].

4.5. TRPA1 agonists

Based on the activation mechanism, TRPA1 agonists can be divided into two primary categories: electrophilic and non-electrophilic [109]. Electrophilic agonists can form covalent bonds with nucleophilic groups. Allyl isothiocyanate [110], 15-deoxy-delta(12, 14)-prostaglandin J(2) [77], and other electrophilic agonists activate TRPA1 by covalently modifying cysteine residues [111]. Three of these cysteine residues, C621, C641, and C665, are critical for the activation of electrophilic stimuli [112], which are all located in the region containing the ankyrin repeats, linker, and pre-S1-helix [11]. It has been found that C621 is located in the first helix-turn-helix, C641 is in the first strand of the putative β-sheet, and C665 is in the flexible loop connecting the β-strands to the second helix-turn-helix, further clarifying the spatial distribution of cysteine residues [16]. The electrophilic agonist first attaches to C621, causing re-orientation of the cytoplasmic loop to enhance nucleophilicity, and C665 is subsequently modified to stabilize the loop in an activated conformation [113]. Cryo-electron microscope (cryo-EM) has provided a high-resolution structure of agonist binding to TRPA1 [114]. For example, Suo et al. [15] determined the ligand-free form of TRPA1 and the cryo-EM structure of binding to covalent agonists (JT010 and BITC), which enriched the mechanistic elucidation of the electrophile-dependent conformational changes in TRPA1. Non-electrophilic agonists, such as menthol [115], eudesmol [116], and protons [117], have target regions that are located in the S5/S6 structural domain [110] and interact with the hydrophobic pocket in the receptor [118]. The menthol-induced increase in permeability was shown to be constant, the clotrimazole-induced increase in permeability recovered gradually, and the carvacrol-induced increase was much higher than that of menthol and clotrimazole. The differences in these responses may arise from changes in binding mode [119].

The current review has the following limitations: 1) The WoSCC database was the only database used in this study; therefore, studies in some other databases may have been overlooked. 2) Due to the literature publication cycle, only publications before December 13, 2022, were included in this study. 3) The names of certain authors are not consistently displayed in publications, which might add biases in author ranking.

5. Conclusion

From 2002 to 2022, TRPA1 has been extensively studied, particularly by Pierangelo Geppetti, Professor of Clinical Pharmacology at the University of Florence, who has had a long history of work related to TRPA1 and migraine pathophysiology. This study reveals the strong multidisciplinary relationship between TRPA1 and respiratory and neurological disorders. Our analysis also found that the application of technical tools, such as chemical optogenetics and sequence analysis, has contributed to the elucidation of the spatial structure and mechanism of action of TRPA1. This bibliometric analysis establishes trends and new frontiers in TRPA1 research, providing researcher with an important reference to understand the current status and future direction of their research.

Declarations

Ethics Approval and Consent to participate: Not applicable.
Consent for publication: Not applicable.
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CRediT authorship contribution statement

Ning Gao: Writing – review & editing, Writing – original draft. **Meng Li:** Writing – review & editing, Writing – original draft. **Weiming Wang:** Validation, Supervision, Software, Methodology. **Zhen Liu:** Project administration, Investigation, Data curation, Conceptualization. **Yufeng Guo:** Project administration, Methodology, Funding acquisition, Conceptualization.

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.

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