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Review article

Research trends and frontier hotspots of TRPV1 based on bibliometric and visualization analyses

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ABSTRACT

Background: Transient receptor potential vanilloid type1 (TRPV1) is a non-selective cation channel with multiple activation mechanisms, which has received increasing attention since it was first cloned in 1997.
Methods: We used bibliometric and visualization analyses to evaluate the theme trends and knowledge structure of TRPV1 research-papers on TRPV1 from 2002 to 2022 obtained from the Web of Science Core Collection. VOSviewer and CiteSpace were used to analyze authors, institutions, countries, co-cited references, and keywords.
Results: A total of 7413 papers were included. The main research area of TRPV1 was neuroscience; the most published country was the United States, and the University of California, San Francisco, had the highest centrality. Two major collaborative sub-networks were formed between the authors. The distribution of keywords shows that TRPV1 was initially studied extensively, and the recent studies focused on TRPV1 structure and diseases. "Oxidative stress," "TRPV1 structure," "cancer," and "model" have been the research hotspots in recent years.
Conclusions: This research provides valuable information for the study of TRPV1. Disease research was focused on pain, cancer, and neurodegenerative diseases. Both agonists and antagonists of TRPV1 are gradually being used in clinical practice, and acupuncture was effective in treating TRPV1-mediated inflammatory pain. TRPV1 is involved in classical endogenous cannabis system signaling, and new signaling pathways continue to be revealed.

1. Introduction

Capsaicin is the main irritating ingredient in chili peppers and can cause a burning sensation. The gene encoding the capsaicin receptor was first cloned in 1997, and researchers found that the capsaicin receptor is an integral membrane protein that can be

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activated over a range of noxious temperatures, thus confirming that it is a sensor of painful thermal stimuli in vivo [1]. With the capsaicin receptor, David Julius discovered various transient receptor potential (TRP) channel proteins related to somatosensation. In 2021, he was awarded the Nobel Prize in Physiology or Medicine for his outstanding contribution to the "discovery of receptors for temperature perception."

Capsaicin receptors were the first members of the vanilloid subfamily of transient receptor potential channels to be identified, also known as TRPV1 and vanilloid receptor 1 [2]. TRPV1 is a non-selective cation channel with multiple activation mechanisms that can be activated by physicochemical stimuli, such as high temperature (>43 °C) [1], acidic conditions (pH < 5.9) [3], osmotic pressure [4], and mechanical forces [5]; exogenous ligands such as capsaicin [6], vanilloid [7], and resin toxin [8]; endogenous ligands such as N-arachidonoyl ethanolamine, lipoxygenase compounds, 2-arachidonic glycerol [9], and endogenous cannabinoids [10,11]; and other mechanisms. The structure of TRPV1 is a homotetramer, and each subunit contains six transmembrane fragments, a pore-forming loop between the fifth and sixth transmembrane structural domains, and the N and C termini on the intracellular side of the plasma membrane [12,13]. TRPV1 mainly distributes in small and medium diameter C fibers and some Aδ fibers in the dorsal root ganglion, trigeminal ganglion, and vagal ganglion [1,14] and in the central projections of sensory neurons in the dorsal horn of the spinal cord [3], the caudal nucleus of the trigeminal nerve, and the solitary bundle nucleus [15]. Recent studies have shown that TRPV1 is similarly expressed in the central nervous system [16–18]. In addition, TRPV1 expresses in non-neuronal cells such as epidermal keratinocytes [19], urinary tract epithelial cells [20], small arterial smooth muscle cells [21], gastric epithelial cells [22], pancreatic islet B cells [23], and respiratory tract epithelial cells [24].

Due to the function, structure, and distribution of TRPV1, several studies have shown that TRPV1 is associated with various diseases, such as pain [25], bladder disease [26], cough [27], diabetes [28], epilepsy [29], and obesity [30]. TRPV1 is also involved in the information transduction of various signaling pathways, such as the endogenous cannabis system. As a receptor for multiple injurious

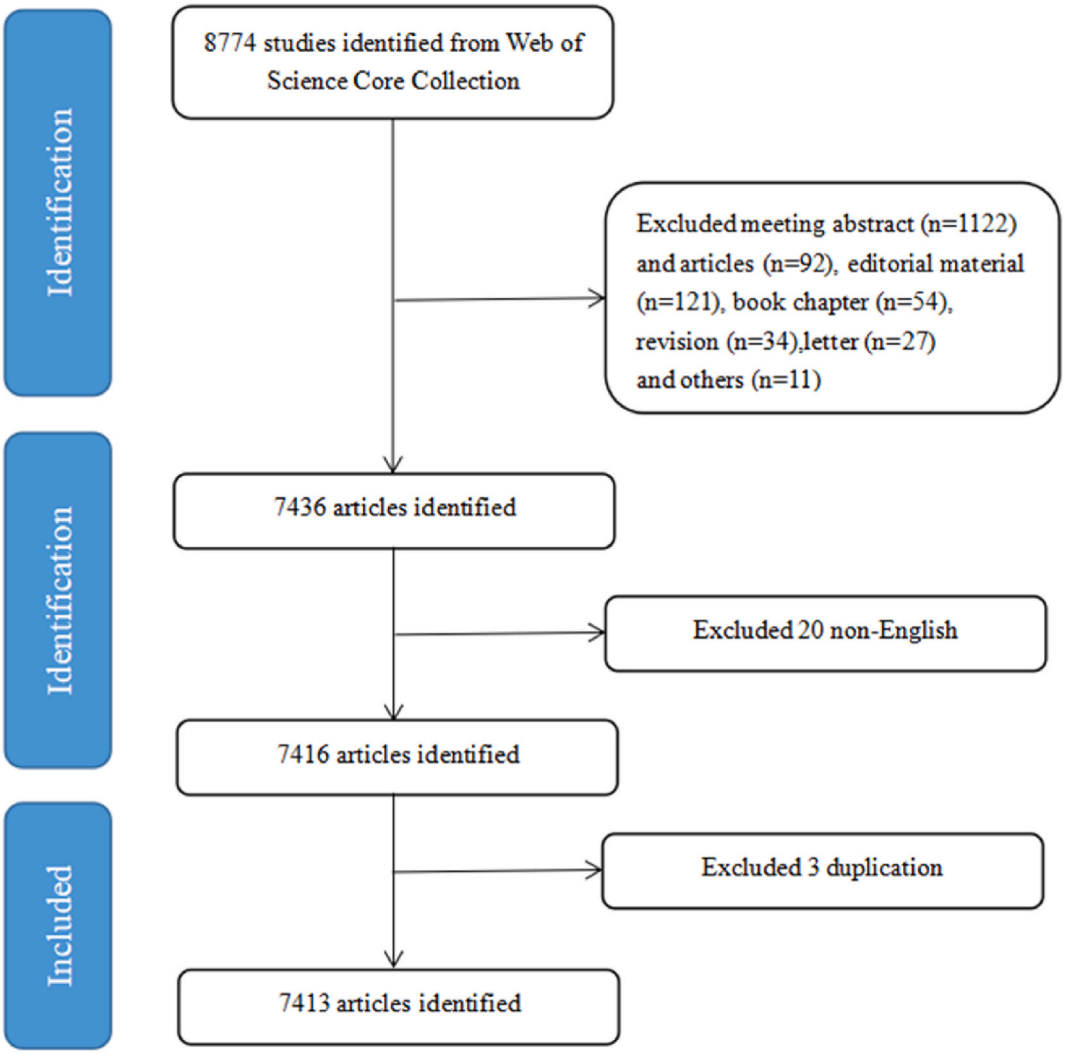

Fig. 1. Study flow diagram.

stimuli, TRPV1 has emerged as a new and promising target for developing analgesic and anti-inflammatory drugs. However, the thematic trends and knowledge structure of TRPV1 have yet to be studied by bibliometrics. This study uses a bibliometric analysis to provide a comparatively comprehensive review of TRPV1 research from 2002 to 2022 to understand the co-citation of the literature, establish research collaboration networks, and assess research trends and frontiers.

2. Materials and methods

2.1. Data and retrieval strategies

The literature search was completed online through the Web of Science Core Collection Science Citation Index-Expanded on September 01, 2022. The data search strategy was as follows: Subject: TRPV1; period: 2002-01-01 to 2022-08-31; article type: full text; and language: English. After eliminating duplicates, 7413 documents were finally included in the bibliometric analysis. The search flowchart is shown in Fig. 1. Fig. 1 shows the search flowchart. CiteSpace V.6.1.R2 (64-bit) Advanced and VOSviewer 1.6.18 import the data. Furthermore, the generated data were imported into Excel 2019.

2.2. Statistical methods

CiteSpace is a Java-based application that downloads for free. It was developed by Professor Chaomei Chen in 2004. It aims to analyze and visualize the trends and patterns of scientific literature, present the structure, patterns, and distribution of scientific knowledge, and show new trends and developments in scientific progress.

VOSviewer is also a Java-based and freely downloadable application developed by Nees Jan van Eck and Ludo Waltman of Erasmus University Rotterdam. It is used to analyze cooperative networks, co-citation networks, coupling networks, and thematic co-occurrence networks of scientific and technical literature, and it can generate three visualization maps depicting the network, superposition, and density to visualize measurements of the scientific and technical literature [31].

2.3. Parameter settings for CiteSpace

The period chosen was from January 2002 to August 2022, and the time section was chosen to be one year. The node types were selected as institution, keyword, and cited literature. The network was pruned to improve readability when the network was dense. The network pruning options were pathfinder, pruning sliced networks, and pruning the merged network. After the parameters were set, institutional co-occurrence mapping, keyword timeline mapping (clustering using the log-likelihood ratio method), keyword emergence mapping, Sankey mapping, and literature co-citation mapping were carried out to visualize and analyze the research content and hotspots.

The graph generated by CiteSpace was mainly composed of nodes and lines, with the size of nodes representing the frequency of

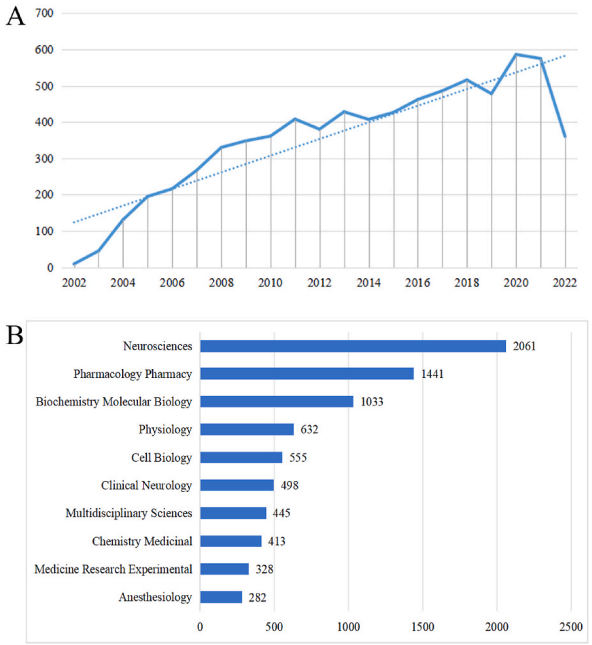

Fig. 2. (A) Number of publications in TRPV1 research from 2002 to 2022. (B) Top 10 areas in TRPV1 research.

occurrence and the thickness of lines representing the co-occurrence intensity. The color of the nodes and lines represented the year, and the color faded from cool to warm, indicating that the literature was published further in the past to more recently. Centrality is a measure of the importance of nodes in the network. If a purple circle surrounded a node, it indicated that the node had greater mediated centrality ($\geq$0.1), indicating a critical point or turning point. If there was a red chronology in the node chronology, the co-cited frequency was or is still increasing rapidly, indicating that this is a hotspot for research. In the cluster analysis, the fewer the labels, the more the included keywords. N in the upper left parameters indicates the number of network nodes, E indicates the number of connected lines, and density indicates the network's density. The modularity Q and weighted mean silhouette S were critical indicators to evaluate the significance and reasonableness of the clustering effect. The value range of Q was [0, 1]. The larger the value of Q, the better the effect of network clustering. $Q > 0.3$ implied that the structure of the clustering association was significant. The value of S was used to measure the homogeneity of the network; the closer the value of S was to 1, the higher the homogeneity of the network; $S > 0.5$ indicated that the clustering result was reasonable, and $S > 0.7$ indicated that the clustering results had high confidence.

In the visualization results generated by VOSviewer, one node represented one country/institution/author, the node size represented the number of articles issued by the country/institution/author, and nodes with the same color belonged to the same cluster. The connected lines in the network represented the cooperation of countries/institutions/authors, and the lines' thickness indicated the cooperation's strength.

3. Results

3.1. Trends of publications

A total of 7413 papers were included from literature published from 2002 to 2022, with an overall increasing trend in the number of publications, with an average annual growth of 29.7 publications/year. The growth rate began to slow down after 2014, as shown in Fig. 2A.

3.2. Research area analysis

A total of 119 research areas were represented, with neuroscience (2061 articles), pharmacology (1441 articles), and biochemistry and molecular biology (1033 articles) accounting for the top three. The total number of publications was 61 % of all research areas. Fig. 2B shows the top 10 research areas for TRPV1 from 2002 to 2022: neurosciences, pharmacology and pharmacy, biochemistry, molecular biology, physiology, cell biology, clinical neurology, multidisciplinary sciences, chemistry medicinal, medicine research experimental, and anesthesiology.

3.3. Distribution of journals and cited articles

A total of 1337 academic journals have published articles on TRPV1; the top 10 journals in terms of the number of articles published are listed in Table 1. The top 10 journals published 1416 TRPV1-related articles, accounting for 19 % of the total, with impact factors ranging from 3.197 to 9.473. *Journal of Neuroscience* published the most articles (172 articles, 2.319 %), followed by *Pain* (163 articles, 2.19 %) and *PLOS One* (161 articles, 2.17 %). Fig. 3 shows the dual-map overlay of journals. The journals on the left cited articles from the journals on the right. The curves are citation-linked, showing the complete ins and outs of citations. In the left panel, the more papers a journal published, the longer the vertical axis of the ellipse; the greater the number of authors, the longer the horizontal axis of the ellipse; and the labels represent the disciplines covered by the journal. The yellow path indicates that molecular biology and immunology journals mainly cite journals in molecular biology, genetics, health, nursing, and medicine. In contrast, the green path indicates journals in medicine and clinical areas, mainly citing journals in molecular biology and immunology. Molecular biological, immunological, and clinical medical fields cite each other.

Table 1
Top 10 journals in TRPV1 research.

Rank	Journal	Count	Country	Percent	IF 2021
1	*Journal of Neuroscience*	172	USA	0.02319	6.709
2	*Pain*	163	USA	0.02198	7.926
3	*PLOS One*	161	USA	0.02171	3.752
4	*British Journal of Pharmacology*	154	England	0.02077	9.473
5	*Molecular Pain*	145	England	0.01955	3.37
6	*International Journal of Molecular Sciences*	141	Switzerland	0.01901	6.208
7	*European Journal of Pharmacology*	127	the Netherlands	0.01713	5.195
8	*Neuroscience*	126	England	0.01699	3.708
9	*Scientific Reports*	125	England	0.01686	4.996
10	*Neuroscience Letters*	102	the Netherlands	0.01375	3.197

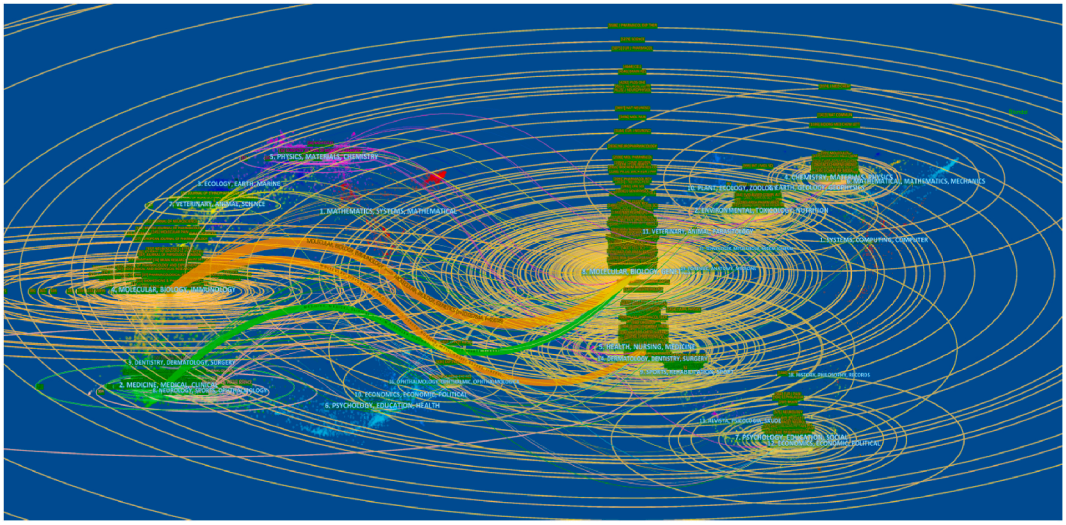

Fig. 3. Dual-map overlay of journals.

3.4. Distribution of countries and institutes

A total of 90 countries or regions have published papers on TRPV1. Fig. 4A shows the geographical visualization mapping of the posting countries. Each node represents a country, the node size represents the country's posting volume, the connecting lines in the network represent the countries' cooperation relationship, and the line thickness indicates the cooperation strength. The graph shows that TRPV1 research is mainly concentrated in North America, Asia, and Europe, with the most significant number of publications in the United States, in close cooperation with China, Japan, Germany, the United Kingdom, and Italy, the countries with more publications. Fig. 4B shows the top 10 countries regarding the number of publications, which account for 75.7 % of the total number of

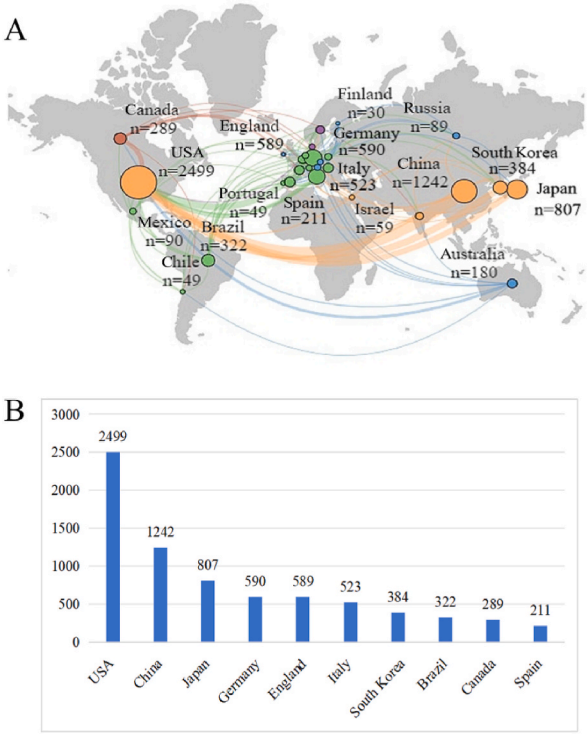

Fig. 4. (A) Geographical visualization of the countries with the highest number of publications. (B) Top 10 countries with TRPV1 research publications.

publications, showing a concentration of countries publishing TRPV1 research papers.

Four thousand institutions participated in TRPV1 research, and 47 institutions had a centrality ≥0.1, indicating that multiple institutions were publishing pivotal or transformative research. The highest centrality (centrality = 0.43) was found at the University of California, San Francisco. Seoul National University had the highest number of publications, followed by Consiglio Nazionale Delle Ricerche, the University of Pittsburgh, the University of São Paulo, and King's College London. The cooperation between the major institutions with the most publications was weak. In contrast, cooperation between institutions within countries was stronger (Fig. 5A). Fig. 5B shows the cluster analysis of institutions, and Table 2 summarizes each cluster's main research content and representative institutions.

3.5. Distribution of authors and references

Twenty-five thousand one hundred-one authors contributed to TRPV1 research. Fig. 6A lists the authors with >50 publications. Vincenzo Di Marzo (135 articles) ranked first, followed by Makoto Tominaga (86 articles) and Jeewoo Lee (84 articles). Using CiteSpace to analyze the author collaboration information, 878 nodes, and 1438 connections were obtained, with a density of 0.0037. Two major collaborative sub-networks were formed, as shown in Fig. 6B, with Di Marzo V as the core of the Consiglio Nazionale Delle Ricerche research team and Seoul National University's Lee Jeewoo and Blumberg, Peter M. at the National Cancer Institute as the core of the Korean-US research team.

The literature co-citations were analyzed using CiteSpace, and the top 10 high-frequency cited and co-cited literature reports are listed in Table 3.

The co-citation clustering profile contained.

- 1903 nodes and 10,515 connected lines with modularity Q = 0.6996 (>0.5),
- implying that the clusters were reasonable, while the weighted mean silhouette S was 0.8715 (>0.5),
- indicating that the homogeneity of the clusters was acceptable.

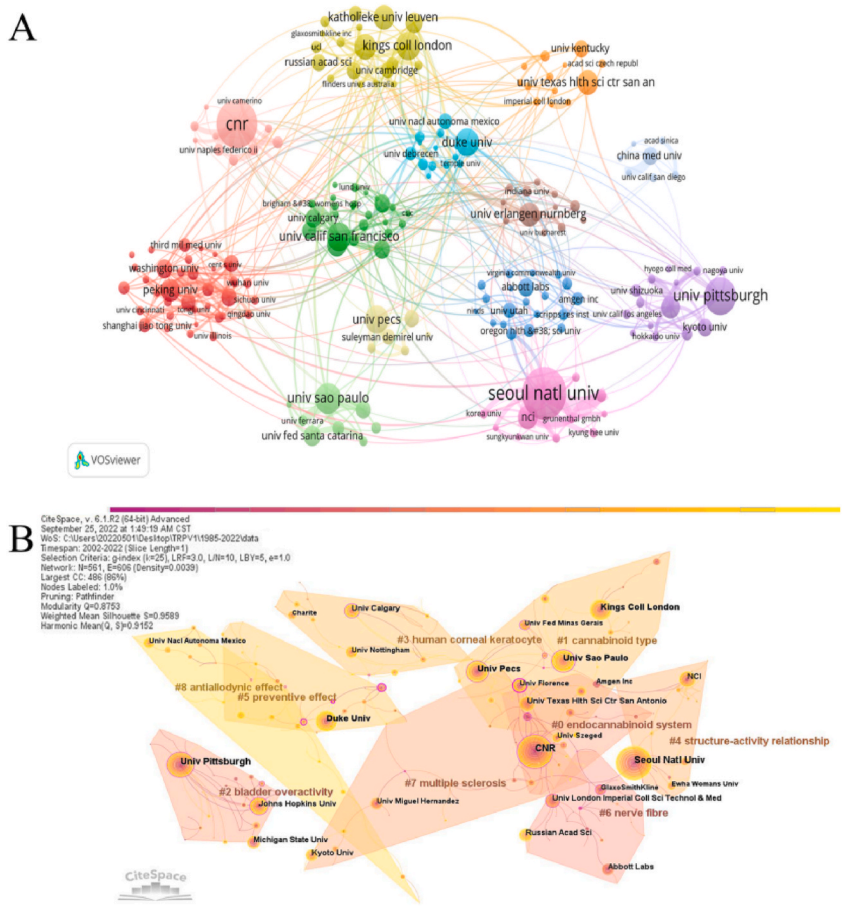

Fig. 5. (A) Cooperation between institutions. (B) Cluster map for institutions conducting TRPV1 research.

Table 2
Analysis of institutions in keyword clusters.

Clusters	Labels	Major Research Institutions	Silhouette
#0	endocannabinoid system	Consiglio Nazionale delle Ricerche, The University of Texas Health Science Center at San Antonio	0.831
#1	cannabinoid type	University of São Paulo, King's College London, University of Florence, University of Pécs	0.751
#2	bladder overactivity	University of Pittsburgh, Johns Hopkins University, Michigan State University	0.839
#3	human corneal keratocyte	University of Calgary, University of Nottingham, Charité-Universitätsmedizin Berlin	0.807
#4	structure-activity relationship	Seoul National University, National Cancer Institute, Ewha Womans University	0.873
#5	preventive effect	Duke University	0.821
#6	nerve fiber	Imperial College of Science Technology and Medicine, Russian Academy of Sciences, GlaxoSmithKline, Abbott Laboratories	0.846
#7	multiple sclerosis	Miguel Hernández University of Elche, Kyoto University	0.86
#8	antiallodynic effect	National Autonomous University of Mexico	0.837

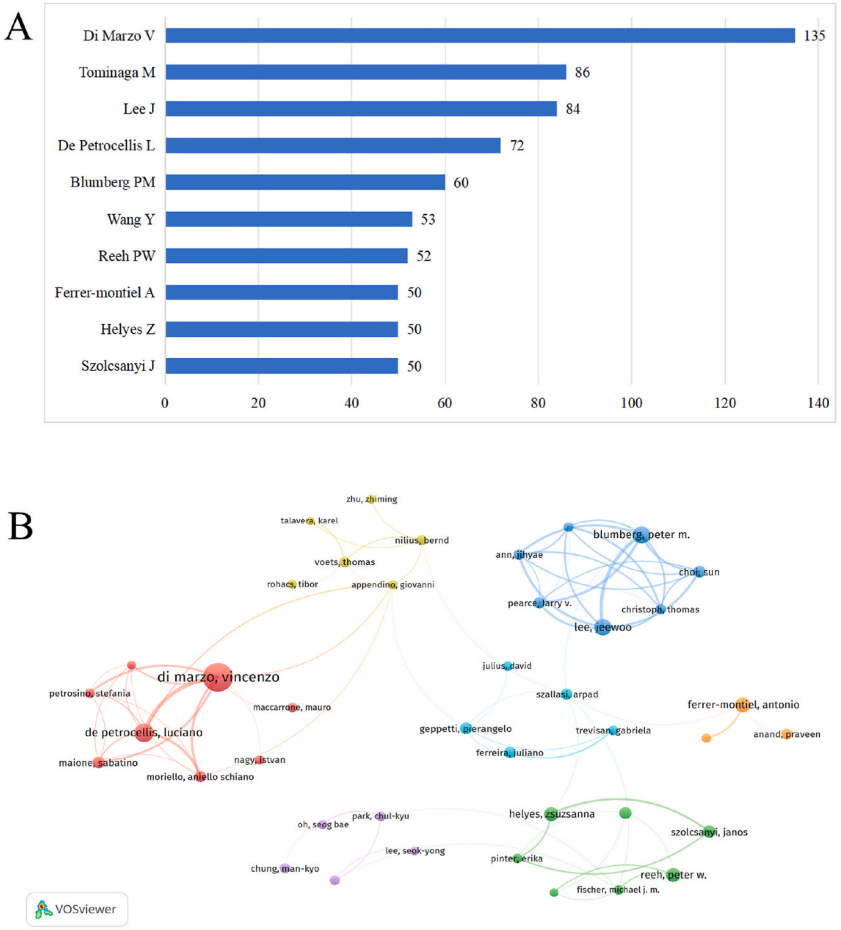

Fig. 6. (A) Authors with >50 publications in TRPV1 research. (B) Author collaborations in TRPV1 research.

The top 10 clustering tags were #0 vanilloid receptor, #1 vanilloid receptor TRPV1, #2 intracellular messenger, #3 transient receptor, #4 ion channel, #5 a-kinase anchoring protein, #6 airway disease, #7 structure-activity relationship, #8 visceral hypersensitivity, and #9 endocannabinoid system (Fig. 7).

3.6. Distribution of keywords

3.6.1. Burst map, Sankey diagram, and time zone map

The keyword burst map refers to the apparent increase in the frequency of a keyword within a short period, which can show the research with increase attention during a period. Twenty-five words were detected by the burst method (Fig. 8). It can be seen from the

Table 3
Top 10 most cited and co-cited articles in TRPV1 research.

Rank	Cited References	Highlights	Co-cited References	Highlights
1	Story GM et al., 2003, DOI 10.1016/s0092-8674(0300158-2)	1. ANKTM1 is a cold-activated channel and a distant family member of TRP channels. 2. ANKTM1 is present in a subset of nociceptive sensory neurons and is co-expressed with TRPV1 but not with TRPM8. 3. Noxious cold-sensitive sensory neurons respond to capsaicin but not to menthol.	Szallasi A et al., 2007, DOI 10.1038/nrd2280	1. TRPV1 antagonists relieved chronic intractable pain secondary to migraine, cancer, AIDS, or diabetes. 2. TRPV1 antagonists also treated conditions other than pain, such as urinary incontinence, chronic cough, and irritable bowel syndrome.
2	Bandell M et al., 2004, DOI 10.1016/s0896-6273(0400150-3)	1. TRPA1, a distant family member of TRPV1, is a cold-sensitive channel protein. 2. Irritating natural compounds in cinnamon oil, wintergreen oil, clove oil, mustard oil, ginger and bradykinin activated TRPA1. 3. Phospholipase C is an important signaling component of TRPA1 activation. 4. Cinnamaldehyde is the most specific TRPA1 activator.	Bautista DM et al., 2006,DOI 10.1016/j.cell.2006.02.023	1. TRPA1 is selectively expressed by a group of unmyelinated peptidergic injury receptors expressing TRPV1. 2. TRPA1 is the sole target through which mustard oil and garlic activate primary afferent nociceptors to produce inflammatory pain. 3. TRPA1 was found not to be required for the initial detection of noxious cold or sound.
3	Liao MF et al., 2013, DOI 10.1038/nature12822	1. Electron cryo-microscopy was used to determine the structure of TRPV1. 2. TRPV1 exhibited quadruple symmetry around a central ion channel formed by transmembrane helices S5–S6 and an intermediate pore loop flanked by the S1–S4 voltage sensor-like structural domains. 3. TRPV1 has a wide extracellular "mouth" with a short selective filter. 4. The conserved TRP domain interacted with the S4–S5 linker.	Liao MF et al., 2013, DOI 10.1038/nature12822	Same as cited references NO.3.
4	Ji RR et al., 2002, DOI 10.1016/s0896-6273(0200908-x)	1. Activation of p38 in the dorsal root ganglion is a secondary product of peripheral nerve growth factor production during inflammation and was required to induce elevated TRPV1. 2. Activation of p38 increased TRPV1 levels in the peripheral terminals of nociceptive receptors in a transcription-independent manner.	Cao EH et al., 2013, DOI 10.1038/nature12823	1. Pharmacological probes were used to determine the structure of the two activation states of the capsaicin receptor TRPV1. 2. The opening of TRPV1 was associated with significant structural rearrangements in the outer pore. 3. The allosteric coupling between the upper and lower gates may be responsible for the rich physiological modulation mechanisms exhibited by TRPV1 and other TRP channels.
5	Voets T et al., 2004, DOI 10.1038/nature02732	Kinetic analysis of gating at different temperatures showed that the temperature sensitivity of the cold-sensitive channel TRPM8 and the heat-sensitive channel TRPV1 was due to a 10-fold difference in the voltage-dependent activation energy for turning on and off.	Caterina MJ et al., 2000,DOI 10.1126/science.288.5464.306	1. Sensory neurons in TRPV1 knockout mice were severely under-responsive to vanilloid compounds, protons, or heat (>43 °C). 2. TRPV1 was found to be essential for nociception in particular modalities and tissue injury-induced thermal hyperalgesia.
6	Watanabe H et al., 2003, DOI 10.1038/nature01807	1. TRPV4 is a widely expressed cation channel of the TRP family and is a close family member of TRPV1. 2. Endogenous cannabinoids and its metabolite arachidonic acid indirectly activated TRPV4 and were involved in cytochrome P450 epoxygenase-dependent formation of epoxyeicosatrienoic acids.	Julius D, 2013, DOI 10.1146/annurev-cellbio-101011-155833	1. TRP channel functions and expression analyses confirmed the presence of nociceptors. 2. Studies on TRP channels also provide insight into the coding logic of nociceptors and how the specification of nociceptor subtypes underlies behavioral discrimination of noxious thermal, chemical, and mechanical stimuli. 3. TRP channel biophysical and pharmacological properties provide the intellectual and technical basis for developing novel analgesics.
7	Güler AD et al., 2002, DOI 10.1523/JNEUROSCI.22-15-06408.2002	1. Experiments have confirmed that another member of the TRP family, TRPV4, was also activated by heat. 2. TRPV4 may be a transducer of warm stimuli within the hypothalamus.	Gao Y et al., 2016, DOI 10.1038/nature17964	The structure of TRPV1 ion channels in a native bilayer environment was determined by a combination of electron cryo-microscopy with lipid nanodisk technology.
8	Cao EH et al., 2013, DOI 10.1038/nature12823	Same as co-cited references NO.4.	Kwan KY et al., 2006, DOI 10.1016/j.neuron.2006.03.042	1. TRPA1 is expressed in small-diameter neurons of the trigeminal and dorsal root ganglia and is co-expressed with TRPV1. 2. TRPA1 was not required for hair cell transduction but was involved in the transduction of mechanical, cold, and chemical stimuli in nociceptor sensory neurons.
9	Julius D, 2013, DOI 10.1146/annurev-cellbio-101011-155833	Same as co-cited references NO.6.	Huang SM et al., 2002, DOI 10.1073/pnas.122196999	N-arachidonic-dopamine is an endogenous capsaicin-like substance in mammalian nervous

(*continued on next page*)

Table 3 (*continued*)

Rank	Cited References	Highlights	Co-cited References	Highlights
10	Szallasi A et al., 2007, DOI 10.1038/nrd2280	Same as co-cited references NO.1.	Jordt SE et al., 2004, DOI 10.1038/nature02282	tissues, similar in chemical structure to capsaicin and with potency at TRPV1 receptors. Mustard oil and Δ9-tetrahydrocannabinol (THC) excited sensory nerve fibers via ANKTM1 (TRPA1), a TRP channel family member co-expressed with TRPV1.

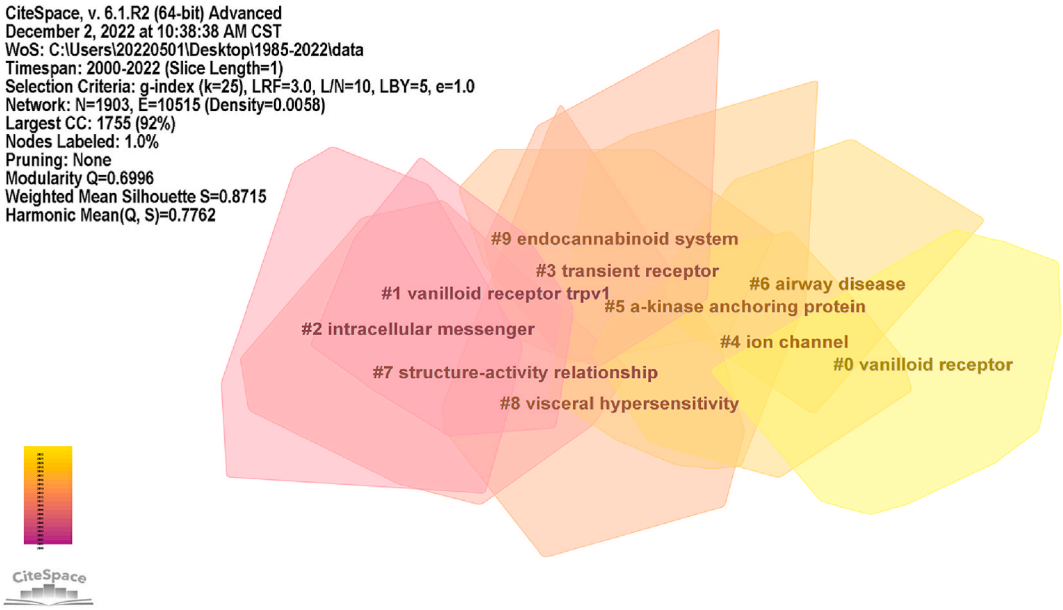

Fig. 7. Cluster analysis of co-cited references in TRPV1 research.

figure that TRPV1 was initially studied extensively, mainly focusing on the activation mechanism of TRPV1, antagonists, neural and non-neural distribution, and signaling pathways. Subsequently, the experimental animals "adult rats" and "mice lacking" became the new focus of attention. “Oxidative stress,” “TRPV1 structure,” “cancer,” and “model” have been the research hotspots in recent years.

Sankey diagrams are a specific type of flowchart consisting of edges, flows, and nodes, where nodes represent different classifications to delineate different stages or partitions of energy flow, and edges connect nodes of different stages or partitions, representing the flow of energy or data, which can visualize the trend of data flow. The Sankey diagram (Fig. 9) shows the evolutionary trend of the TRPV1 keywords from 2002 to 2022. The leftmost nodes indicates the initial research direction, divided into three color categories. The green node contains "cell", the blue node contains "capsaicin_receptor," "homolog" and "identification". The red node contains “activation,” “anandamide,” “hyperalgesia,” “mutation” and “pain”. The rightmost node indicates the current research direction. After 20 years of evolutionary development, TRPV1 is now widely studied in various diseases, such as “long-term depression,” “stress,” “diet-induced obesity,” “insulin resistance,” and “erosive esophagitis.” Meanwhile, scholars have focused on studying other TRPV1 family members, such as TRPA1. Researchers have further studied the distribution and signaling of TRPV1 ，such as “skin,” “spinal cord” and “intracellular calcium,” “gene expression,” “afferent neuron”.

The time zone diagram is a collection of nodes in the same time zone, and the same time refers to the time when the keywords first appeared. The time series is arranged from far to near, showing the research trends and characteristics of the field (Fig. 10). In 2002 and before, “capsaicin receptor,” “sensory neuron,” “pain” and “nerve growth factor” were first and most studied. “Protein kinase c,” “substance P,” “inflammation,” “neuropathic pain” and “cannabinoid receptor” began to be studied consistently between 2003 and 2004. “Irritable bowel syndrome,” “oxidative stress” and “hypersensitivity” have been the focus of research since 2007 and 2008. Subsequently, “atopic dermatiti,” “long-term depression” and “molecular mechanism” also began to receive scholars’ attention.

As shown in the figure, the research field of TRPV1 is vast. For example, regarding TRPV1 distribution, the research evolved from the peripheral nervous system to the central nervous system. In diseases, the research gradually evolved from painful inflammation to various systemic diseases of the human body and neuropsychiatric diseases.

3.6.2. Analysis of clusters

Considering the different types of included literature, we re-screened the 7413 articles into three sections: "disease," "signaling pathways," and "intervention methods." There were 3037 articles on "disease," with keyword co-occurrence mapping yielding 694

Keywords	Year	Strength	Begin	End	2002 - 2022
capsaicin receptor	2002	40.78	2002	2007	
vanilloid receptor 1	2002	26.15	2002	2008	
capsazepine	2002	19.44	2002	2007	
root ganglion neuron	2002	19.42	2002	2006	
messenger rna	2002	17.34	2002	2007	
noxious heat	2002	15.46	2002	2008	
vanilloid receptor	2002	83.26	2003	2009	
vr1	2002	44.88	2003	2008	
protein kinase c	2002	24.01	2003	2009	
heat	2002	16.82	2003	2008	
direct phosphorylation	2002	14.44	2003	2009	
pain pathway	2002	12.65	2003	2009	
primary sensory neuron	2002	12.45	2003	2007	
urinary bladder	2002	12.36	2003	2009	
immunoreactivity	2002	12.28	2003	2010	
rat	2002	12.06	2003	2006	
iodo resiniferatoxin	2002	12.04	2003	2007	
adult rat	2002	12.12	2004	2010	
mice lacking	2002	17.17	2005	2009	
vanilloid receptor trpv1	2002	13.12	2010	2012	
oxidative stress	2002	17.58	2016	2022	
trpv1 structure	2002	16.97	2017	2022	
trpv1 channel	2002	13.4	2017	2022	
cancer	2002	12.15	2018	2022	
model	2002	16.02	2020	2022	

Fig. 8. Keywords with the most powerful citation bursts for publications in TRPV1 research.

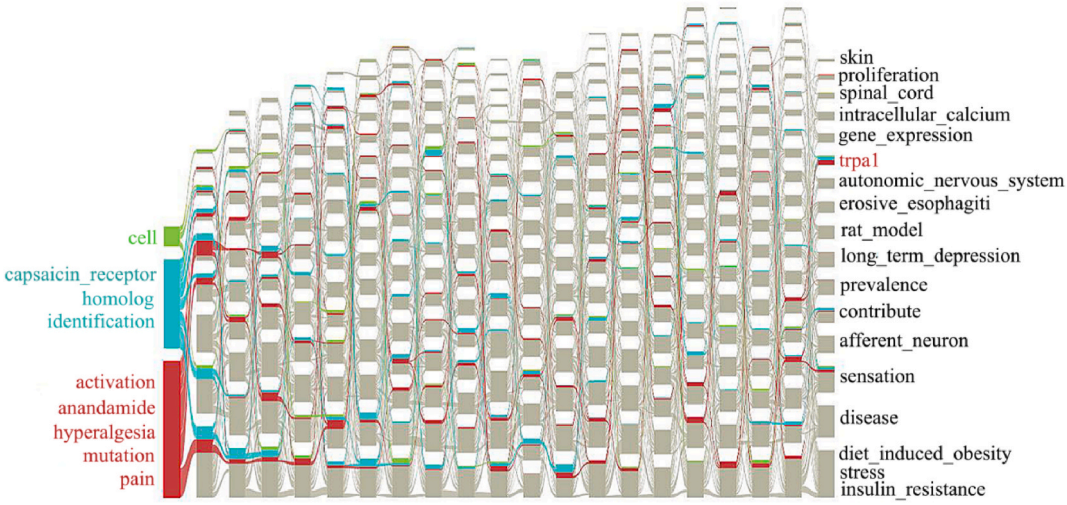

Fig. 9. Sankey diagram.

nodes and 6996 links (Fig. 11A). Smaller numbers represent large clusters. The seven clusters in the figure are "#0 neurogenic inflammation," "#1 trp channel," "#2 parkinsons disease," "#3 preventive effect," "#4 functional dyspepsia," "#5 diabetic neuropathic pain" and "#6 central diabetes insipidus". There were 1742 "signaling pathway" articles with 684 nodes and 6453 links (Fig. 11B). "#0 potential a1," "#1 endocannabinoid system," "#2 inflammatory pain", "#3 trp channel," "#4 mouse len," "#5

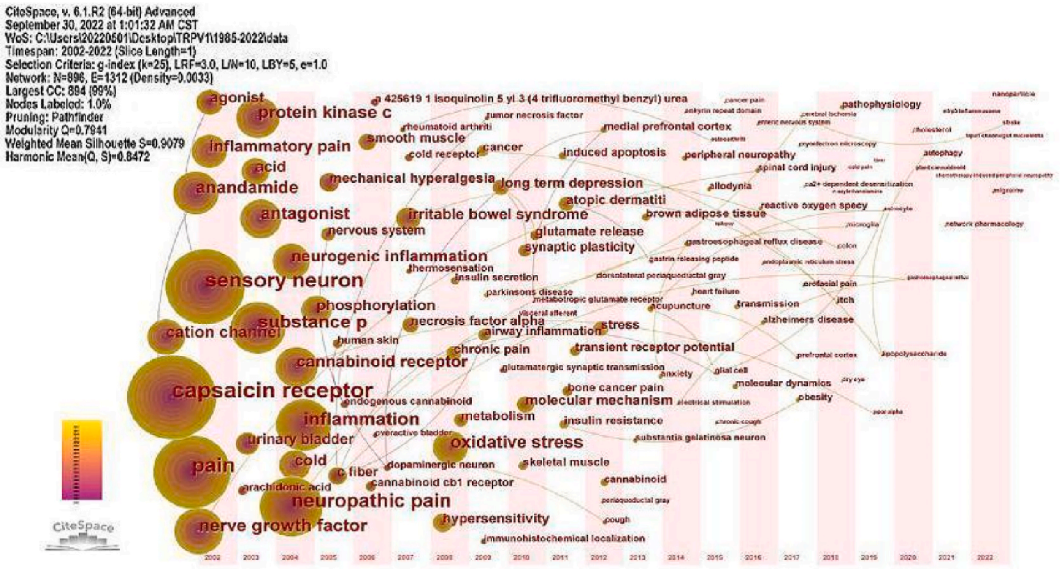

Fig. 10. Time zone diagram.

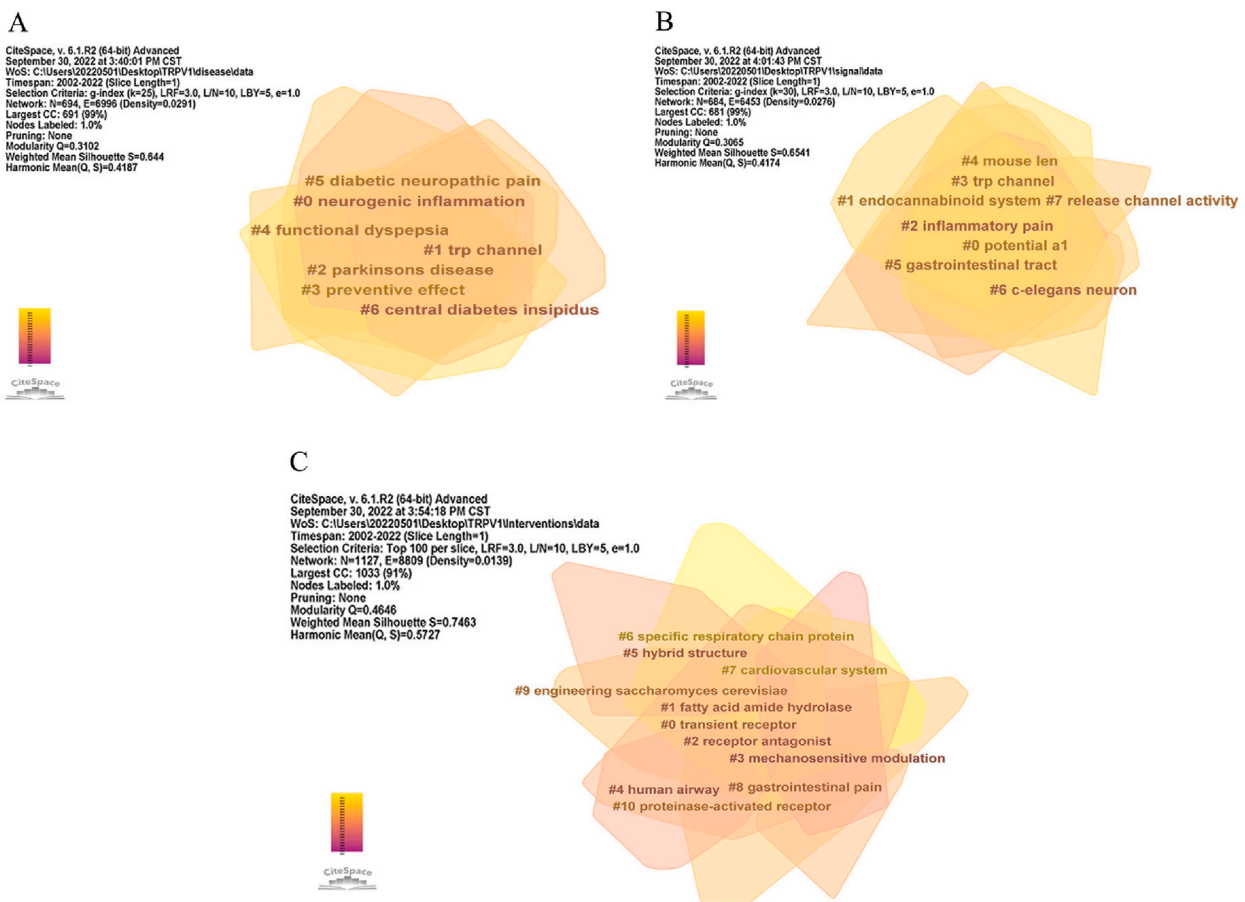

Fig. 11. (A) Keyword cluster map of TRPV1 for "disease." (B) Keyword cluster map of TRPV1 for "signaling pathways." (C) Keyword cluster map of TRPV1 for "intervention methods."

gastrointestinal tract," "#6 c-elegans neuron" and "#7 release channel activity" are the first eight of these clusters. For the 2634 articles on "intervention methods," the keyword co-occurrence map yielded 1127 nodes and 8809 lines (Fig. 11C). These clusters include "#0 transient receptor," "#1 fatty acid amide hydrolase," "#2 receptor antagonist," "#3 mechanosensitive modulation," "#4 human airway," "#5 hybrid structure," "#6 specific respiratory chain protein," "#7 cardiovascular system," "#8 gastrointestinal pain," "#9 engineering saccharomyces cerevisiae" and "#10 proteinase-activated receptor".

All three clustering profiles had a modularity $Q > 0.3$ and weighted mean silhouette $S > 0.5$, indicating that the clusters were reasonable and the homogeneity was acceptable.

4. Discussion

4.1. General information

TRPV1 research has continued to receive attention since its discovery. The number of papers published between 2002 and 2022 has shown a year-over-year increase, and TRPV1 research has focused on the nervous system, drug development, and the exploration of molecular structure function and metabolic mechanisms. Many countries are involved in TRPV1 research, and the United States has the most significant number of publications and has cooperated closely with other countries on many publications. Hence, the United States dominates the research on TRPV1. The higher the node centrality, the greater the influence. The highest centrality was at the University of California, San Francisco, where David Julius, the 2021 Nobel Laureate in Physiology or Medicine, is based and where they have the most significant influence TRPV1 research. There were two major collaborative sub-networks in the TRPV1 research community. Vincenzo Di Marzo is the core of the Consiglio Nazionale Delle Ricerche Endocannabinoid Research Team, with endocannabinoid systems pharmacology and its mechanisms as the primary research. Lee Jeewoo of Seoul National University and Peter M Blumberg of the National Cancer Institute are the core of the Korean-US research team, with TRPV1 antagonists and agonist-related drug development as the primary research.

As seen in the high-frequency cited and co-cited references, temperature-sensitive TRP channels have received the same attention from TRPV1 researchers. Six temperature-sensitive TRP channels cover almost the entire temperature range that mammals can sense. Four TRPV subfamily channels are activated by heat (TRPV1 > 43 °C, TRPV2 > 52 °C, TRPV3 > 32–39 °C, and TRPV4 > 27–35 °C, while TRPM8 and TRPA1 (ANKTM1) are activated by cold (TRPM8 < 25–28 °C; and TRPA1 < 17 °C) [32]. Scholars have extensively studied the cold-sensitive channel protein TRPA1 because it is co-expressed with TRPV1 and is also a multimodal nociceptor capable of being activated by multiple chemical, cold, mechanical, and osmolar stimuli.

4.2. Distribution of TRPV1

The burst map (Fig. 8), Sankey diagram (Fig. 9), and time zone map (Fig. 10) show the changes in the hotspots of TRPV1 research from 2002 to 2022. Regarding neural distribution, the earliest studies showed that TRPV1 was mainly distributed in primary sensory neurons and C and Aδ fibers of the dorsal root and trigeminal ganglion. Further studies found that it was also expressed in the vagus nerve. Due to technical limitations, some early studies suggested that TRPV1 was rarely or not expressed in the central nervous system [1,15]. With the advent of new techniques such as pharmacological characterization, immunohistochemistry, radioligand binding, RT-PCR, and in situ hybridization, it was well established that TRPV1 is distributed in the CNS [33], such as the paraventricular nucleus, anterior cingulate gyrus, hippocampal region, medial prefrontal cortex, gray matter around the dorsolateral aqueduct, and ventral medulla of the medulla oblongata. In recent years, it has also been found to be present in glial cells, and TRPV1 has now been identified in microglia [34], astrocytes [35], and satellite glial cells [36]. TRPV1 was initially thought to be a nervous system-specific receptor, and subsequent studies have shown that in addition to being expressed in the nervous system, TRPV1 is also widely distributed in non-neural tissue cells. Since capsaicin also positively affects in weight reduction and regulation of blood lipids, blood glucose, and blood pressure, these multiple biological functions led to the discovery of TRPV1 in non-neural tissues. Early studies found TRPV1 distributed in the bladder, pancreatic B cells, gastrointestinal tract, skin, and smooth muscles; TRPV1 was found in almost all major systems of the human body. In addition, for the sake of convenience, we categorized the different types of literature, which are described below in terms of "signaling pathways," "diseases," and "intervention methods."

4.3. Signaling pathways

4.3.1. Classical signaling pathway

The endocannabinoid system consists of the cannabinoid receptors 1 and cannabinoid receptors 2, and their major endogenous ligands, 2-arachidonic glycerol and arachidonic ethanolamine (AEA), and their synthesis and degradation enzymes. The endocannabinoid system is associated with brain development, memory formation, learning, mood, anxiety, depression, feeding behavior, analgesia, and drug addiction. Although two G protein-coupled receptors, cannabinoid receptors 1 and cannabinoid receptors 2, have been identified as central cannabinoid receptors [37], there is a significant overlap between the ligands of cannabinoid and TRP channels. Thus, many TRP channels, including TRPV1, have been identified as ionotropic cannabinoid receptors [38,39]. AEA was the first endogenous agonist identified to activate TRPV1, which activates vanilloid receptors on perivascular sensory nerves and causes the release of calcitonin gene-related peptides [40]. Although AEA and capsaicin have similar affinities for TRPV1, AEA has a much lower activation potency. In acutely dissociated small dorsal root ganglion neurons, AEA triggered inward calcium flow via TRPV1, suggesting that the primary mode of regulation of TRPV1 by AEA differed from that of capsaicin, a classical exogenous agonist [41]. In

addition to AEA, another endogenous cannabinoid, N-arachidonoyl dopamine, was identified in the brain as a potent TRPV1 agonist. N-arachidonoyl dopamine is an endogenous capsaicin-like substance in mammalian neural tissues that activates human and rat TRPV1 overexpressed in human embryonic kidney HEK293 cells. It has strength similar to capsaicin [42].

4.3.2. Newly discovered signaling pathways

An increasing number of signaling pathways associated with TRPV1 are being discovered. For example, orphan G protein-coupled receptor 177 (GPR177) in A-fiber neurons was shown to drive diabetic neuropathic pain (DNP) via WNT5a-mediated activation of TRPV1 ion channels. GPR177 mediated the secretion of WNT5a from A-fiber dorsal root ganglion neurons into the cerebrospinal fluid, which was shown to be required to maintain DNP. Extracellular perfusion of WNT5a generated fast currents on TRPV1-expressing heterogeneous cells and nociceptive dorsal root ganglion neurons. Computer simulations have shown that WNT5a has the potential to bind residues on the extracellular S5–S6 loop of TRPV1 [43]. A peptide that disrupted the predicted WNT5a/TRPV1 interaction inhibited rodents' DNP- and WNT5a-induced neuropathic pain symptoms. This result revealed the role of WNT5a as an endogenous and potent TRPV1 agonist and the GPR177-WNT5a-TRPV1 axis as a driver of rodent DNP pathogenesis [44]. The study identified potential analgesic targets that might alleviate neuropathic pain in diabetic patients. The nerve growth factor (NGF)-pro-myosin receptor kinase A signaling pathway significantly enhanced the pain behavior of glutamate and metabotropic glutamate (mGlu) 1/5 receptor agonists in Freund's adjuvant-induced inflammatory mice. The underlying mechanism was an increase in the subpopulation of dorsal root ganglion neurons that activated mGlu1/5 receptor signaling. This was attributed to the functional coupling of mGlu receptors to TRPV1 channels due to increased expression of TRPV1 and A-kinase anchoring protein 5 and subsequent phosphorylation of TRPV1 channels. This NGF-mediated ease of mGlu1/5 receptor-TRPV1 channel signaling explained the ability of glutamate to act as an endogenous pain agent, producing spontaneous pain and severe nociceptive hyperalgesia under inflammatory conditions [45].

4.3.3. Diseases

4.3.3.1. Pain. As can be seen from the time-zone diagram (Fig. 10), the relationship between TRPV1 and inflammatory pain was the most researched at the beginning. It then gradually expanded to "neuropathic pain", "cancer pain", "postoperative pain" and other causes of pain, both acute and chronic pain. The mechanism starts with TRPV1 activation, causing the intracellular Ca^{2+} concentration to rise. Nerve endings generate depolarizing action potentials, which convert the perceived stimuli into chemical signals that affect the function of several systems in the body and stimulate the body to perform many critical physiological activities, such as promoting the release of neuropeptides and excitatory amino acids from nerve endings. When TRPV1 was activated in the dorsal root ganglion, it was found to promote the release of substance P and nociceptive-related substances such as calcitonin gene-related peptide, which led to nociception in the cerebral cortex [45].

The relationship between TRPV1-mediated pain and pruritus has recently attracted scholarly interest. TRPV1 appears to be a hub for analgesic, inflammatory, and pruritic factors, and increased expression and function of these factors led to enhanced neuronal excitability [46]. TRPV1 also appears to be metabolically coupled to most neuroreceptors that recognize analgesic and pruritic molecules. The current topical application of softened, deactivated TRPV1 antagonists is an innovative approach to improving chronic pain or pruritic symptoms [47]. Studies have shown that capsaicin attenuates pain and itching associated with variety sensory disorders by selective excitation of TRPV1+ fibers (pain and itch fibers) and their subsequent desensitization. The mechanism by which TRPV1 mediates the link between pain and pruritus is unclear and needs further exploration.

4.3.4. Cancer

TRPV1 expression is elevated in many cancers, and its overexpression inhibits cell proliferation and induces apoptosis in high-grade astrocytomas [48], prostate carcinoma [49], pancreatic cancers [50] and breast cancer [51]. These findings support the hypothesis that TRPV1 is a tumor suppressor gene. However, depending on the cancer cell type, TRPV1 can promote cell death or inhibit cell death, implying that it has cancer or tissue-specific functions. From the research data, it is likely that TRPV1 is a suppressor of tumor metastasis, and the role of TRPV1 in metastasis may be environmentally relevant and depend on the circumstances [52]. Many studies have shown that TRPV1 agonists/antagonists affect cancer proliferation, cell death and metastasis by activating TRPV1 channels and increasing intracellular Ca^{2+} levels [53–55]. However, the effects are complex and depend on the concentration used and the duration of treatment. In addition, agonists or antagonists may activate other receptors and thus act in a manner independent of TRPV1 [56,57]. However, the effects and mechanisms are unknown and require further study using gene silencing or knockout approaches. Finally, since TRPV1 also plays multiple roles within the cell, it remains unclear whether the role of TRPV1 in cancer progression is independent of its channel activity. It is recommended that the role of the TRPV1 gene in tumorigenesis and progression be further investigated using gene overexpression and knockdown approaches [58].

4.3.5. Neurodegenerative diseases

Studies have shown that a capsaicin diet had a strong correlation with Aβ deposition and cognitive function in Alzheimer's disease (AD) patients, decreased blood markers (Aβ30) associated with AD, and improved long-term potentiation deficits and spatial learning memory function in the CA1 region of the hippocampus. The mechanism was mainly related to reduced mRNA levels and promoter activity of the critical enzyme for Aβ production, β-site cleavage enzyme 1, and inhibition of a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor endocytosis [59]. The TPRV1 receptor reduced β-site cleavage enzyme 1 expression by enhancing peroxisome proliferator-activated receptor gamma expression [60]. In addition, activated TRPV1 receptors significantly increased the number of

hippocampal synapses and synaptic density and thickness in AD model mice and contributed to increased long-term potentiation through an increased calcium inward flow and neurotransmitter release, which in turn contributed to improved hippocampal morphology and cognitive function in mice [61]. However, it was also found that memory function was improved in TRPV1 receptor-deficient AD model mice compared to normal mice, mainly in the hippocampal region, with reduced levels of Ca^{2+}, Aβ protein, and tau protein phosphorylation [62].

It was demonstrated that astrocytes play an essential role in synaptic plasticity, neuronal network oscillations, and related cognitive disorders [63]. Excitation of astrocytes produces ciliary neurotrophic factors to protect neurons [64]. TRPV1 receptors are widely expressed in glial cells, the substantia nigra, and dorsal striatum. When activated, TRPV1 produces large amounts of ciliary neurotrophic factor to prevent dopamine neuron degeneration, effectively alleviating disease progression and preventing progressive cognitive decline in Parkinson's disease [65]. However, it has also been shown that excessive activation of TRPV1 receptors led to striatal dopamine neuronal cell death and impairment of motor function and that inhibition of TRPV1 receptor expression contributed to the recovery of motor function in Parkinson's disease patients [66].

The studies above show that TRPV1 receptors may be a potential target for treating neurodegenerative diseases such as AD and PD. However, the molecular mechanisms need to be further investigated.

4.4. Intervention methods

4.4.1. TRPV1 modulators

4.4.1.1. TRPV1 antagonists. TRPV1 acts as a nociceptive sensor, and its inhibition is an essential strategy in the current development of analgesics. However, the development of TRPV1 antagonists has been hampered by side effects associated with hyperthermia or loss of thermal pain sensation. Capsazepine was the first TRPV1 competitive antagonist identified [67]. Although a derivative of capsaicin, capsazepine had poor selectivity for TRPV1 and was found to block nicotinic receptors, voltage-gated calcium channels, and TRPM8, thus making it unsuitable for clinical application [68,69]. This was followed by the developing of other more potent and selective TRPV1 antagonists. Many of these compounds have shown promise in preclinical pain models, such as BCTC (Paduan Pharmaceuticals) [70] and ABT116 (Abbott) [71], that effectively reversed inflammatory and neuropathic pain. First-generation TRPV1 antagonists have successfully blocked TRPV1 channel activity, including the proton and heat-activated pathways. However, this leads to hyperthermia, a side effect that limits their clinical application. On the other hand, second-generation TRPV1 antagonists have been designed to remain inactive under normal body temperature conditions and thus do not participate in the proton and heat-activated pathways. These novel antagonists are effective in relieving pain without interfering with thermoregulation [72,73].

It should be emphasized that even the most potent second-generation TRPV1 antagonists may induce hyperthermia as a side effect when administered at high doses. Future studies could focus on exploring new TRPV1 binding sites or conformations and developing new mode-selective TRPV1 antagonists to improve drug potency and selectivity while overcoming toxic side effects. Optimizing the mode of administration or dosage of TRPV1 antagonists can improve their pharmacokinetic and pharmacodynamic properties and reduce problems such as drug metabolic stability and drug-drug interactions. For example, topical formulations that avoid systemic side effects and soft drugs that rapidly inactivate after exerting biological activity are promising research directions [74]. Although many TRPV1 antagonists have been developed, none have received clinical approval, which may indicate that targeting only the TRPV1 channel may not be the optimal strategy for developing analgesic drugs. The development of multi-targeted or multifunctional TRPV1 antagonists may enable multilevel modulation of multiple TRP subtypes, other pain-related targets, and synergize with other drugs or therapies to achieve better analgesic effects [75].

4.4.1.2. TRPV1 agonists. An effective analgesic strategy based on agonist-induced channel desensitization has been found, in which capsazepine effectively activated TRPV1 and induced an intense burning sensation. Activation of the channel resulted in Ca^{2+} passing through the pore region, entering the cell and stimulating a series of calcium-dependent processes that eventually lead to channel desensitization. Subsequently, the channel entered an experimental nonresponsive phase and no longer responded to further stimulation, leading to the paradoxical analgesic effects of these compounds [76]. However, capsaicin may cause discomfort or even acute pain upon initial use, and capsaicin may cause impairment of injurious terminal function, which may lead to loss of the ability to recognize potentially noxious stimuli [77]. Resiniferatoxin (RTX) is a natural compound extracted from plants, and it has a much higher affinity and desensitizing activity than capsaicin. Resinotoxin is the most potent agonist of TRPV1, and it causes a lower burning sensation than that caused by capsaicin [78]. However, Initial transient stimulation and continuous activation of the channel-induced desensitization to a variety of noxious stimuli hinder the development of TRPV1 agonists.

Researchers have found that TRPV1 agonists (capsaicin and RTX) caused not only desensitization of nociceptive neurons expressing TRPV1 but also dormancy of other receptors. This development has renewed interest in TRPV1 agonists. Currently, low-concentration capsaicin creams such as Zostrix (0.075 %) and Axsain (0.025 % capsaicin mixed with lidocaine) are popular over-the-counter (OTC) pain relievers. In addition, highly concentrated capsaicin skin patches (NGX-4010), liquid formulations (NGX-1998), and site-specific injections (ALGRX-4975) have been developed. In addition, the safety and clinical efficacy of RTX is an active area of research. In August 2020, RTX (NCT04044742) entered a Phase III clinical trial to evaluate its efficacy and safety for the treatment of osteoarthritis pain in the knee [79]. Therefore, rational development and refinement of delivery systems for TRPV1 agonists (especially RTX) would be an excellent and safe strategy.

4.4.2. Acupuncture

It has been found that acupuncture reduced sensory neuron sensitivity by decreasing the release and expression of pro-inflammatory neuropeptides (substance P and calcitonin gene-related peptide), pro-inflammatory cytokines (tumor necrosis factor-α, IL-1β, and IL-6), and NGFs, thereby downregulating TRPV1 expression and sensitivity [80]. For example, in the acute inflammatory pain signaling pathway, TRPV1 was shown to be a primary downstream target of Mas-associated G protein-coupled receptor C activation [81]. Electroacupuncture of Zusanli (ST36) and Kunlun (BL60) bilaterally in rats inhibited phosphorylation of TRPV1 residues by protein kinase C through downregulating of Mas-associated G protein-coupled receptor C expression. This decreased the sensitivity and openness of TRPV1 channels, thereby reducing internal Na+ and K+ flow and inhibiting pain transmission [82]. Electroacupuncture of bilateral ST36 points inhibited the expression of TRPV1 and its downstream signaling molecules in the dorsal root ganglion of the animal model of complete Freund's adjuvant pain, downregulating phosphorylated protein kinase A, p-extracellular signal-regulated protein kinase, p-*c*-Jun-N-terminal kinase, p38 mitogen-activated protein kinase, several transcription factors, p-cAMP response element binding protein, p-nuclear factor κB, and injurious activation of the ion channel Nav1.7 [83,84], thus relieving pain. In TRPV1-deficient mice, electroacupuncture treatment produced no analgesic effect, suggesting that TRPV1 was critical for electroacupuncture-mediated analgesia in cases of inflammatory pain [85]. In addition, the fire needle effectively relieved peripheral neuralgia in rats with postherpetic neuralgia by effectively modulating the expression of PKA, TRPV1, and pTRPV1 proteins in the dorsal root ganglion, promoting TRPV1 phosphorylation, activating the PKA/TRPV1 pathway, and inhibiting nociceptive hyperalgesia [86].

4.5. Research frontiers

4.5.1. Modulation of TRPV1 activity enhances oxidative stress and anticancer effects in cancer cells

It has been shown that by activating calcium channels in cancer cells, an increase in intracellular calcium ion concentration may attenuate key aspects of cancer progression, including proliferation and metastasis [87]. Cell surface death receptor-dependent exogenous pathways and mitochondria-dependent intrinsic pathways are well known apoptotic pathways. In addition to these pathways, apoptosis is induced by oxidative stress in the endoplasmic reticulum, which is primarily caused by an increase in intracellular free Ca^{2+} concentration [88]. Through oxidative stress and activation of cation channels, the increase in free Ca^{2+} concentration induces different cell proliferation and cell damage effects. Studies have shown that apoptosis and oxidative stress occur in colorectal cancer cells through activation of TRPV1 channels, but carbamazepine, a TRPV1 antagonist, enhances apoptotic and oxidative stress effects [89]. Increased intracellular calcium ion concentrations in cancer cells through activation of TRP cation channels such as TRPV1 and TRPM2 and the role of calcium signaling in proliferation and apoptosis have led to studies evaluating calcium channel inhibitors as a potential therapeutic approach for certain cancers [90].

4.5.2. TRPV1 is involved in chemotherapy-induced peripheral neuropathy

Many of the first-line chemotherapeutic agents currently used in the clinic, such as platinum-based anticancer drugs, proteasome/angiogenesis inhibitors, Vinca alkaloids, and paclitaxel, cause a dose-limiting side effect called chemotherapy-induced peripheral neuropathy (CIPN). Depending on the anticancer drug, 38–100 % of cancer patients are affected by CIPN. Anti-cancer drugs may cause neuronal damage in a variety of ways, such as nuclear and mitochondrial DNA damage, ion channel disruption, axonal transport damage, and inflammatory processes [91]. Recently, experimental evidence points to oxidative stress and mitochondrial dysfunction as one of the common pathophysiological mechanisms leading to CIPN neurotoxicity [92]. Thus, overproduction of reactive oxygen species may affect the redox state and interfere with antioxidant defense systems and cellular functions. Research shows that TRP channels are involved in paclitaxel-induced pain. In fact, a specific cellular signaling pathway has been described in mice that includes mast cell triphosphatase-activated protease-activated receptor 2 and downstream enzymes phospholipase C as well as protein kinases A and C, resulting in TRPV1, TRPV4 and TRPA1 sensitization [93]. In addition, several studies have demonstrated the effectiveness of antioxidant therapy in this type of neuropathic pain, and antioxidants are potential therapeutic agents [94].

5. Conclusion

The bibliometric and visual analyses of TRPV1 research presented in this study using CiteSpace and VOSviewer software will help researchers understand the knowledge structure and research trends of TRPV1. This article focuses on three main areas. In terms of disease research, pain has been extensively studied since TRPV1 was discovered, while inflammation and neurodegenerative diseases have been received increased attention in recent years. Regarding intervention methods, TRPV1 agonists and antagonists are effective agents acting on TRPV1 targets, and acupuncture for TRPV1-mediated inflammatory pain is gaining increasing attention. In terms of signaling pathways, research on the endocannabinoid system signaling pathway is becoming more mature, and additional new TRPV1-related signaling pathways are being revealed. The molecular biological mechanisms of TRPV1 still need to be further explored.

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Jingchun Zeng: Visualization, Validation. **Yiqian Lu:** Visualization, Data curation. **Hui Chu:** Visualization. **Liming Lu:** Writing – review & editing. **Yuexuan Chen:** Visualization. **Kaisong Ji:** Writing – original draft. **Yeze Lin:** Writing – original draft. **Jingjing Li:** Supervision, Methodology. **Shuxin Wang:** Supervision, Methodology.

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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Abbreviations

TRPV1	transient receptor potential vanilloid type1
TRP	transient receptor potential
AEA	arachidonic ethanolamine
GPR177	G protein-coupled receptor 177
DNP	diabetic neuropathic pain
mGlu	metabotropic glutamate
AD	Alzheimer's disease
RTX	resiniferatoxin
CIPN	chemotherapy-induced peripheral neuropathy

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