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# Exploring the TRP channel superfamily: research hotspots and development trends from function to disease

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**Abstract. – OBJECTIVE: Transient receptor potential (TRP) channels are a superfamily of permeable cation channels activated by various mechanisms and play a role in nearly all types of sensory signal transduction. In academia, few have comprehensively discussed the research status of TRP channels. This study aims to summarize the knowledge structure and research hotspots of TRP channels using bibliometrics.**

**MATERIALS AND METHODS: TRP channel-related publications from 2003 to 2022 were searched in the Web of Science Core Collection (WoSCC) database. VOSviewer was used for the bibliometric analysis of the literature.**

**RESULTS: We included 12,242 articles from 102 countries, primarily from the United States, China, and Japan. Our research indicates that the number of publications related to TRP channels has increased annually from 2003 to 2022. The leading research institutions are KU Leuven, Harvard University, and the Chinese University of Hong Kong. The Journal of Biological Chemistry is the foremost in this field. The main research topics include the structure and function of TRP channels, their role in pathogenesis, and potential therapeutic strategies for diseases such as pain and respiratory diseases. Among these, "transient receptor potential vanilloid 1 (TRPV1)", "transient receptor potential ankyrin 1 (TRPA1)", "TRPV4", "pain", and "therapy" are emerging research hotspots.**

**CONCLUSIONS: This study offers a comprehensive summary of the current research status and development trends of TRP channels and pinpoints the research hotspots in this field. It not only aids individuals interested in TRP channel-related research in quickly gauging the trends but may also guide the future research directions of researchers.**

*Key Words:*

Transient receptor potential channels, Bibliometrics, Cellular functions, Related diseases, Drug developments.

### Abbreviations

TRP: Transient receptor potential; TRPV: Transient receptor potential Vanilloid; TRPA: Transient receptor potential Ankyrin; TRPC: Transient receptor potential Canonical; TRPM: Transient receptor potential Melastatin; TRPP: Transient receptor potential (Polycystin); TRPML: Transient receptor potential Mucolipin; SCI-E: Science Citation Index-Expanded; WoSCC: Web of Science Core Collection; RT-PCR: Reverse Transcription Polymerase Chain Reaction; ROS: Reactive Oxygen Species; P38 MAPK: p38 Mitogen-Activated Protein Kinase; ERK: Extracellular Signal-Regulated Kinase; AKT: Protein Kinase B; IASP: International Association for the Study of Pain; NHIS: National Health Interview Survey; CVD: Cardiovascular Disease; WHO: World Health Organization; RA: Rheumatoid arthritis; OA: Osteoarthritis; NPSLE: Neuropsychiatric systemic lupus erythematosus.

## Introduction

Transient receptor potential (TRP) channels are a class of widely distributed non-selective ion channels in organisms. In mammals, these channels encompass 28 distinct types distributed across six categories: transient receptor potential vanilloid (TRPV) (Vanilloid), transient receptor potential ankyrin (TRPA) (Ankyrin), transient receptor potential canonical (TRPC) (Canonical), transient receptor potential melastatin (TRPM) (Melastatin), transient receptor potential polycystin (TRPP) (Polycystin), and transient receptor potential mucolipin (TRPML) (Mucolipin). They mediate the transmembrane transport of various cations, such as Na+, K+, Mg2+, and Ca2+, and can perceive various physical and chemical stimuli in the environment. They play essential roles in numerous physiological and pathological processes, including sensory transmission, temperature perception, pain transmission, and cell proliferation[1,2].



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Research on TRP channels primarily encompasses (1) the physiological functions of TRP channels[3-8]; (2) the correlation between TRP channel abnormalities and various diseases, such as pain[9], neurological diseases[10,11], cardiovascular diseases[12,13], metabolic diseases[14,15], and autoimmune diseases[16-21]; (3) exploring the drug targets of TRP channels[22-24], and conducting precision medicine research based on these findings, like devising more precise treatment plans for chronic pain[25] and inflammation[26,27]. Although numerous studies in the literature have delved into TRP channels from these three perspectives, a comprehensive discussion of research in this domain is lacking.

Bibliometric analysis is a mathematical and statistical approach used to measure and identify the strengths and weaknesses of research, as well as map the relationships between citations in academic journals[28,29]. Bibliometrics is an established approach for gauging progress across various scientific domains[30]. Bibliometric analysis offers distinct advantages: (1) it facilitates the quantitative assessment of specific research fields over a designated timeframe; (2) it presents a scientific method to uncover the knowledge creation process in particular research areas[31] systematically.

This study seeks to review the global research literature on TRP channels from 2003 to 2022. Through bibliometric methods, we can outline the literature by analyzing subject categories, journals, institutions, countries, citations, and keyword usage. Furthermore, we can delve deep into the frequency of literature citations. This investigation will not only assist individuals with interests in TRP channel-related research in swiftly discerning trends but might also steer the subsequent research directions of scholars.

## Materials and Methods

### Search Strategy

The data for this cross-sectional study were obtained from the Science Citation Index-Expanded (SCI-E) of the Web of Science Core Collection (WoSCC). Searches were conducted using various Boolean logics in March 2023, and all searches were finalized on March 23, 2023, to prevent daily database updates from introducing bias. We excluded conference abstracts, editorial materials, book chapters, letters, corrections, express articles, news items, and retracted publications. We undertook thorough data cleaning of institutions and keywords in preparation for keyword and text mining analysis. Both singular and plural forms of keywords were searched, and both full names and abbreviations were searched as abbreviations. Words with similar meanings were consolidated to prevent redundant counting of terms with identical meaning, such as "transient receptor potential cation channel 3" and "TRPC3", "T helper 2" and "T helper type 2", "cancer" and "tumor". Ambiguous general terms and words with overlapping meanings were omitted to improve the reliability of the analysis results. The search strategies for the articles are detailed in Table I.

**Table I.** Summary of data source and selection.

| Category | Specific Standard Requirements |
|---|---|
| Database | Web of Science core collection |
| Citation indexes | SSCI and SCI Expanded |
| Search string | (TI =("Transient Receptor Potential*" OR "Transient Receptor Potential Channel*" OR "TRP Cation Channel* " OR "Transient Receptor Potential Cation Channel* " OR " TRP Membrane Protein* ")) OR (AK =(" Transient Receptor Potential* " OR " Transient Receptor Potential Channel*" OR "TRP Cation Channel*" OR "Transient Receptor Potential Cation Channel*" OR "TRP Membrane Protein*")) OR AB =( " Transient Receptor Potential* " OR " Transient Receptor Potential Channel*" OR "TRP Cation Channel*" OR "Transient Receptor Potential Cation Channel* " OR " TRP Membrane Protein* ")) |
| Searching period | January 2003 to December 2022 |
| Language | "English" |
| Document types | "Articles" and "reviews" |
| Data extraction | Conference proceedings, editorial materials, reports, book chapters, letters, and non-English documents |
| Sample Size | 12,242 articles |

The "*" represents the "wildcard character" in the literature retrieval process.

### Data Analysis

VOSviewer (version 1.6.19; https://www.vosviewer.com/download) is a software designed for bibliometric analysis. It can extract crucial information from vast numbers of publications and is typically employed to form collaboration, co-citation, and co-occurrence networks. In this study, the software mainly completed trend analysis of publications and citations, journals, institutions, countries/regions, keywords, and scientific cooperation.

## Results

### Distribution of Publication Output

Figure 1 clearly illustrates the changes in publication output related to TRP channels over different periods. The research on TRP channels has consistently increased since 2003, with the number of published papers rising from 113 in 2003 to 984 in 2020, marking its highest point in nearly two decades. In the last two years, the publication output in this field has hovered around 900, suggesting that the area remains a focal point of research.

### Analysis of Prolific Countries/Regions and the Network of Country Cooperation

The analysis included all countries/regions mentioned in the papers, comprising a total of 102 countries/regions. Table II displays the top 10 countries/regions and their cumulative number of papers. The top 10 countries account for 76.79% of all publications. Of these, the United States has the highest number of published papers, followed by China and Japan. Together, these three countries contribute to 49.75% of the total publications.

Figure 2 depicts the collaborations among countries/regions with more than 10 published papers. In the national clustering diagram, the size of the dots signifies a country's academic influence, the width of the lines indicates the collaboration intensity between two countries, and the color denotes the country's cluster. The findings indicate robust cooperation between the United States, China, and Japan. The research cooperation network diagram reveals that China has fostered ties with several nations, such as the United States, Japan, South Korea, Canada, and Russia, to bolster international collaboration and advance the production, distribution, and commercialization of top-tier research outcomes.

### Analysis of Prolific Institution and Cooperation Network Relationship

A total of 6,320 institutions worldwide are involved in research in this domain. Table III presents the top 10 institutions with the highest productivity from 2003 to 2022. Six of these institutions hail from the United States, underscoring the nation's leading role in the research arena. The high total publications (TP) (221) and times cited (TC) (20,194) of Leuven University attest to the exceptional quality and influence of their publications.

For visualization, we incorporated 245 institutions that met the criterion of publishing 25 or more articles. We then built a collaboration network centered on the volume of articles produced by each institution and their affiliations (Figure 3).

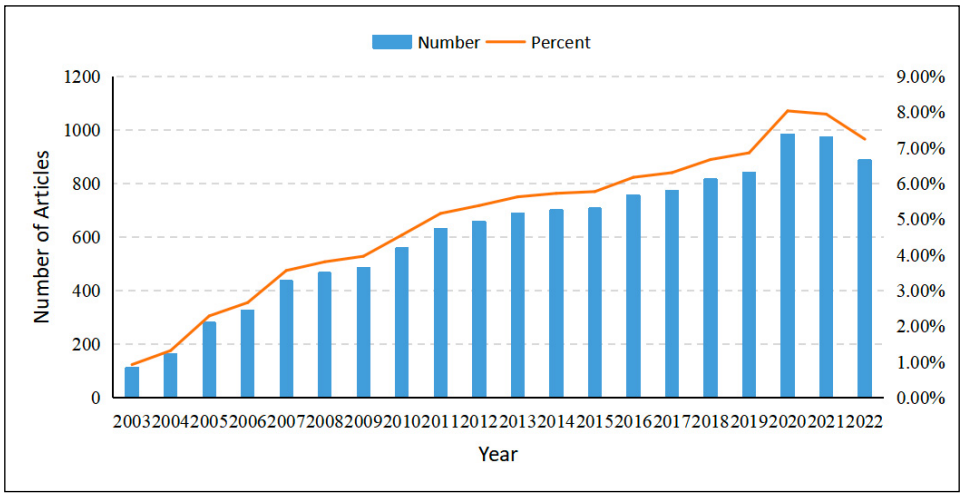


**Figure 1.** Annual output of research of the TRP channels.

**Table II.** The top 10 countries/regions contributed to publications.

| Country | TP | TC | ACPP |
|---|---|---|---|
| USA | 4,292 | 223,676 | 52.11 |
| China | 2,323 | 44,893 | 19.33 |
| Japan | 1,517 | 47,812 | 31.52 |
| Germany | 1,143 | 51,627 | 45.17 |
| UK | 810 | 42,866 | 52.92 |
| South Korea | 620 | 16,161 | 26.07 |
| Italy | 604 | 29,938 | 49.57 |
| Canada | 510 | 20,886 | 40.95 |
| France | 417 | 17,465 | 41.88 |
| Belgium | 317 | 11,381 | 35.90 |

TP = Total publications; TC = Times cited; ACPP = Average number of citations per publication.

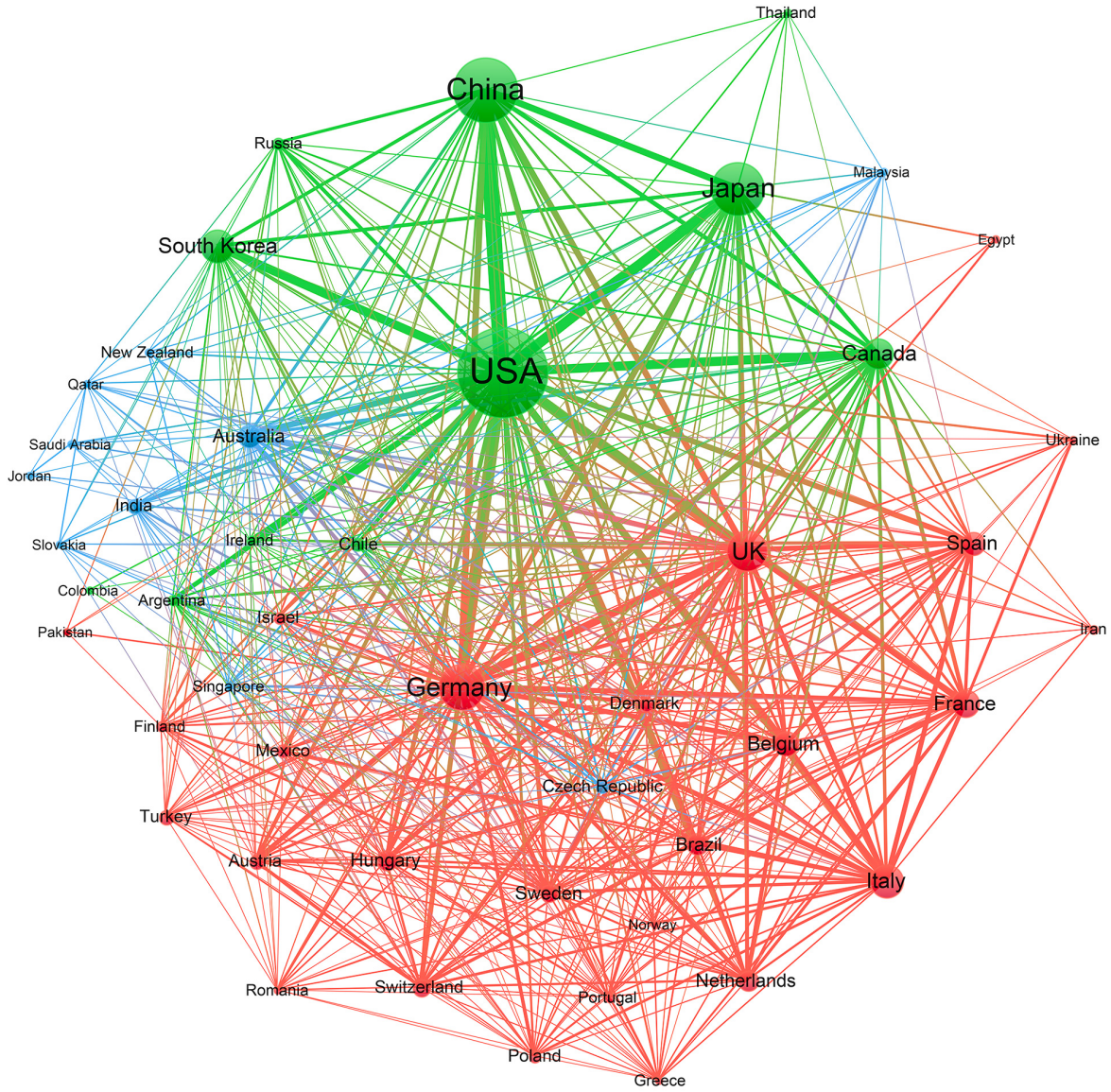


**Figure 2.** National cooperation network.

**Table III.** Top 10 institutions ranked by total number of publications.

| Institution | Country | TP | TC | ACPP | H | > 300 | > 100 | > 50 |
|---|---|---|---|---|---|---|---|---|
| Leuven University | Belgium | 221 | 20,194 | 91.38 | 76 | 12 | 64 | 105 |
| Seoul Natl University | South Korea | 188 | 5,775 | 30.72 | 42 | 1 | 9 | 34 |
| Kyoto University | Japan | 175 | 7,856 | 44.89 | 51 | 1 | 19 | 52 |
| Johns Hopkins University | USA | 161 | 12,198 | 75.76 | 63 | 3 | 39 | 74 |
| Harvard University | USA | 159 | 16,965 | 106.7 | 73 | 13 | 51 | 97 |
| Saarland University | Germany | 103 | 5,227 | 50.75 | 39 | 1 | 15 | 33 |
| Maryland University | USA | 101 | 4,912 | 48.63 | 41 | 1 | 13 | 32 |
| NIEHS | USA | 99 | 6,106 | 61.68 | 42 | 1 | 18 | 38 |
| Pittsburgh University | USA | 94 | 3,581 | 38.1 | 38 | 0 | 5 | 29 |

H: H-index of a country/region; ≥ 300, ≥ 100, ≥ 50: publication counts of publications with more than 300, 100, or 50 citations; NIEHS: National Institute of Environmental Health Sciences. TP = Total publications; TC = Times cited; ACPP = Average number of citations per publication.

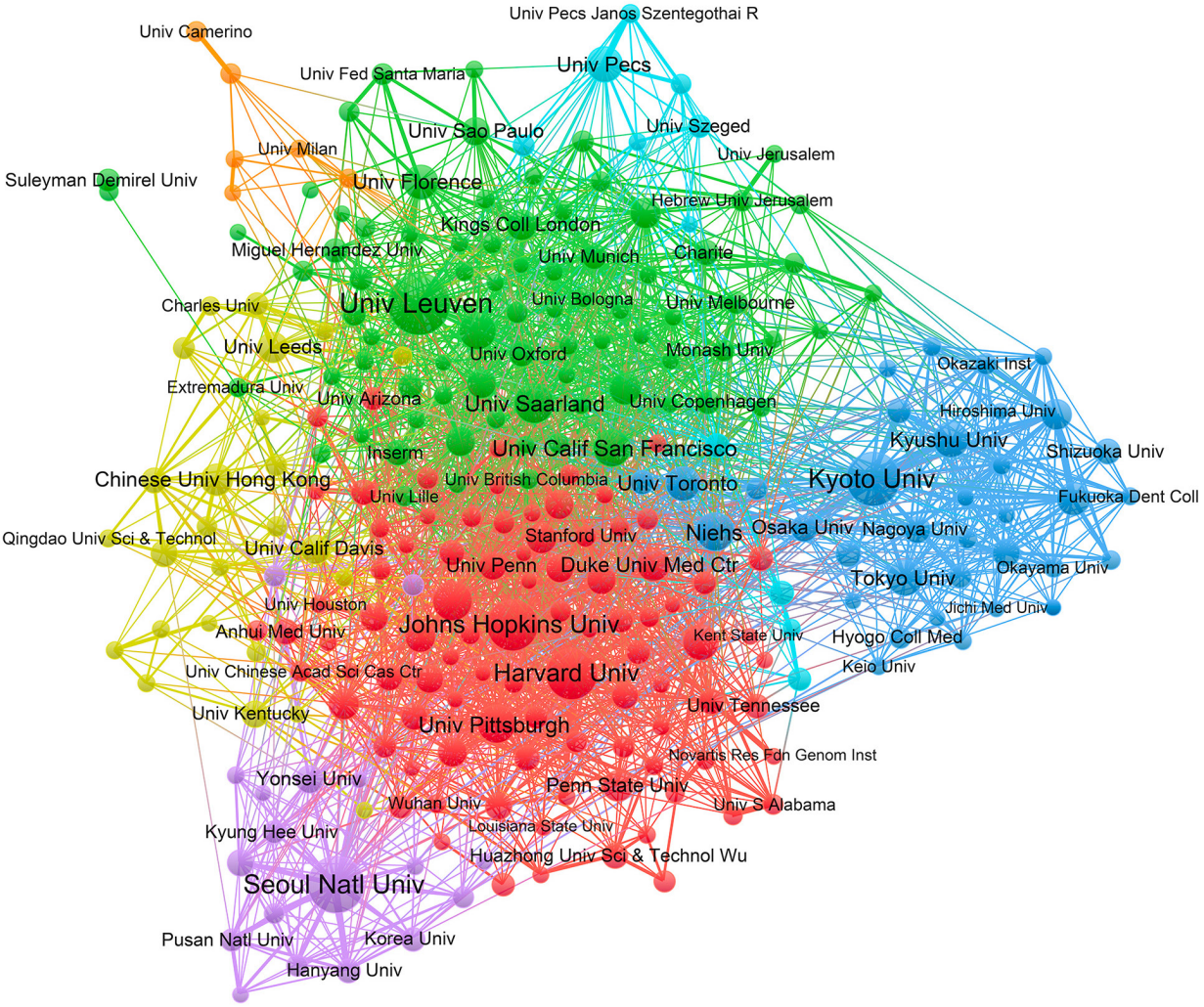


**Figure 3.** Institutional cooperation network.

Figure 3 reveals a tight-knit collaboration among Harvard University, Johns Hopkins University, and the University of Pittsburgh. In contrast, Leuven University, the University of Salzburg, and the University of Oxford exhibit strong collaborative ties. Despite producing the most articles, we also noted that Süleyman Demirel University maintains limited partnerships with other entities.

### Prolific Journals Analysis

The 12,242 articles encompassed in this study were disseminated across 1,700 distinct journals, showcasing the breadth of research topics in this sector. Table IV enumerates the top 10 most active journals, collectively responsible for roughly 17.19% of the total articles. The Journal of Biological Chemistry leads the pack (16.29%) with 343 articles. It is closely followed by the International Journal of Molecular Sciences (12.02%) and PloS One (11.88%), occupying the second and third ranks, respectively.

### Co-Citation Analysis of References

In co-citation analysis, the strength of the relationship between two references is determined by how often they are cited together. For this analysis, VOSviewer was utilized with the minimum number of paper citations set to "100". Consequently, 425 references were automatically displayed. Table V lists the top 10 co-cited references in TRP channel research. "The capsaicin receptor: a heat-activated ion channel in the pain pathway[3]" is the most cited reference, with 2,151 citations, followed by "Impaired nociception and pain sensation in mice lacking the capsaicin receptor[4]", with 1,033 citations. The third most cited article is "TRP channels as cellular sensors[6]", with 1,031 citations.

The resulting network is depicted in Figure 4, emphasizing the research trajectory of TRP channels. The co-citation analysis identified four primary clusters: the red cluster (Cluster 1), focused on "TRP channels as cellular sensors[6]" and research mainly concerning TRP channels' role as cellular sensors; the green cluster (Cluster 2), emphasizes "The capsaicin receptor: a heat-activated ion channel in the pain pathway[3]" and research predominantly on pain-related TRP channels; the blue cluster (Cluster 3), centered on "ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures[7]", predominantly delves into the expression and function of TRP channels within the nervous system; and the yellow cluster (Cluster 4), centered on "Vanilloid receptor-related osmotically activated channel (VR-OAC), a candidate vertebrate osmoreceptor[32]", largely revolves around TRP channel agonists like osmotically activated channels.

### Findings Concerning Research Themes and Analysis of Their Evolution

#### Research keywords and analysis of their evolution

A comprehensive analysis of keywords provides valuable insights into the predominant research themes and evolving trends of the domain. Table VI presents the top 20 keywords based on frequency, with "TRPV1" taking the lead at a count of 2,333. Other prevalent keywords encompass "TRPA1" (970), "mice" (805), and "TRPV4" (726). A significant majority of these keywords

**Table IV.** The top 10 most published journals on the TRP channels.

| Journal | TP | TC | ACPP |
|---|---|---|---|
| Journal of Biological Chemistry | 343 | 21,090 | 61.49 |
| International Journal of Molecular Sciences | 253 | 2,758 | 10.90 |
| PloS One | 250 | 7,385 | 29.54 |
| Journal of Neuroscience | 223 | 20,711 | 92.87 |
| Pflugers Archiv European Journal of Physiology | 186 | 9,138 | 49.13 |
| Scientific Reports | 184 | 3,909 | 21.24 |
| British Journal of Pharmacology | 177 | 11,023 | 62.28 |
| Proceedings of the National Academy of Sciences of the United States of America | 176 | 16,893 | 95.98 |
| Neuroscience | 157 | 5,606 | 35.71 |
| Cell Calcium | 156 | 6,777 | 43.44 |

TP = Total publications; TC = Times cited; ACPP = Average number of citations per publication.

**Table V.** TOP 10 co-citation analysis of cited references on TRP channels research.

| Rank | Title | First author | Source | Publication year | Citations (n) |
|---|---|---|---|---|---|
| 1 | The capsaicin receptor: a heat-activated ion channel in the pain pathway | Caterina MJ | Nature | 1997 | 2,151 |
| 2 | Impaired nociception and pain sensation in mice lacking the capsaicin receptor | Caterina MJ | Science | 2000 | 1,033 |
| 3 | TRP channels as cellular sensors | Clapham DE | Nature | 2003 | 1,031 |
| 4 | ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures | Story GM | Cell | 2003 | 993 |
| 5 | The cloned capsaicin receptor integrates multiple pain-producing stimuli | Tominaga M | Neuron | 1998 | 856 |
| 6 | Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1 | Jordt SE | Nature | 2004 | 770 |
| 7 | Identification of a cold receptor reveals a general role for TRP channels in thermosensation | McKemy DD | Nature | 2002 | 745 |
| 8 | Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin | Bandell M | Neuron | 2004 | 726 |
| 9 | A TRP channel that senses cold stimuli and menthol | Peier AM | Cell | 2002 | 721 |
| 10 | TRP channels | Venkatachalam K | Annu Rev Biochem | 2007 | 721 |

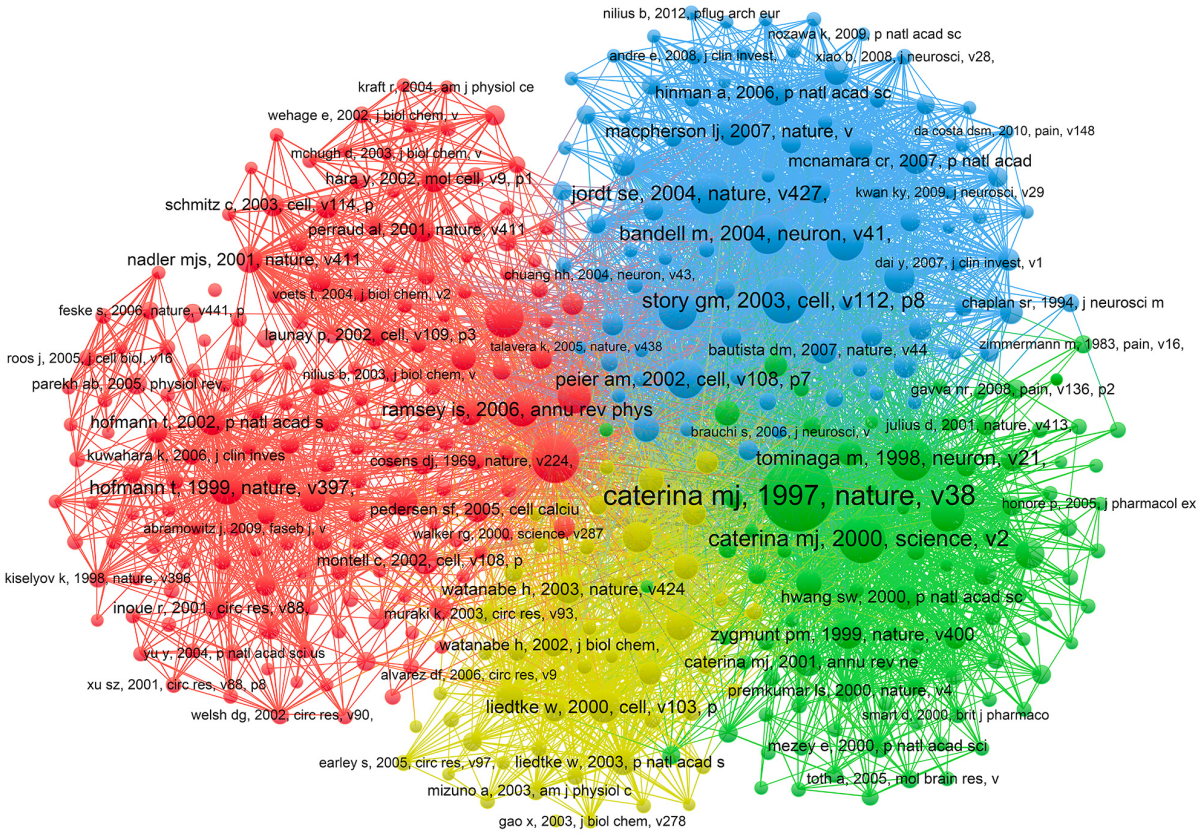


**Figure 4.** Network map of co-citation analysis of references with more than 100 citations.

**Table VI.** Top 20 keywords ranked by total frequency for different periods of time

| Keyword | 2003-2022 | | 2003-2007 | | 2008-2012 | | 2013-2017 | | 2018-2022 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | R (TP) | % | TP | % | TP | % | TP | % | TP | % |
| TRPV1 | 1 (2,333) | 19.26 | 135 | 5.79 | 616 | 26.40 | 772 | 33.09 | 810 | 34.72 |
| TRPA1 | 2 (970) | 8.01 | 19 | 1.96 | 183 | 18.87 | 350 | 36.08 | 418 | 43.09 |
| Mice | 3 (805) | 6.65 | 58 | 7.20 | 207 | 25.71 | 273 | 33.91 | 267 | 33.17 |
| TRPV4 | 4 (726) | 5.99 | 34 | 4.68 | 131 | 18.04 | 201 | 27.69 | 360 | 49.59 |
| Ca2+ | 5 (710) | 5.86 | 59 | 8.31 | 177 | 24.93 | 239 | 33.66 | 235 | 33.10 |
| Pain | 6 (699) | 5.77 | 49 | 7.01 | 198 | 28.33 | 224 | 32.05 | 228 | 32.62 |
| Expression | 7 (618) | 5.10 | 58 | 9.39 | 157 | 25.40 | 203 | 32.85 | 200 | 32.36 |
| Human | 8 (525) | 4.33 | 64 | 12.19 | 146 | 27.81 | 158 | 30.10 | 157 | 29.90 |
| Mechanism | 9 (499) | 4.12 | 71 | 14.23 | 135 | 27.05 | 146 | 29.26 | 147 | 29.46 |
| Inflammation | 10 (488) | 4.03 | 25 | 5.12 | 95 | 19.47 | 166 | 34.02 | 202 | 41.39 |
| Treatment | 11 (478) | 3.95 | 38 | 7.95 | 98 | 20.50 | 157 | 32.85 | 185 | 38.70 |
| TRPM8 | 12 (471) | 3.89 | 31 | 6.58 | 113 | 23.99 | 143 | 30.36 | 184 | 39.07 |
| Regulation | 13 (438) | 3.62 | 51 | 11.64 | 142 | 32.42 | 141 | 32.19 | 104 | 23.74 |
| DRG | 14 (385) | 3.18 | 33 | 8.57 | 136 | 35.32 | 108 | 28.05 | 108 | 28.05 |
| TRPC6 | 15 (374) | 3.09 | 42 | 11.23 | 78 | 20.86 | 122 | 32.62 | 132 | 35.29 |
| *In Vivo* | 16 (346) | 2.86 | 30 | 8.67 | 95 | 27.46 | 105 | 30.35 | 116 | 33.53 |
| Development | 17 (341) | 2.82 | 18 | 5.28 | 97 | 28.45 | 127 | 37.24 | 99 | 29.03 |
| TRPM2 | 18 (310) | 2.56 | 20 | 6.45 | 52 | 16.77 | 91 | 29.35 | 147 | 47.42 |
| Antagonists | 19 (297) | 2.45 | 23 | 7.74 | 90 | 30.30 | 92 | 30.98 | 92 | 30.98 |
| TRPM7 | 20 (300) | 2.48 | 18 | 6.00 | 60 | 20.00 | 106 | 35.33 | 116 | 38.67 |

R = Rank. DRG = Dorsal root ganglion of spinal cord. TP = Total publications.

witnessed a growth in usage over the period, notably "TRPV4" and "inflammation". On the disease front, several conditions correlate with the TRP channel, with "hypertension" and "asthma" taking prominent positions in Table VII.

### Research Hotspot Analysis

Co-word analysis using VOSviewer provides deeper insight into the research field. By adjusting the threshold for keyword co-occurrence, various clusters become apparent. Analyzing these clusters aids in tracking the evolution of research trends and hotspots within the domain. Using VOSviewer for the analysis and setting the occurrence for each term at "20", the total number of the most frequently employed keywords in the research was determined to be "310". Figure 5 displays the visualization map of these prevalent keywords. The co-word analysis identified three primary clusters: the red cluster emphasized the structural and functional characteristics of TRP channels, including terms like plasma membrane, structure, homeostasis, regulation, electrophysiology, Ca2+, channel activation, mechanotransduction, and signal transduction. It also incorporated keywords associated with G protein-coupled receptors, endoplasmic reticulum, lysosomes, and the cellular cytoskeleton. The blue cluster revolved around experimental studies concerning TRP channels in specific ailments, including cancer, obesity, diabetes, and heart failure. It concentrated on the exploration of various TRP channel phenotypes using techniques like siRNA, knockout, immunofluorescence, immunocytochemistry, reverse transcription-polymerase chain reaction (RT-PCR), and western blotting in both *in vitro* and *in vivo* models, including mice and humans. These phenotypes comprised cellular proliferation, differentiation, migration, death, apoptosis, autophagy, oxidative stress, Reactive Oxygen Species (ROS), mitochondria, and metabolism. Furthermore, it delved into the associated signaling pathways such as p38 mitogen-activated protein kinases (MAPK), extracellular-signal-regulated kinases (ERK), and protein kinase B (AKT). The green cluster was delineated by terms like TRPV1, and TRPA1, along with symptoms, conditions, and treatments associated with them, such as pain, inflammation, asthma, migraine, itchiness, anxiety, depression, irritable

**Table VII.** Top 20 keywords about diseases ranked by total number of publications.

| Rank | Keyword | TP | TC | ACPP | H | ≥ 300 | ≥ 100 | ≥ 50 |
|---|---|---|---|---|---|---|---|---|
| 1 | Hypertension | 127 | 5,590 | 43.33 | 45 | 0 | 17 | 41 |
| 2 | Asthma | 120 | 9,706 | 77.65 | 49 | 6 | 23 | 49 |
| 3 | Obesity | 81 | 3,072 | 37.46 | 32 | 0 | 5 | 23 |
| 4 | Diabetes | 80 | 3,184 | 38.83 | 30 | 1 | 7 | 20 |
| 5 | Prostate cancer | 78 | 4,492 | 56.86 | 31 | 2 | 8 | 22 |
| 6 | Pulmonary hypertension | 58 | 2,345 | 39.75 | 24 | 1 | 6 | 17 |
| 7 | Heart failure | 57 | 3,299 | 57.88 | 27 | 2 | 10 | 20 |
| 8 | Osteoarthritis | 55 | 2,212 | 40.22 | 27 | 0 | 5 | 17 |
| 9 | Anxiety | 43 | 2,559 | 58.16 | 24 | 1 | 4 | 13 |
| 10 | Breast cancer | 39 | 3,833 | 95.83 | 21 | 3 | 10 | 17 |
| 11 | Sepsis | 39 | 1,730 | 44.36 | 20 | 1 | 5 | 11 |
| 12 | Alzheimer's disease | 36 | 1,746 | 47.19 | 20 | 1 | 4 | 11 |
| 13 | Parkinson's disease | 36 | 1,662 | 46.17 | 22 | 0 | 5 | 13 |
| 14 | Atopic dermatitis | 35 | 1,675 | 46.53 | 21 | 0 | 5 | 14 |
| 15 | Polycystic kidney disease | 35 | 3,398 | 97.09 | 23 | 2 | 8 | 17 |
| 16 | Seizures | 34 | 4,418 | 129.94 | 21 | 4 | 15 | 16 |
| 17 | Osteoporosis | 32 | 1,367 | 42.72 | 20 | 0 | 2 | 12 |
| 18 | Cardiovascular disease | 25 | 927 | 37.08 | 14 | 0 | 2 | 7 |
| 19 | Multiple sclerosis | 21 | 617 | 29.38 | 16 | 0 | 0 | 3 |
| 20 | Rheumatoid arthritis | 20 | 872 | 43.6 | 16 | 0 | 3 | 6 |

TP = Total publications; TC = Times cited; ACPP = Average number of citations per publication.

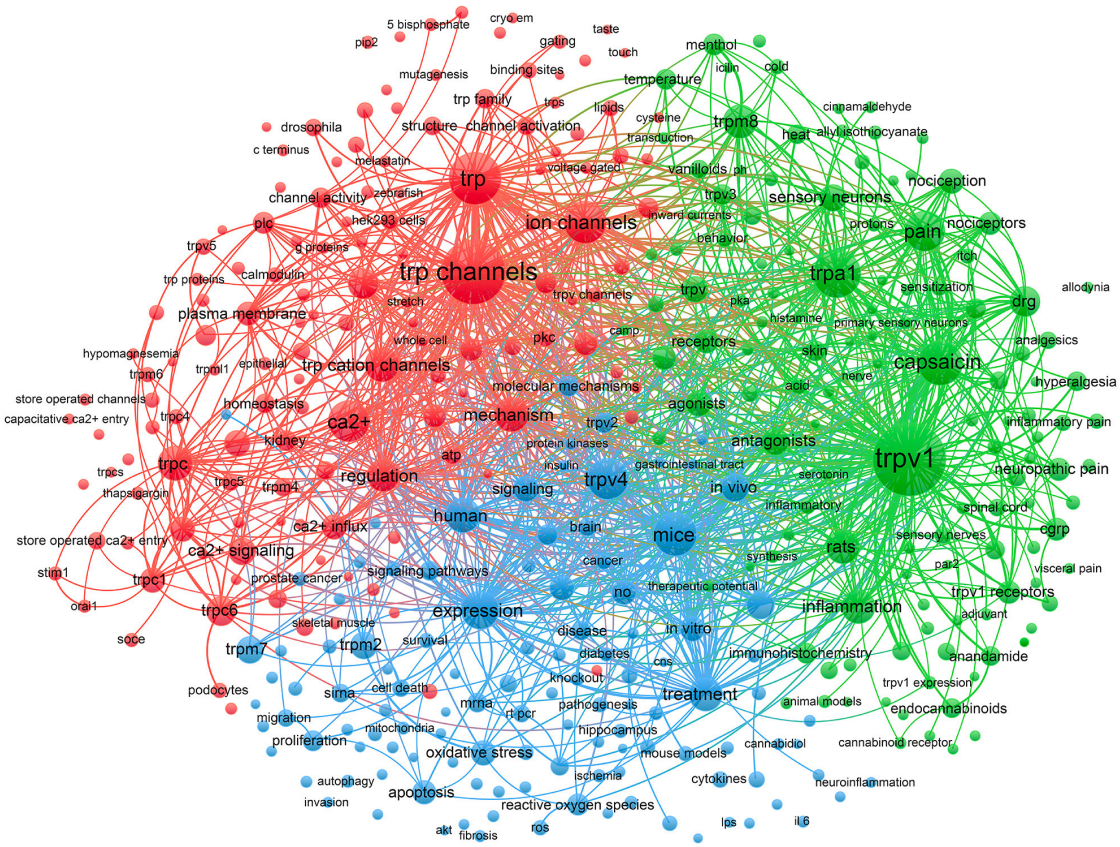


**Figure 5.** The most frequently used keywords in the TRP channels' studies.

bowel syndrome, visceral hypersensitivity, antagonists, and agonists. This cluster scrutinized the entire spectrum related to TRP channels (e.g., TRPV1, TRPA1), spanning from their functionality to diseases resulting from functional anomalies, and subsequently to potential treatments. Thus, it also identified the variety of chemical stimuli these channels can react to, including capsaicin, endocannabinoids, acid, heat, and cold, among others.

It should be highlighted that keyword analysis does not always pinpoint specific TRP channel types like "TRPV3", "TRPC6", or "TRPM1"; they were also referenced in a minority of articles. This research particularly emphasizes keywords like "TRPV1", "TRPV4", and "TRPA1", typically signifying the functionality of individual channels.

## Discussion

This study revealed that the number of papers and citation rates on TRP channels have consistently risen over the past 20 years. Specifically, the USA has delivered more papers, which highlights its leading role in the domain. Moreover, the Journal of Biological Chemistry publishes the most TRP channel research. Concerning co-cited journals, it is evident that many are high-caliber, impactful international publications championing TRP channel research. More crucially, contemporary TRP channel research is transitioning from molecular and biochemical studies toward neuroscience, pharmacology, medicinal chemistry, and beyond, marking a shift from pure scientific inquiry to clinical research.

### Analysis of TRP Channels Research Hotspot Trend

#### Structure and characteristics of TRP channels

Research on TRP channels began in the 1990s. TRPC1 was the first mammalian TRPC discovered, identified by Montell and Rubin[33] in blind flies in 1989, followed by the discovery of TRPC1 in humans by Zitt et al[34] in 1996, activated by the depletion of intracellular calcium stores. Other subtypes of TRP channels were identified in the subsequent decade[2].

Currently, the TRP channel family comprises 28 members and features a structure that includes six transmembrane domains and an ion channel domain[2]. The activation mechanisms of TRP channels encompass voltage gating[35], temperature gating[36], chemical gating[37,38], and mechanical gating[39]. The activity of TRP channels can be regulated through various means, including signals such as calcium ions, temperature, pH value, small molecules, and G protein-coupled receptors[6].

TRP channels are ubiquitously distributed within cells, found in the endoplasmic reticulum[40], lysosomes[41,42], cytoskeleton[43,44], mitochondria, plasma membrane[45], and more, serving vital electrophysiological, mechanical, and chemical signal transduction functions[46]. Research has identified that TRPML channels, unique TRP subfamilies on lysosomal membranes[41], play roles in lysosomal acidification[42], lipid metabolism[47], autophagy[48], and antibacterial[49]. TRP channels' functions in the cytoskeleton involve regulating cell morphology, movement, and migration[43]. Specifically, the cytoskeleton facilitates the binding of stromal interaction molecule 1 (STIM1) with the Ca2+ channel subunit Orai1 and TRPC1[50]. TRPV4 channels can create imbalances between intracellular and extracellular calcium ion concentrations, thereby modulating cell movement and migration by affecting cytoskeletal remodeling and activating the RhoA signaling pathway[51]. Multiple interactions exist between TRP channels and mitochondria, influencing various physiological processes. Some studies[52,53] suggest that TRP channels can impact energy metabolism and cell death by modulating calcium ion levels in mitochondria. In conclusion, after over two decades of research, the structural characteristics of the TRP channel protein family are well understood. Building on this foundation, scientists have delved deeper into the role of TRP channels in cellular functions.

### Cellular Functionality of TRP Channels

TRP channels play a vital role in cellular proliferation. Studies[54] indicate that the TRPC6 channel is upregulated in liver and colon cancer and influences cell proliferation by promoting cell cycle transition and augmenting cell apoptosis. The TRPV1 channel also promotes cell proliferation in breast cancer[55]. Research[56,57] has determined that TRP channels regulate cell proliferation by directly or indirectly affecting intracellular signaling pathways. For instance, the TRPM7 channel is linked to cytoskeleton stability and cell division, and its absence can cause cells to stagnate in the G1 phase. In conclusion, TRP channels have a multifaceted and significant role in cell proliferation.

TRP channels are intricately connected to cell differentiation and development. They can modulate the physiological functions of cells through mechanisms like calcium ion signaling and thermosensitivity. Selective activation of TRPV3 channels, for example, can initiate oocyte activation by mediating a substantial calcium influx[58]. TRPV4 is involved in the activation and differentiation of innate immune cells[59]. Furthermore, TRPV4 channels also influence the growth and differentiation of stem cells[60]. These findings highlight the crucial role of TRP channels in cell differentiation and development.

TRP channels are pivotal in cell migration. For instance, the TRPM7 channel, a member of the TRP channel family, affects cell migration by regulating intracellular calcium concentration and acid-base balance. The TRPM7 channel is also linked to the invasion and metastasis of tumors. Studies[61] have demonstrated that inhibiting the high expression of the TRPM7 channel in colorectal cancer cells can mitigate their invasiveness and metastasis. Moreover, the TRPV1 channel influences cell migration. Studies[62] indicate that TRPV1-mediated calcium-dependent inactivation contributes to Orai1 cell migration and wound healing.

Certain TRP channels participate in cell death processes. The most prominent is the TRPA1 channel, which fosters cell apoptosis and necrosis by generating oxidative stress reactions and regulating calcium ion balance. TRPA1 mediates cisplatin-induced renal tubular cell apoptosis by activating the T cell-p53 signaling pathway and calcium-dependent phosphatase-nuclear factor[63]. TRPV4 prompts glial proliferation of Müller cells and tumor necrosis factor-alpha (TNF-α)-mediated retinal ganglion cell apoptosis in glaucoma rats *via* the Janus Kinase 2 (JAK2)/signal transducer and activator of transcription (STAT3)/Nuclear factor-kappaB (NF-κB) pathway[64]. Moreover, a strong connection exists between TRP channels and autophagy. For instance, 6-gingerol inhibits NLRP1 inflammasomes and cell apoptosis mediated by TRPV3/Fas-associated factor 1 (FAF1) complex dissociation-induced autophagy, preventing cerebral ischemia/reperfusion injury[65]. These findings suggest that TRP channels have multifaceted roles in cell apoptosis.

TRP channels also play a role in regulating oxidative stress. Their regulatory functions are evident in two main ways: the activity and expression levels of TRP channels are affected by oxidative stress, and oxidative stress can influence cellular physiological processes through the modulation of TRP channel functions. For instance, oxidative stress can alter the electrical activity, calcium ion transmission, and chemical sensitivity of TRP channel proteins by oxidatively modifying cysteine residues on these channels[66]. Reactive oxygen species (ROS) are a category of highly reactive oxidizing molecules essential for signal transduction and regulation in normal physiological functions. However, when overproduced, ROS can induce cellular damage and disease[67]. Research[68,69] indicates that certain TRP channel subtypes (such as TRPC, TRPV, and TRPM) can be directly or indirectly modulated by ROS. For example, ROS can amplify the activity of TRPC and TRPV channels through oxidative modifications like sulfhydrylation. Moreover, ROS can foster calcium ion flow *via* TRPM channels, leading to alterations in cellular calcium signaling[70]. These observations highlight the significance of the relationship between TRP channels and ROS in cellular physiology and disease development.

Furthermore, the interaction between TRP channels and various signaling pathways, including p38 MAPK[71-74], ERK[75-77], and AKT[78,79], has garnered significant interest.

Based on the understanding of the structure and function of TRP channels, researchers have increasingly focused on the relationship between TRP channels and various diseases. They have developed, or are in the process of developing, a range of therapeutic drugs for these diseases to enhance patients' prognosis and quality of life.

## Diseases and Treatments of TRP Channels

### Pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage[80]". Currently, chronic pain categories include nociceptive pain, neuropathic pain, and dysfunctional pain[81]. Various pain types necessitate distinct medications, such as anticonvulsants, antidepressants, neuromodulators, nonsteroidal anti-inflammatory drugs, opioids, and others[82]. However, prolonged use of analgesics can result in drug dependence and misuse. Treatment outcomes can differ among individuals. Existing treatments do not eradicate pain but merely alleviate its intensity, making chronic pain particularly challenging to manage.

TRP channels, a class of ion channel proteins, play roles in numerous sensory pathways and several pathological states, including inflammatory pain[83], neuropathic pain[82], and cancer pain[84]. In cases of inflammatory pain, the expression and activity of TRP channels change, heightening neuron sensitivity to painful stimuli[83]. For example, the TRPV1 channel, which sees increased expression during inflammation, exacerbates inflammatory pain by facilitating the release of inflammatory agents like prostaglandin E2 (PGE2)[85]. Moreover, the Epac-protein kinase C (PKC) signaling pathway is pivotal in boosting TRPV1 function during inflammation[83]. TRPV4 channels are also significant in inflammation, and their activation can induce pain and inflammation[86]. In neuropathic pain, several TRP channels, including TRPV1[85,87], TRPA1[88,89], and TRPM8[90], are perceived as molecular thermosensors. They influence neuronal activity and transmission by modulating calcium ion flow, thus facilitating pain signal transmission.

Consequently, the potential of TRP channels as therapeutic targets has piqued pharmaceutical companies' interest, anticipating a broader spectrum of TRP targets for pain mitigation in the future.

### Cardiovascular Disease (CVD)

According to data from the World Health Organization (WHO), CVD is the leading cause of death worldwide. In 2019, it was estimated that 17.9 million people died from CVDs, representing 32% of all global deaths[91]. Of these deaths, 85% resulted from heart attacks and strokes[91].

Abnormalities in TRP channels are present in various cardiovascular diseases. For instance, the natural TRPC3 protein is involved in the ATP-dependent expression of vascular cellular adhesion molecule-1 (VCAM-1) and monocyte adhesion in coronary artery endothelial cells, suggesting a potential pathophysiological role of TRPC3 in coronary heart disease[92]. Activation of the TRPC6 channel relates to the proliferation and contraction of cardiovascular smooth muscle cells; excessive activation of TRPC6 channels can contribute to conditions like hypertension[93]. TRPM4 channels play roles in the heart's pacemaking and conduction; abnormalities in TRPM4 channels can lead to arrhythmias[94]. Moreover, TRPV1 channels play a part in the development of atherosclerosis. Some studies[95,96] indicate that reduced expression or loss of TRPV1 channels might diminish the macrophages' ability to phagocytose cholesterol crystals, thus encouraging atherosclerosis development.

Therapies targeting TRP channels could address certain treatment challenges associated with cardiovascular disease. By modulating TRP channel activity to influence intracellular calcium ion levels, impacting cardiac cell contraction and relaxation, there is potential to alleviate conditions like arrhythmias, control the onset and progression of diseases such as hypertension, and inhibit atherosclerosis development. Hence, therapeutic strategies in this area might be beneficial in the early disease stages for prevention and intervention.

### Respiratory Disease

According to data from the WHO[97], the prevalence of asthma and chronic obstructive pulmonary disease has been increasing globally since the 1990s. Owing to the widespread expression of TRP in immune and structural cells of the lung[98-100], strategies targeting TRP channels might address several therapeutic challenges for asthma and chronic obstructive pulmonary disease: (1) Easing bronchospasm: TRP channels have a significant role in airway smooth muscle cells, and regulating these channels could lessen bronchospasm, enhancing breathing[101]. (2) Diminishing mucus secretion: TRP channels contribute to mucus secretion, and targeting these channels might decrease mucus production and reduce airway resistance[102]. (3) Mitigating inflammation: TRP channels are also present in immune cells, and addressing these channels could alleviate inflammation and minimize lung tissue damage[103]. Hence, the TRP pathway is a promising target for treating respiratory diseases. It is important to note, however, that TRP channel treatment methods remain in the research phase and have not been extensively employed in clinical settings. Their specific therapeutic impacts need further validation.

### Metabolic Diseases

Since the 1990s, global rates of obesity and diabetes have been consistently on the rise. Data[104] from the International Diabetes Federation shows that the number of adult diabetes cases worldwide surged from 136 million people in 1995 to 463 million people in 2019. Additionally, a WHO report[105] from 2016 states that over 1.3 billion adults are overweight globally, with more than 600 million classified as obese. These figures suggest that obesity and diabetes are global public health concerns, with trends that may persist.

TRP channels are integral to the development of obesity and type 2 diabetes. Literature indicates that TRP channel abnormalities can influence insulin secretion and intracellular calcium ion concentration, resulting in conditions like insulin resistance and elevated blood sugar levels. In one preclinical study[106], TRPM5-/- mice retained normal weight on a high-carbohydrate diet, whereas wild-type mice showed a higher susceptibility to obesity. Conversely, TRPM8-/- mice became obese from excessive consumption. Mounting evidence[107] proposes that the somatosensory nervous system perpetuates low-grade inflammation *via* TRPV1, contributing to the advancement of T1DM. In a study[107] using TRPV1-/- mice treated with a small molecule TRPV1 inhibitor, both oral glucose tolerance and glucose-stimulated insulin secretion improved.

Consequently, therapeutic approaches targeting TRP channels could potentially overcome certain limitations of existing obesity and type 2 diabetes treatments, such as enhancing insulin sensitivity and regulating blood sugar levels[108]. Nonetheless, current TRP channel treatment strategies remain under research and necessitate additional clinical trials and validation.

### Central Nervous System

In the past decade, the overall incidence of neurological diseases has increased, especially Alzheimer's and Parkinson's disease among the elderly population[109,110]. These neurological conditions have profoundly impacted the quality of life for patients and their families, also placing significant strain on public health and the economy, thus garnering widespread attention[111]. Scientists continuously delve into the etiology, pathogenesis, and therapeutic methods for these diseases to enhance prevention, bolster treatment efficacy, and alleviate disease burden.

Recent investigations in the literature have identified correlations between TRP channel abnormalities and neurological disorders. Studies[112] indicate that over-activation of the TRPV1 channel can result in neuronal damage. TRPA1 is implicated in depressive and anxiety-like behavior in mouse models of multiple sclerosis[113]. Overstimulation of the TRPC3 channel might contribute to pathological processes like cerebral vasoconstriction and thrombosis, amplifying neuronal death[114]. TRPM2, TRPM3, and TRPM4 are potential therapeutic targets for conditions such as bipolar disorder[115], epileptic seizures[116-118], and multiple sclerosis[11, 119]. However, further research is essential to verify the viability of these therapeutic approaches and to discern their clinical potential.

### Autoimmune Diseases

TRP channel abnormalities can influence the function of various immune cells, facilitating the emergence of multiple immune disorders. Rheumatoid arthritis (RA) is characterized by synovitis and vasculitis. Investigations[120,121] reveal that TRPA1, TRPV1, and TRPV4 channels are linked with RA's development. Notably, TRPA1 and TRPV1 channels regulate pain transmission and inflammatory responses, while the TRPV4 channel might have distinct roles in cell proliferation and inflammatory responses[122-124]. Aberrant activation of these TRP channels may play a part in RA's progression. Conversely, other research suggests that TRPC5[19], TRPV2[20], TRPM2[125], and TRPM8[126] can decelerate RA's progression by diminishing inflammation and synovial fibroblast invasiveness. In osteoarthritis (OA), reduced TRPC5 expression can accelerate matrix metalloprotein (MMP) release, hinder chondrocyte growth, encourage chondrocyte apoptosis, and play a role in OA's onset. Neuropsychiatric systemic lupus erythematosus (NPSLE) presents as a severe complication of SLE. When SLE impacts the nervous system, causing neurological and/or psychiatric symptoms, it often leads to a grim prognosis and high mortality rates. The TT genotype of the rs7925662 single nucleotide polymorphism (SNP) in the *TRPC6* gene elevates the risk of NPSLE in SLE patients. Conversely, patients possessing the C allele have a reduced incidence of NPSLE[17,127]. Research on Sjogren's syndrome indicates that TRPC1[128], TRPC3[18], TRPV1[129], and TRPV4[129] all facilitate salivary gland secretion. Meanwhile, TRPM2, TRPM8, and TRPA1 hinder this secretion[128,129]. Gout flares correlate with the body's uric acid concentration. Urate accumulations in the joint space can provoke acute joint pain. Findings[26] suggest that gene silencing or pharmacological suppression of TRPV1, TRPM2, and TRPA1 can mitigate joint pain and inflammation in mice suffering from gouty arthritis.

It can be observed that TRP channels play pivotal roles in the onset and progression of many autoimmune diseases. Thus, targeting TRP channels might offer several advantages for the precise treatment of these diseases: (1) targeted therapy: addressing TRP channels, as regulators of autoimmune diseases, can influence relevant pathological processes more directly. (2) person-

alized therapy: given the variability in abnormal expression and functional changes of TRP channels across autoimmune patients, targeting TRP channels can facilitate more tailored treatment plans. (3) minimal side effects: although TRP channels are ubiquitous in the human body, their antagonists and agonists usually target a specific subtype or channel. (4) potential new targets: the unique mechanism of TRP channels in the immune system renders them promising targets for drug development, thus expanding therapeutic options for clinical applications.

### *Cancer*

Cancer, a severe ailment, has varying incidence and impact depending on the individual. Presently, cancer ranks among the primary global causes of mortality. TRP channels correlate with numerous cancer types. Research[130] indicates that breast cancer exhibits elevated TRPV6 channel expression, fostering cancer cell proliferation and migration. Activating TRPV2 might offer a novel treatment approach that boosts chemotherapy uptake and effectiveness in TNBC patients[131,132]. Furthermore, other TRP channels, such as TRPV11[55], and TRPV4[133], are also intricately linked to breast cancer. Additionally, TRP channel irregularities relate to liver cancer[134], pancreatic cancer[135], colon cancer[136], prostate cancer[137], and lung cancer[138]. In solid tumor therapy, TRP channel targeting can amplify chemotherapy drug potency, restrain tumor cell migration and invasion, enhance the tumor microenvironment, and subsequently elevate cancer treatment outcomes and patient quality of life. In essence, TRP channels significantly influence cancer's genesis and progression. These findings pave the way for unveiling the molecular mechanisms underpinning various cancers and inaugurate new avenues for crafting TRP channel-centric treatment modalities.

TRP channel aberrations are intimately associated with the emergence and progression of ailments such as pain, cardiovascular diseases, respiratory conditions, metabolic disorders, neurological ailments, autoimmune disorders, and cancer (Figure 6). Designing precise, targeted therapeutic regimes centered on the pertinent targets can substantially uplift patient quality of life.

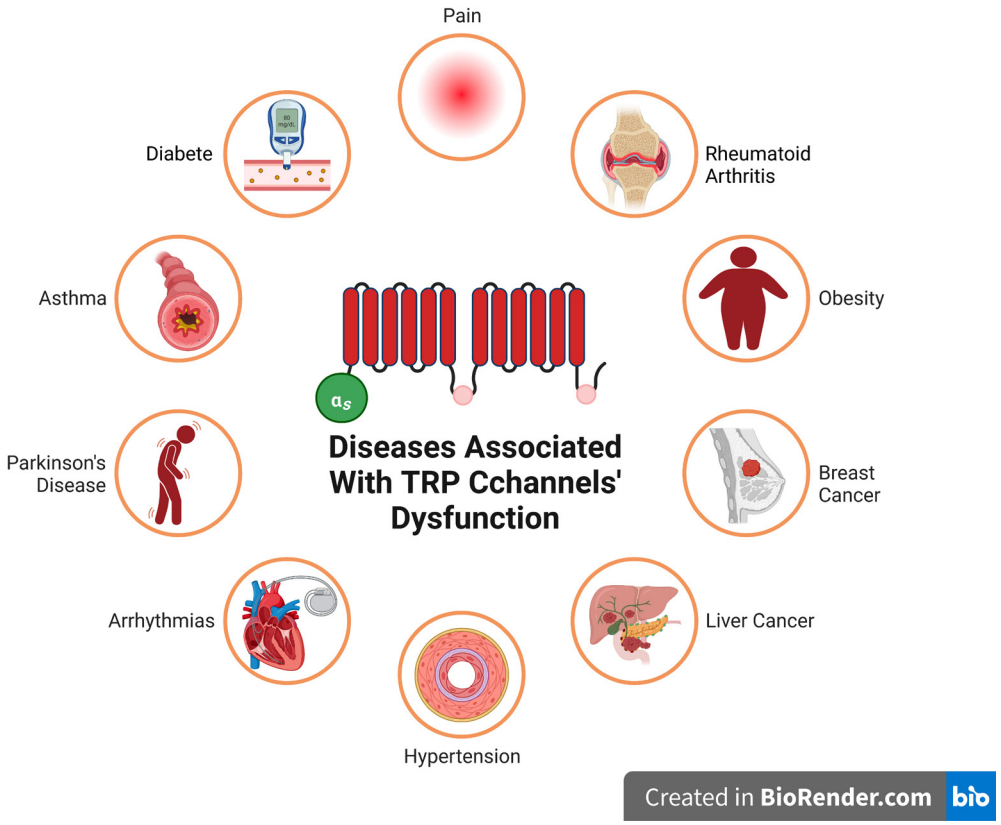


**Figure 6.** Diseases associated with TRP channels' dysfunction.

### Strengths and Limitations

This study boasts distinct strengths. Firstly, we executed a bibliometric analysis grounded in TRP channels and potential clinical drug transition, offering a holistic reference for researchers delving into related domains. Secondly, we employed VOSviewer for our examination, a tool prevalent in bibliometric assessments, ensuring an objective data analysis trajectory. Contrasted with conventional reviews, bibliometric scrutiny affords holistic insights into research hotspots and vanguard topics. Naturally, some limitations exist. Our data solely derives from the WoSCC database, overlooking other repositories, possibly leading to overlooked pertinent studies. Additionally, we prioritized English-language publications, potentially undervaluing non-English contributions. Moreover, due to data constraints, 2023's publications were not incorporated.

## Conclusions

After decades of detailed research, the structure and physiological functions of TRP channels have been elucidated. Over the past decade, research has primarily concentrated on the role and mechanism of TRP channels in various diseases. Future research priorities and trends may be to use different TRP channels as therapeutic targets to develop novel drugs that are more precise, targeted, and individualized for different diseases, thereby expanding therapeutic options for clinical use, improving patient prognosis, and enhancing quality of life. It not only aids individuals interested in TRP channel-related research in quickly gauging the trends but may also guide the future research directions of researchers.

### Ethics Approval

There was no need for ethical approval because the data for the bibliometric research were extracted directly from the database without further human intervention.

### Informed Consent

Not applicable.

### Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

### Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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### Authors' Contributions

Yang Liu and Xueyan Gong contributed equally to this study and are co-first authors. Yang Liu and Xueyan Gong designed the research and drafted the article. Pengyan Qiao, Zewen Wu, and Rong Li were responsible for literature retrieval and data acquisition, and they also contributed to the analysis and interpretation of the data. Liyun Zhang critically revised the content of the study and gave final approval for the version to be published.

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