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REVIEW

Bibliometric Analysis of Global Research Trends in Adverse Drug Reactions in Oral Cancer Treatment: A 30-Year Perspective (1995–2025)

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ABSTRACT

Objective: **To analyze the global research landscape of adverse drug reactions in oral cancer treatment through bibliometric analysis, examining publication trends, collaboration networks, and research hotspots from 1995 to 2025.**

Methods: **A comprehensive search was conducted in Web of Science Core Collection and Scopus databases, retrieving 424 publications after deduplication. Bibliometric analysis was performed using VOSviewer 1.6.20 and CiteSpace 6.2R6 to visualize author collaboration networks, institutional cooperation, journal distribution, country contributions, and keyword co-occurrence patterns. Origin 2025 was used for graphical representation of publication trends. Network parameters were analyzed using silhouette index, clustering algorithms, and burst detection techniques.**

Results: **Research output showed a consistent upward trend, with significant acceleration after 2010 and peak production in 2022 (53 publications). China (118 publications), USA (84), and Japan (62) emerged as leading contributors, though citation impact varied considerably across countries. Analysis of 12 major research clusters (silhouette values 0.723–1.000) revealed distinct thematic concentrations, from traditional treatment modalities to emerging approaches like immunotherapy. Keyword burst analysis identified temporal shifts in research focus from risk factors (2001–2005) to treatment modalities (2011–2020) and most recently to advanced therapeutic approaches including nanoparticles and precision medicine (2022–2025).**

Conclusion: **The bibliometric analysis reveals a maturing research landscape in oral cancer drug adverse reactions, characterized by increasing international collaboration and evolution toward more sophisticated treatment paradigms. Recent research emphasis on recurrent disease management, immunotherapy, and nanoparticle-based approaches suggests promising directions for future clinical innovations and improved patient outcomes.**

Keywords: Adverse drug reactions, bibliometric analysis, oral cancer, research trends.

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1. Introduction

Oral cancer remains a critical global health issue, distinguished by its notable prevalence, significant mortality rates, and the considerable burden it places on healthcare systems worldwide [1]. Treatment strategies for oral cancer are often multimodal, encompassing surgical interventions, radiotherapy, chemotherapy, targeted therapies, and immunotherapeutic approaches. While these treatments are designed to eliminate malignant cells and control disease progression, they frequently induce a spectrum of adverse reactions that can substantially impair a patient's overall well-being [2]. These adverse reactions, stemming from diverse mechanisms of action and affecting various organ systems, can range from localized issues such as oral

mucositis, xerostomia (dry mouth), and dysphagia (difficulty swallowing) to systemic complications that impact major organ functions [3]. The presence and severity of these adverse effects can significantly diminish a patient's quality of life, hinder their adherence to prescribed treatment regimens, and ultimately compromise clinical outcomes. Therefore, meticulous monitoring, proactive management, and targeted interventions aimed at mitigating these adverse reactions are essential components of comprehensive oral cancer care.

Bibliometric analysis presents a robust and systematic methodology for mapping the contours of scientific landscapes and discerning prevailing research trends within specific domains. By employing quantitative techniques to analyze publication metadata, including authorship, citation patterns, keywords, and institutional affiliations, bibliometric methods offer valuable insights into the intellectual structure, collaborative networks, and the dynamic evolution of knowledge within a given field [4]. These techniques, often implemented using software like CiteSpace [4], enable researchers to identify influential publications, assess the impact of specific studies, and trace the dissemination of ideas across the scientific community. Numerous previous bibliometric studies have been successfully applied across a wide range of medical disciplines to reveal research hotspots and knowledge gaps [5]. For instance, bibliometric analyses have been used to investigate trends in cancer research [4], the correlation of betel quid chewing with oral cancer [6], [7], and research related to pharmacovigilance [4]. However, a comprehensive bibliometric analysis specifically dedicated to investigating adverse drug reactions in the context of oral cancer treatment is notably absent from the existing literature. Undertaking such an analysis holds the potential to uncover critical research hotspots, pinpoint existing knowledge gaps, and effectively guide the direction of future research endeavors within this clinically significant area.

The present study aims to conduct a comprehensive bibliometric analysis of research on adverse drug reactions in oral cancer treatment from 1995 to 2025, providing a systematic mapping of publication trends, collaboration networks, and evolving research themes. Using VOSviewer and CiteSpace software, we analyzed 424 publications retrieved from Web of Science and Scopus databases to identify key research clusters, influential contributors, and emerging trends. Through this analysis, we sought to illuminate the historical development and future directions of research in oral cancer drug adverse reactions to guide clinical practice and future investigations.

2. Methods

2.1. Data Collection and Sources

Bibliometric data on adverse drug reactions in oral cancer were retrieved from Web of Science Core Collection [8] and Scopus databases [9] spanning from 1995 to 2025. For Web of Science, a comprehensive search strategy was implemented using the TOPIC field with the following query: ("Oral Cancer∗" OR "Oral Cavity Cancer∗" OR "Oral Squamous Cell Carcinoma" OR "OSCC" OR "Mouth Neoplasm∗" OR "Oral Neoplasm∗" OR "Oral Cavity Neoplasm∗" OR "Oral Cavity Malignancy" OR "Tongue Neoplasm∗" OR "Tongue Cancer∗" OR "Gingival Neoplasm∗" OR "Gingival Cancer∗" OR "Gum Cancer∗" OR "Palatal Neoplasm∗" OR "Palatal Cancer∗" OR "Palate Cancer∗" OR "Floor of Mouth Neoplasm∗" OR "Floor of Mouth Cancer∗" OR "Cheek Neoplasm∗" OR "Buccal Cancer∗" OR "Buccal Mucosa Cancer∗" OR "Alveolar Ridge Cancer∗" OR "Retromolar Trigone Cancer∗" OR "Oral Malignancy" OR "Intraoral Cancer∗" OR "Intraoral Carcinoma") AND TOPIC ("Adverse Effect∗" OR "Drug-Related Side Effect∗" OR "Adverse Reaction∗" OR "Drug Toxicity" OR "Pharmacovigilance" OR "Drug Monitoring" OR "Adverse Drug Reaction∗" OR "ADR" OR "ADRs" OR "ADR Reporting" OR "Adverse Event∗" OR "Drug-Induced" OR "Drug-Induced Reaction∗" OR "Drug Safety" OR "Medication Safety"). For Scopus, we employed a similar approach but used TITLE field for oral cancer terms and TITLE-ABS-KEY fields for adverse reaction terms. After deduplication and manual screening, a total of 424 publications were included in the final analysis, comprising 384 articles from Web of Science and 782 articles from Scopus before deduplication. To ensure data quality and reliability, all retrieved publications underwent independent assessment by three authors (S.L., D.K., and G.S.) using predefined inclusion and exclusion criteria. Any discrepancies in study selection were resolved through discussion and consensus among the research team.

2.2. Bibliometric Analysis Software

VOSviewer [10] and CiteSpace [11] were employed as the primary visualization tools for conducting the bibliometric analysis. CiteSpace was utilized to analyze author collaboration networks, institutional cooperation patterns, keyword co-occurrence networks, research hotspots, and research trends. After data processing in CiteSpace, Origin 2025 was used for generating publication volume graphs to visualize annual publication frequencies and temporal distribution patterns.

2.3. Network Analysis Parameters and Metrics

The analytical framework incorporated several key bibliometric indicators including silhouette index, clustering year, and burst strength to identify research patterns. For co-occurrence network analysis, we applied a pathfinder network scaling algorithm with a threshold of 2 co-occurrences minimum. The silhouette index (ranging from 0.723 to 1.000 across identified clusters) was calculated to evaluate clustering quality and coherence. Time-sliced visualization was implemented with a one-year interval, and modularity Q values were calculated to assess the network structure's significance and cluster divisions.

2.4. Cluster Detection and Trend Analysis

Cluster analysis was performed to identify thematic concentrations, with 12 major clusters (numbered 0–11) identified based on semantic relationships between keywords. Each cluster was characterized by the number of keywords (ranging from 13 to 29), silhouette index value, and cluster mean year to reflect temporal characteristics.

Burst detection analysis was conducted using Kleinberg's algorithm to identify keywords with significant increases in usage frequency, with burst strength values (ranging from 1.96 to 4.10) calculated to quantify the intensity of research attention during specific periods. Institutional and author productivity were measured by publication frequency, while national research output was evaluated through country-specific publication counts.

3. Results

3.1. Publication Trends in Oral Cancer Drug Adverse Reactions Research

Fig. 1 and Table I illustrates the annual publication output on oral cancer drug adverse reactions from 1995 to 2025. The publication volume demonstrates a clear upward trend with notable fluctuations over the three-decade period. Starting with minimal research interest in 1995 (1 publication), the field experienced gradual growth until a significant inflection point in 2010 (17 publications), marking the beginning of sustained research attention. The most productive period occurred between 2020–2024, with peak output in 2022 (53 publications), representing more than a twelve-fold increase compared to the early 2000s. Despite slight decreases in publication numbers in 2023 (33 publications) and 2025 (10 publications), the overall trend indicates growing research interest in oral cancer drug adverse reactions, particularly in recent years, likely driven by increased clinical application of novel therapeutic agents and greater recognition of treatment-related toxicities.

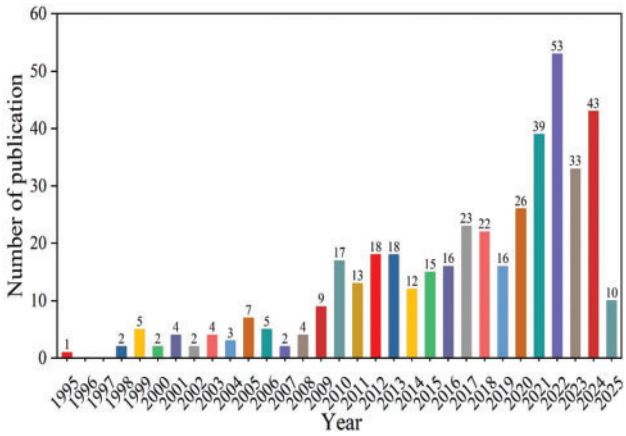

Fig. 1. Annual publication volume of oral cancer drug adverse reactions research (1995–2025).

TABLE I: Annual Publication Distribution of Oral Cancer Drug Adverse Reactions Research from 1995 to 2025

Year	Publication number
1995	1
1998	2
1999	5
2000	2
2001	4
2002	2
2003	4
2004	3
2005	7
2006	5
2007	2
2008	4
2009	9
2010	17
2011	13
2012	18
2013	18
2014	12
2015	15
2016	16
2017	23
2018	22
2019	16
2020	26
2021	39
2022	53
2023	33
2024	43
2025	10

3.2. Author Collaboration and Impact in Oral Cancer Drug Adverse Reactions Research

Fig. 2 and Table II presents the author collaboration network in oral cancer drug adverse reactions research, complemented by comprehensive bibliometric data in the table. Worthington, Helen V. demonstrates the highest productivity with 6 publications and an exceptional total link strength of 10,999, positioning her as the central figure in collaborative research networks across the field. Glenny, Anne Marie follows closely with 5 publications and comparable link strength (10,731), while Kirita, Tadaaki and Wang, Jing also contributed 5 publications each but with notably lower link strengths (1,325 and 897 respectively), suggesting different collaboration patterns. Interestingly, Conway, David I. and Macluskey, Michaelina exhibit identical metrics (4 publications, 9,854 link strength, 166 citations), indicating they likely collaborate closely within the same research cluster, while Chaturvedi, Pankaj, despite having only 3 publications, accumulated the highest citation count (849), revealing the substantial impact of his research despite fewer collaborative connections.

3.3. Institutional Collaboration Network and Research Productivity in Oral Cancer Drug Adverse Reactions Research

Fig. 3 and Table III illustrates the institutional collaboration network in oral cancer drug adverse reactions research, with color gradients representing the temporal evolution of collaborations from 2014 (blue) to 2022 (red). The University of Michigan and Sichuan University emerge as the most productive institutions with 9 publications each, though they differ in total link strength (865 vs. 533) and citation impact (160 vs. 147), indicating different collaboration patterns and research influence. Notable research clusters can be observed around Asian institutions including Shanghai Jiao Tong University, Chang Gung University, and Tokyo Medical and Dental University, suggesting strong regional collaborative networks particularly in East Asia. Despite having fewer publications [7], Tata Memorial Hospital achieved the highest citation count (980) among all institutions, demonstrating

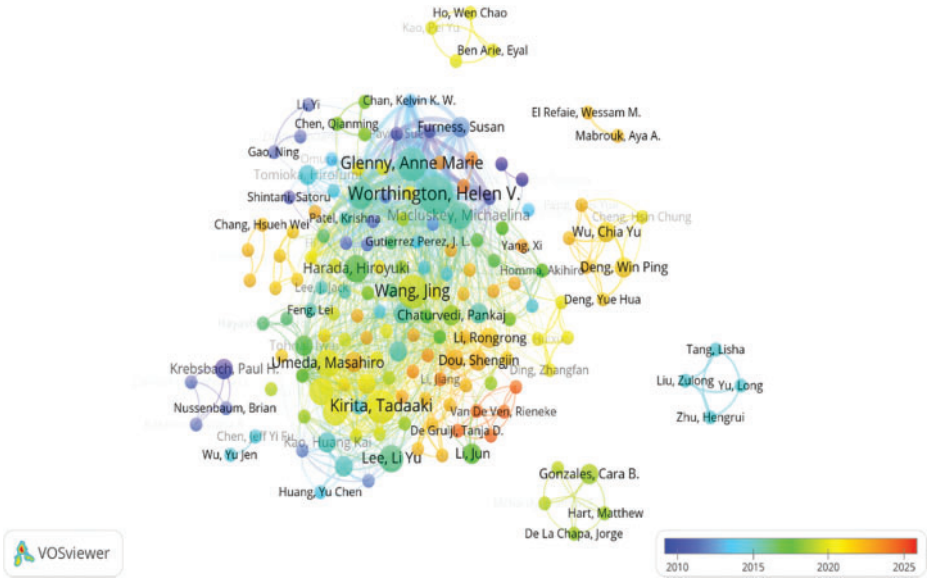

Fig. 2. Author collaboration network analysis.

TABLE II: Bibliometric Analysis of Authors with ≥3 Publications in Oral Cancer Drug Adverse Reactions Research

Label	Weight<Documents>	Weight<Total link strength>	Weight<Citations>
Worthington, Helen V.	6	10999	355
Glenny, Anne Marie	5	10731	200
Kirita, Tadaaki	5	1325	71
Wang, Jing	5	897	44
Conway, David I.	4	9854	166
Macluskey, Michaelina	4	9854	166
Lee, Li Yu	4	903	155
Kurita, Hiroshi	4	1274	70
Umeda, Masahiro	4	1274	70
Yanamoto, Souichi	4	1274	70
Harada, Hiroyuki	4	662	55
Chaturvedi, Pankaj	3	188	849
Furness, Susan	3	7266	156
Noronha, Vanita	3	830	107
Prabhash, Kumar	3	830	107
Chang, Kai Ping	3	581	103
Kao, Huang Kai	3	581	103
Krebsbach, Paul H.	3	252	88
Li, Jun	3	316	70
Hayashi, Ryuichi	3	257	62
Tohnai, Iwai	3	802	55
Tomioka, Hirofumi	3	366	55
Yamada, Shin Ichi	3	765	51
Deng, Win Ping	3	675	36
Gonzales, Cara B.	3	277	36
Wu, Chia Yu	3	675	36
Dou, Shengjin	3	975	25
Zhu, Guopei	3	975	25
Li, Rongrong	3	721	8
Yamakawa, Nobuhiro	3	702	7

exceptional research impact relative to publication volume. The visualization also reveals strong collaborative connections between Western institutions such as the University of Manchester, University of Glasgow, and University of Dundee (link strengths: 4464, 4051, and 4047 respectively), suggesting established multinational research partnerships in this field.

3.4. Journal Distribution and Citation Impact in Oral Cancer Drug Adverse Reactions Research

Fig. 4 and Table IV illustrates the journal co-citation network in oral cancer drug adverse reactions research, with color gradients indicating the temporal evolution of publications from 2012 (blue) to 2022 (red). Oral Oncology emerges as the leading journal with 16 publications,

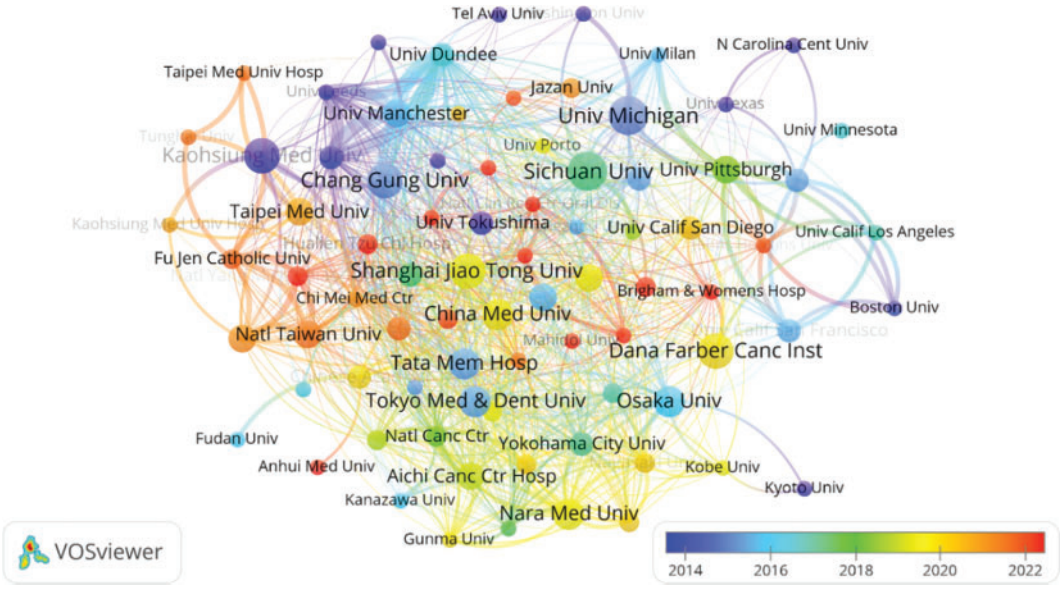

Fig. 3. Institutional collaboration network.

TABLE III: Institutional Productivity and Impact Metrics for Organizations with ≥5 Publications in Oral Cancer Drug Adverse Reactions Research

Label	Weight<Documents>	Weight<Total link strength>	Weight<Citations>
Univ Michigan	9	865	160
Sichuan Univ	9	533	147
Dana Farber Canc Inst	8	449	256
Chang Gung Univ	8	394	243
Kaohsiung Med Univ	8	638	185
Shanghai Jiao Tong Univ	8	683	72
Tata Mem Hosp	7	307	980
Nara Med Univ	7	990	140
Tokyo Med & Dent Univ	7	665	139
Osaka Univ	7	790	110
China Med Univ	7	643	72
Univ Manchester	6	4464	355
Aichi Canc Ctr Hosp	6	540	186
Univ Pittsburgh	6	1305	153
Univ Sao Paulo	6	187	93
Univ Texas Md Anderson Canc Ctr	6	255	89
Taipei Med Univ	6	943	49
Natl Taiwan Univ Hosp	6	1210	22
Natl Taiwan Univ	6	1004	14
Kings Coll London	5	465	266
Univ Glasgow	5	4051	230
Univ Dundee	5	4047	199
Ohio State Univ	5	920	177
Ucl	5	260	139
Univ Calif San Diego	5	398	118
Univ Calif San Francisco	5	767	108
Yokohama City Univ	5	446	89
Univ Tokushima	5	77	70
Chinese Acad Sci	5	428	68
Fujian Med Univ	5	118	21

substantial link strength (372), and high citation impact (394), positioning it as the central publication venue in this research domain. Head and Neck Journal and International Journal of Oral and Maxillofacial Surgery follow with 9 and 8 publications respectively, though their citation patterns differ considerably. Despite having fewer publications [6], the Cochrane Database of Systematic Reviews demonstrates the highest link strength (452) and citation count (355) among all journals, indicating its exceptional influence and interconnectedness in providing evidence-based reviews for clinical decision-making in this field. The visualization reveals distinct journal clusters focused on specific aspects of oral cancer research, with newer collaborations (represented in orange and red) forming

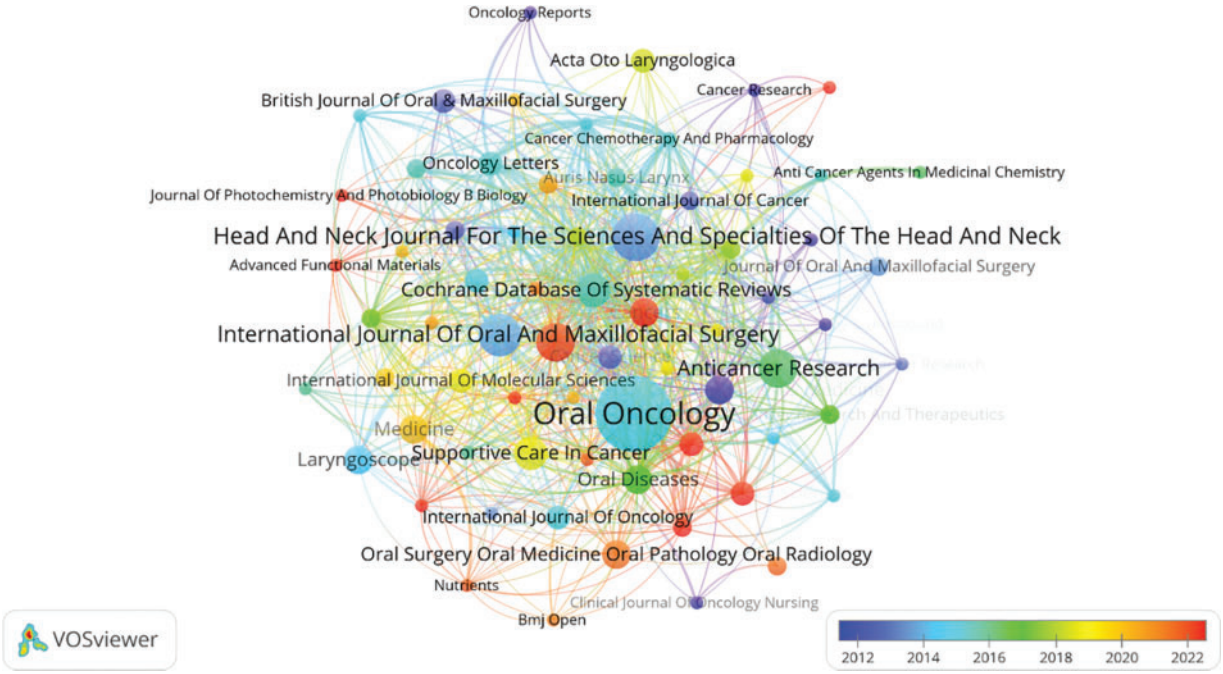

Fig. 4. Journal co-citation network analysis highlighting key publication venues.

around journals like Frontiers in Oncology and Cancers, suggesting emerging research directions in recent years (2018–2022).

3.5. Geographic Distribution and International Collaboration in Oral Cancer Drug Adverse Reactions Research

Fig. 5 and Table V depicts the international collaboration network in oral cancer drug adverse reactions research, highlighting the global distribution of research output and collaborative relationships. China dominates the field with the highest publication count (118 documents), although the United States demonstrates superior citation impact (2,632 citations) and stronger collaborative connections (link strength: 5,614) despite fewer publications (84). England exhibits exceptional collaborative engagement with the highest total link strength (5,733), indicating its pivotal role in facilitating international research partnerships despite contributing only 31 publications. The visualization reveals distinct regional collaboration clusters, with particularly strong connections between Asian countries (China, Japan, India) and Western nations (USA, England, Germany), while Japan's significant contribution (62 publications, 1,146 citations) establishes it as the third most productive country in this research domain. India deserves special mention for its disproportionately high citation impact (1,767) relative to publication count (36), suggesting high-quality, influential research output that has garnered substantial recognition within the international scientific community.

3.6. Keyword Co-occurrence Network and Research Focus in Oral Cancer Drug Adverse Reactions Research

Fig. 6 and Table VI presents the keyword co-occurrence network in oral cancer drug adverse reactions research, with color transitions from blue to red indicating temporal evolution from 2014 to 2020. "Oral cancer" emerged as the most frequently occurring keyword (131 occurrences since 1995) with high centrality (0.43), establishing it as the fundamental research focus and connecting hub across various research clusters. "Squamous cell carcinoma" (82 occurrences) and "head" (80 occurrences) followed as predominant keywords, reflecting the specific cancer type and anatomical focus most studied in relation to drug adverse reactions. The visualization reveals several distinct research themes emerging in different time periods, with earlier research (blue nodes) concentrating on fundamental concepts like "cancer" (62 occurrences, centrality 0.43) and "expression" (41 occurrences), while more recent studies (yellow to red nodes) focus on emerging therapeutic approaches such as "immunotherapy" and advanced topics including "nanoparticles" (11 occurrences in 2020), demonstrating the field's evolution toward more sophisticated treatment modalities and their associated adverse reactions.

3.7. Keyword Clustering and Research Themes in Oral Cancer Drug Adverse Reactions Research

Fig. 7 and Table VII illustrates the twelve major research clusters (Clusters 0-11) identified in oral cancer drug adverse reactions literature, with each cluster representing a distinct research theme. Cluster 0, the largest cluster with 29 keywords and excellent cohesion (silhouette value 0.842), focuses on clinical therapeutic approaches including "adjuvant chemotherapy" and "immune checkpoint inhibitor," reflecting recent research interests (mean year 2016). Cluster 2 demonstrates the strongest internal consistency (silhouette 0.871) with emphasis on molecular mechanisms involving "mTOR inhibitors" and represents the most contemporary research direction (mean year 2019). The visualization reveals clear thematic boundaries between clusters, with Clusters 3, 7, and 10 representing the earliest research foundations (mean year 2001) focusing on radiation therapy, tobacco risk factors, and drug permeability studies respectively, while the perfect silhouette

TABLE IV: Journal Distribution and Citation Impact for Periodicals with ≥3 Publications in Oral Cancer Drug Adverse Reactions Research

Label	Weight<Documents>	Weight<Total link strength>	Weight<Citations>
Oral Oncology	16	372	394
Head And Neck Journal For The Sciences And Specialties Of The Head And Neck	9	240	293
International Journal Of Oral And Maxillofacial Surgery	8	111	224
Anticancer Research	7	109	121
Frontiers In Oncology	7	123	62
Cochrane Database Of Systematic Reviews	6	452	355
Supportive Care In Cancer	6	88	191
Cancers	5	139	50
Journal Of Oral Pathology & Medicine	5	63	147
Laryngoscope	5	46	119
Medicine	5	74	72
Oral Diseases	5	121	128
Oral Surgery Oral Medicine Oral Pathology Oral Radiology	5	40	58
Acta Oto Laryngologica	4	15	45
British Journal Of Oral & Maxillofacial Surgery	4	34	115
Cancer Science	4	45	272
International Journal Of Molecular Sciences	4	31	60
International Journal Of Oncology	4	20	85
Jama Otolaryngology Head & Neck Surgery	4	104	32
Journal Of Dental Sciences	4	57	3
Oncology Letters	4	116	17
Plos One	4	22	67
Auris Nasus Larynx	3	47	57
Bmc Cancer	3	85	57
European Journal Of Pharmacology	3	115	133
Indian Journal Of Cancer	3	63	79
International Journal Of Cancer	3	33	39
International Journal Of Environmental Research And Public Health	3	8	43
Japanese Journal Of Clinical Oncology	3	62	62
Journal For Immunotherapy Of Cancer	3	79	0
Journal Of Cancer Research And Therapeutics	3	28	43
Journal Of Oral And Maxillofacial Surgery	3	23	46
Lasers In Medical Science	3	66	48
Medicina Oral Patologia Oral Y Cirugia Bucal	3	113	82
Scientific Reports	3	24	39

value (1.000) of Cluster 9 indicates its highly distinctive focus on comparative studies between synthetic and herbal drugs in oral cancer treatment.

3.8. Temporal Evolution of Research Themes in Oral Cancer Drug Adverse Reactions

Fig. 8 illustrates the timeline visualization of keyword evolution in oral cancer drug adverse reactions research from 1995 to 2025, revealing distinct chronological patterns in research focus. The visualization demonstrates how foundational concepts like "oral cancer" and "cancer" emerged as earliest research priorities (1995–2000), establishing the conceptual framework for subsequent investigations. A clear progression is evident as research evolved from basic cancer biology toward treatment modalities, with "chemotherapy" and "apoptosis" gaining prominence during the middle period (2004–2010), followed by increased attention to specific therapeutic approaches such as "radiotherapy" and "immunotherapy" (2011–2017). The most recent research trends (2018–2025) show growing interest in advanced topics including "nanoparticles," "recurrent" disease management, and precision medicine approaches, reflecting the field's maturation toward more sophisticated treatment paradigms and their associated adverse effects management. This temporal mapping provides valuable insights into the historical development and future directions of research in oral cancer drug adverse reactions.

3.9. Keyword Burst Analysis in Oral Cancer Drug Adverse Reactions Research

Fig. 9 presents the top 25 keywords with the strongest citation bursts in oral cancer drug adverse reactions research from 1995 to 2025. "In vitro" demonstrates the most intense burst strength (4.62) during 2017–2021, suggesting a significant surge in laboratory-based experimental research during this period. "Recurrent" exhibits the second strongest burst (4.10) beginning in 2022 and continuing through 2025, indicating growing recent attention to recurring disease and its management challenges. The visualization reveals distinct temporal patterns in research focus, with earlier bursts (2001–2005) centered

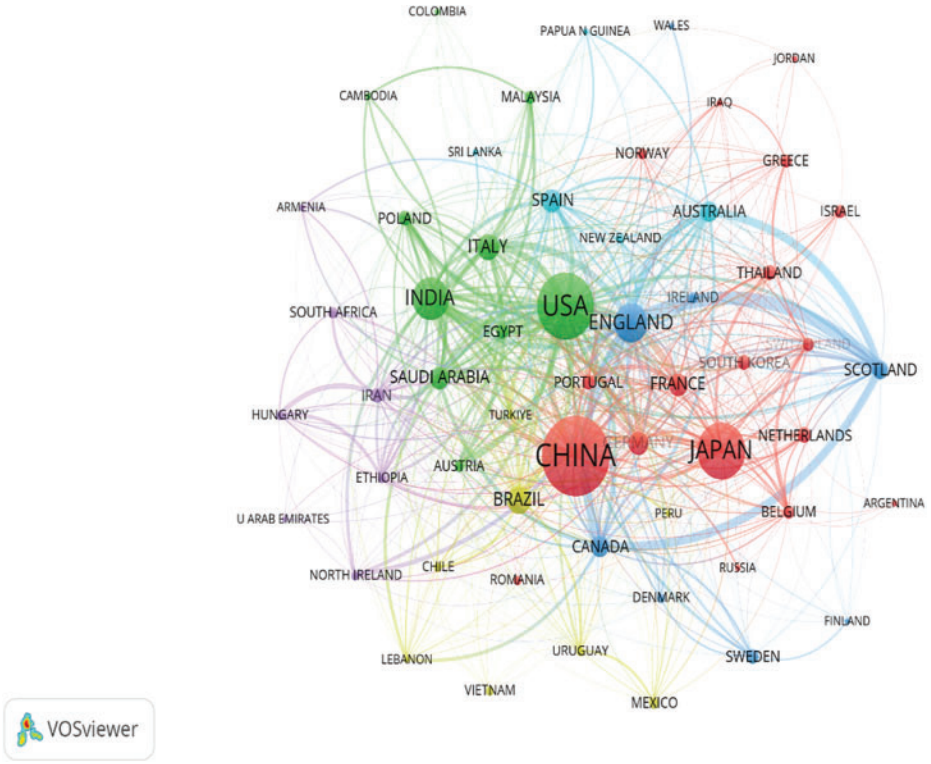

Fig. 5. International collaboration network showing country-level research output and collaborative relationships.

TABLE V: Country-level Research Output and Citation Metrics for Nations with ≥5 Publications in Oral Cancer Drug Adverse Reactions Research

Country	Weight <Documents>	Weight<Total link strength>	Weight <Citations>
China	118	1947	990
USA	84	5614	2632
Japan	62	1434	1146
India	36	3501	1767
England	31	5733	1106
Brazil	16	1172	391
Italy	14	1670	452
Germany	12	1263	236
Spain	12	1172	262
France	11	1118	692
Saudi Arabia	11	1714	207
Canada	10	2533	261
Australia	9	1907	158
Scotland	8	3397	328
Netherlands	6	238	197
Egypt	5	736	193
Iran	5	914	106
Poland	5	963	136
Portugal	5	641	84
South Korea	5	42	50
Sweden	5	245	136
Thailand	5	262	20

on risk factors like "alcohol," transitioning to treatment modalities such as "radiotherapy" (burst strength 3.96, 2011–2020) in the middle period, and evolving toward emerging therapeutic approaches including "nanoparticles" (burst strength 2.91) and "immunotherapy" (burst strength 2.34) in the most recent period (2022–2025). This chronological progression reflects the field's evolution from basic risk factor identification toward increasingly sophisticated treatment approaches and their associated adverse reactions.

4. Discussion

This comprehensive bibliometric analysis of adverse drug reactions in oral cancer treatment revealed several key findings. First, there has been a remarkable increase in

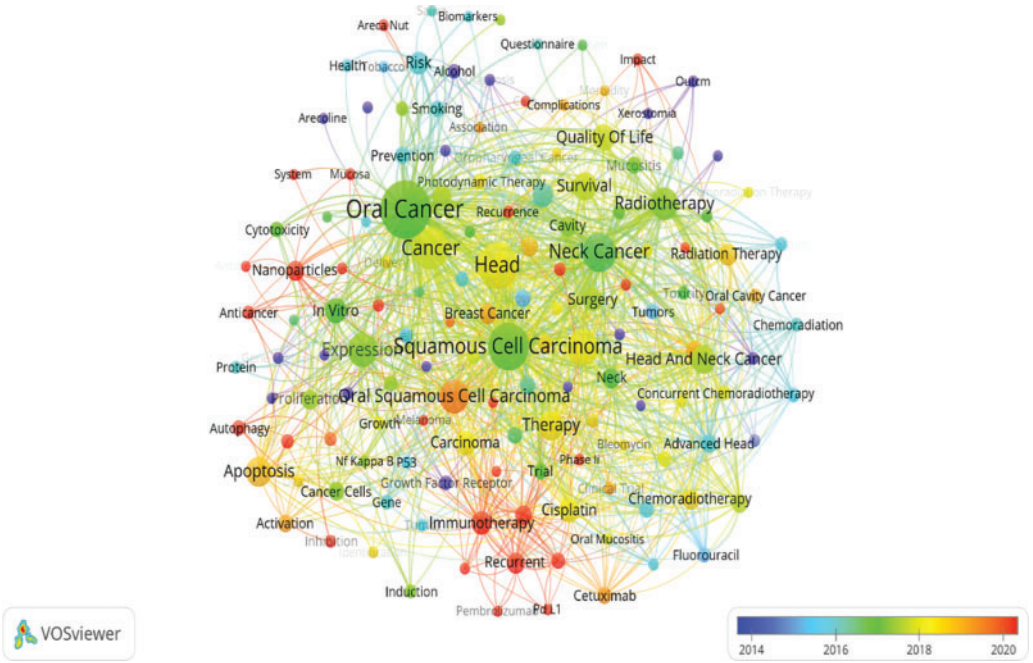

Fig. 6. Keyword co-occurrence network depicting major research themes and their relationships.

TABLE VI: High-frequency Keywords (≥10 occurrences) in Oral Cancer Drug Adverse Reactions Research with Centrality Measures and First Appearance Year

Centrality	Keywords	Occurrence	Year
0.43	Oral cancer	131	1995
0.18	Squamous cell carcinoma	82	2000
0.08	Head	80	2009
0.43	Cancer	62	1999
0.2	Neck cancer	56	1998
0.12	Expression	41	1998
0.1	Oral squamous cell carcinoma	38	2012
0.09	Chemotherapy	35	2007
0.11	Therapy	28	1999
0.07	Head and neck cancer	26	2011
0.24	Apoptosis	24	2004
0.11	Quality of life	20	2012
0.04	Radiotherapy	19	2011
0.05	Carcinoma	18	2013
0.03	Survival	18	2014
0.07	Management	16	2010
0.14	In vitro	15	2017
0.03	Recurrent	14	2020
0.13	Risk	12	1995
0.03	Cisplatin	12	2012
0.05	Efficacy	12	2010
0.06	Breast cancer	11	2006
0.06	Locally advanced head	11	2017
0.17	Activation	11	2008
0.01	Surgery	11	2012
0.03	Advanced head	11	2010
0.08	Nanoparticles	11	2020
0.08	Cavity	10	2002
0.01	Neck	10	2020
0.12	Follow up	10	2009
0.05	5 fluorouracil	10	2007

research output over the past three decades, with publication volume showing exponential growth particularly after 2010, culminating in 53 publications in 2022—representing a twelve-fold increase compared to the early 2000s. Second, while China led in total publication count (118 documents), countries like the United States and England

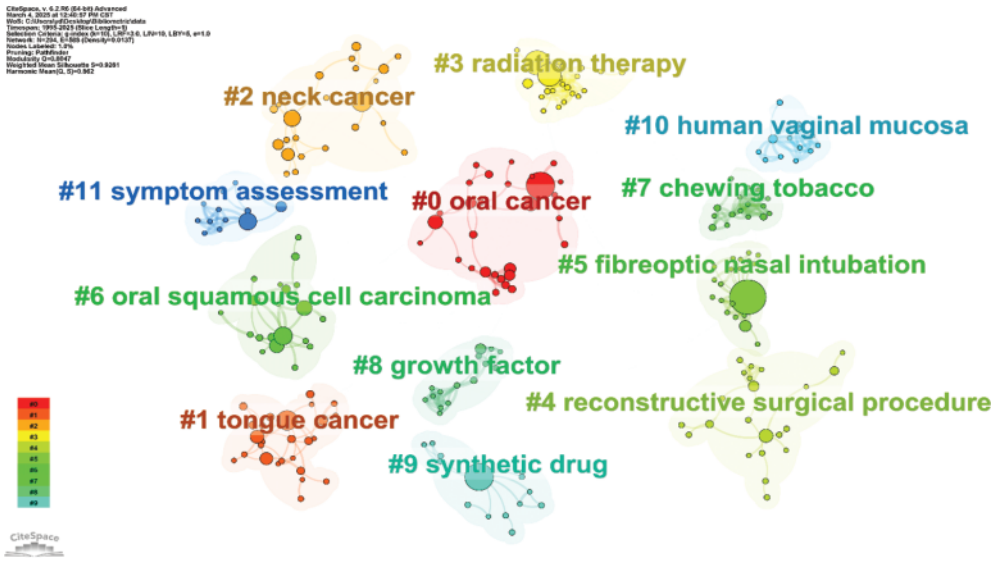

Fig. 7. Cluster visualization of research themes.

TABLE VII: Cluster Analysis of Research Themes in Oral Cancer Drug Adverse Reactions Literature with Silhouette Values and Mean Publication Years

Cluster ID	Size	Silhouette	Mean (Year)	Top Terms (LSI)
0	29	0.842	2016	Oral cancer; retrospective study; adjuvant chemotherapy; immune checkpoint inhibitor; sentinel lymph node biopsy | neck cancer; metronomic chemotherapy; optical imaging; lung cancer; neoadjuvant clinical trial
1	26	0.723	2015	Tongue cancer; combination index; heartwood extracts; acacia catechu; orbitrap fusion | oral cancer; orbitrap fusion; intra arterial infusion chemotherapy; cancer vaccine; tongue cancer
2	25	0.871	2019	Oral cancer; neck cancer; squamous cell carcinoma; mtor inhibitors; oropharyngeal cancer | oral squamous cell carcinoma; major pathological response; neoadjuvant immunochemotherapy; cancer stem cells; low level laser therapy
3	23	0.981	2001	Oral cancer; radiation therapy; proton beam therapy; tongue cancer; intra arterial infusion chemotherapy | oral squamous cell carcinoma; malignant disorders; neoadjuvant phototherapy; intra arterial infusion chemotherapy; analgesia
4	22	0.949	2014	Oral cancer; reconstructive surgical procedure; independent; analgesia; head cancer | inflammatory response; general anesthesia; morphine; ovariohysterectomy; oral tumors
5	21	0.968	2006	Oral cancer; fibreoptic nasal intubation; oral squamous cell; ganoderma lucidum; oral rehabilitation | squamous cell carcinoma; boron neutron capture therapy; 10b biodistribution; oral squamous cell; ganoderma lucidum
6	20	0.954	2011	Oral squamous cell carcinoma; foxo3 pathway; curcumin analogues; transmucosal drug delivery; 5 fu | oral cancer; concurrent chemoradiotherapy; 5 fu; locally advanced head; tongue cancer
7	17	0.975	2001	Chewing tobacco; spit tobacco; smokeless tobacco; free tobacco; smoking cessation | free tobacco; smoking cessation; smokeless tobacco; chewing tobacco; spit tobacco
8	15	0.964	2003	Growth factor; platelet type; human esophageal; cytometry dna; image cytometry | premalignant oral lesion; neck cancer; cancer risk; gross genomic aberration; growth factor
9	14	1	2015	Oral cancer; synthetic drug; herbal drug; vascular anomalies; oropharyngeal cancer | mouth neoplasms; modality therapy; oropharyngeal neoplasms; controlled trials; heme oxigenase
10	13	0.991	2001	Human vaginal mucosa; diffusion studies; permeability studies; anethole trithione; salivary flow rate | anethole trithione; salivary flow rate; permeability studies; human vaginal mucosa; diffusion studies
11	13	0.982	2003	Oral cancer; symptom assessment; coping behaviour; adjuvant chemotherapy; drug compliance | methotrexate; children; childhood; therapy; medication

demonstrated superior citation impact and collaborative network strength, highlighting the importance of international research partnerships in advancing knowledge in this field. Third, our cluster analysis identified 12 distinct research themes with varying temporal distributions, reflecting the evolution from basic risk factor identification toward sophisticated treatment approaches including immunotherapy and nanoparticle-based drug delivery systems. Fourth, influential institutions exhibited diverse collaboration patterns, with Asian institutions forming

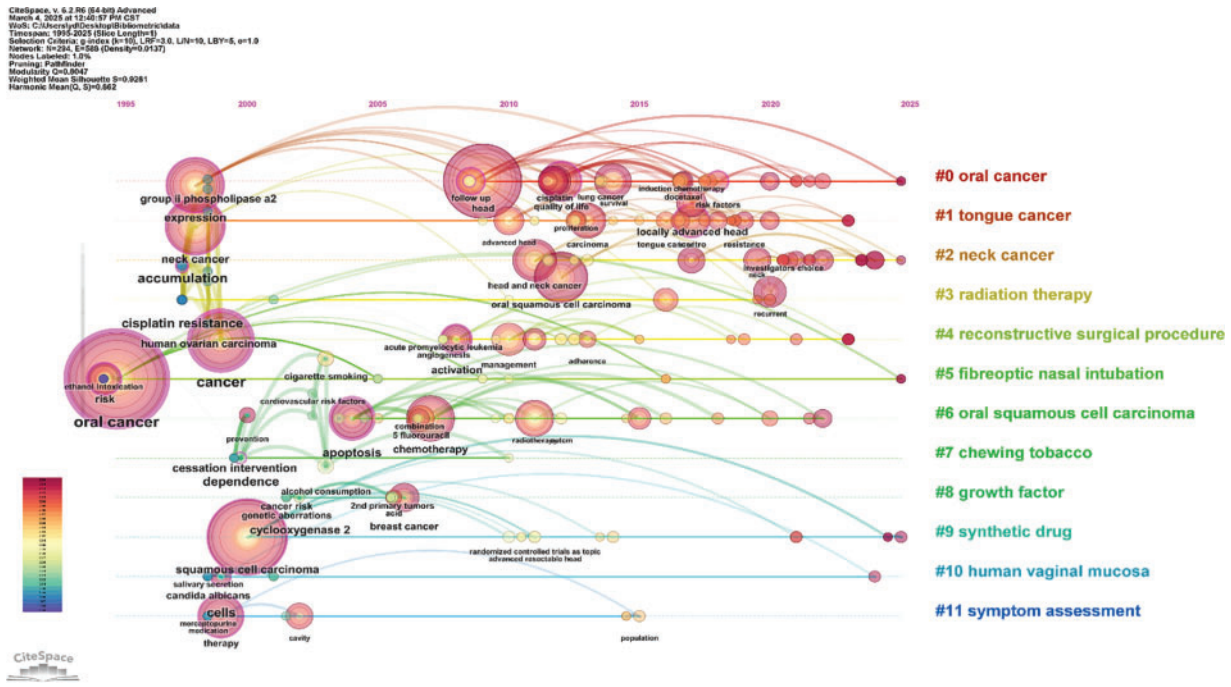

Fig. 8. Timeline visualization of the 12 major research clusters.

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1995 - 2025
alcohol	2001	1.96	2001	2005	
5 fluorouracil	2007	2.26	2007	2017	
management	2010	2.48	2010	2021	
radiotherapy	2011	3.96	2011	2020	
quality of life	2012	2.72	2012	2016	
neck cancer	1998	3.68	2014	2017	
head	2009	2.28	2014	2016	
cancer cells	2015	1.98	2015	2019	
radiation therapy	2016	2.89	2016	2021	
advanced head	2010	2.27	2016	2019	
tongue cancer	2016	2.08	2016	2019	
in vitro	2017	4.62	2017	2021	
efficacy	2010	2.12	2017	2022	
carboplatin	2017	1.95	2017	2020	
risk factors	2018	2.28	2018	2021	
neck	2020	2.91	2020	2022	
cavity	2002	2.21	2020	2022	
therapy	1999	2.86	2021	2025	
recurrent	2020	4.1	2022	2025	
nanoparticles	2020	2.91	2022	2025	
immunotherapy	2022	2.34	2022	2025	
oral squamous cell carcinoma	2012	3.65	2023	2025	
open label	2017	3.08	2023	2025	
apoptosis	2004	2.46	2023	2025	
survival	2014	1.99	2023	2025	

Fig. 9. Top 25 keywords with the strongest citation bursts.

strong regional networks while Western institutions established extensive multinational research partnerships. Fifth, keyword burst analysis revealed clear chronological shifts in research priorities, with recent emphasis (2020–2025) on recurrent disease management, immunotherapy, and advanced therapeutic approaches—suggesting promising directions for future clinical innovations in managing oral cancer drug adverse reactions.

The predominance of cisplatin and 5-fluorouracil in our keyword analysis reflects their central role in oral cancer chemotherapy regimens and the ongoing research interest in their adverse reaction profiles. Table VI shows that cisplatin emerged with higher frequency (12 occurrences, first appearing in 2012) compared to 5-fluorouracil (10 occurrences, first appearing in 2007), suggesting greater research attention to platinum-based therapy complications in recent literature. This finding aligns with clinical evidence demonstrating that cisplatin regimens are associated with a higher incidence of adverse drug reactions compared to other platinum-based combinations such as paclitaxel

with carboplatin [12]. The prominence of cisplatin in our analysis likely reflects both its widespread clinical application and the significant challenges presented by its toxicity profile, including well-documented nephrotoxicity, ototoxicity, and neurotoxicity that necessitate careful monitoring and management [13]. Similarly, 5-fluorouracil's appearance as a high-frequency keyword, particularly in combination regimens with cisplatin and paclitaxel, correlates with clinical observations of its association with alopecia, nausea, and anemia [13]. The temporal difference in keyword emergence—with 5-fluorouracil appearing earlier (2007) than cisplatin (2012)—may indicate shifting research priorities or evolving treatment protocols over time. These findings underscore the importance of robust pharmacovigilance systems for detecting, assessing, and preventing adverse reactions in oral cancer treatment [14], [15], particularly as therapeutic regimens become increasingly complex and personalized.

The prominent position of radiotherapy in our bibliometric analysis, with 19 occurrences (first appearing in 2011), strong citation burst strength (3.96) during 2011–2020, and formation of a distinct research cluster (#3) with excellent cohesion (silhouette value 0.981), reflects its critical role in oral cancer management and the substantial research attention devoted to its adverse effects. This finding aligns with the established position of radiotherapy as a cornerstone in oral cancer treatment, frequently used alone or in combination with surgery and chemotherapy, particularly in cases where surgical intervention is challenging or as an adjunctive therapy to ensure comprehensive treatment coverage [16]. Despite its therapeutic benefits and contributions to improved survival rates, radiotherapy is associated with significant adverse effects in the oral cavity that warrant careful consideration. These adverse effects include mucositis, xerostomia, dysgeusia, osteoradionecrosis, and trismus, resulting from radiation damage to both cancerous and healthy tissues in the oral region (Novais et al., n.d.; Basu et al., 2012; Jagannathan, 2015) [16]–[18]. The severity of these complications varies based on radiation dose, treatment area, and individual patient factors including overall health and presence of comorbidities [19]. The strong research focus on radiotherapy in our analysis likely reflects the ongoing clinical challenges of managing these adverse effects through multidisciplinary approaches, including preventive dental care, cytoprotective agents, advanced radiation techniques, and supportive care measures [20], [21]. Recent developments integrating radiotherapy with novel therapeutic modalities such as immunotherapy demonstrate promising directions for enhancing efficacy while potentially reducing adverse effects [22], [23]. The formation of a distinct research cluster around radiation therapy in our analysis underscores the importance of continued investigation into optimizing radiation protocols and developing personalized approaches to mitigate adverse reactions while maintaining therapeutic benefits in oral cancer management.

The emergence of Cluster 9 with its highly distinctive research theme (perfect silhouette value 1.000, mean year 2015) containing key terms "synthetic drug" and "herbal drug" reflects a significant shift in oral cancer treatment research. This cluster's perfect cohesion indicates a concentrated research focus comparing conventional pharmaceuticals with plant-based alternatives, driven by the recognition that standard oral cancer treatments often cause significant adverse reactions impacting patient quality of life [24]. The growing interest in herbal alternatives stems from their perceived lower toxicity profiles and potential complementary benefits, including anti-inflammatory and antioxidant properties that may enhance treatment outcomes while reducing side effects [25]. Recent bibliometric analyses have identified this comparative approach as an emerging hotspot, revealing increased publications exploring diagnostic aids and treatment strategies that balance efficacy with reduced toxicity [26]. This research direction aligns with broader trends toward personalized medicine in oncology, where treatment strategies are increasingly tailored to individual patient profiles, potentially incorporating both synthetic and herbal components to optimize outcomes [27]. The bibliometric findings suggest future research should emphasize interdisciplinary collaboration integrating bioinformatics, imaging, and clinical studies to advance understanding of oral cancer treatment modalities [28]. Additionally, global perspectives on cancer research highlight the importance of developing treatment strategies that are not only effective but also accessible across diverse healthcare systems, particularly in regions with limited resources where the burden of oral cancer continues to increase [29].

The emergence of "nanoparticles" as a significant keyword in oral cancer drug adverse reactions research (frequency 11, burst strength 2.91 in 2020) signals a pivotal shift toward advanced drug delivery technologies aimed at enhancing therapeutic efficacy while minimizing toxicity. This trend reflects growing recognition that conventional cancer therapies often cause substantial collateral damage to healthy tissues, necessitating more precise targeting approaches. Nanoparticles offer unique advantages in oral cancer treatment through their ability to selectively accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect, potentially reducing systemic exposure and associated adverse reactions [30]. Various nanoformulations including polymeric, lipid-based, and inorganic nanocarriers have demonstrated promising outcomes in preclinical models of oral squamous cell carcinoma by improving drug solubility, enhancing cellular uptake, and enabling controlled release profiles at tumor sites [31], [32]. Beyond conventional chemotherapeutics, nanoparticle platforms are increasingly being explored for delivering novel biological agents, including siRNA and immunomodulators, expanding treatment options for oral cancer patients who experience adverse reactions to standard treatments [33]. Despite their theoretical advantages, translation of nanoparticle-based approaches from bench to bedside faces challenges including manufacturing scalability, regulatory hurdles, and potential long-term toxicity concerns that require further investigation [34]. The strong citation burst observed in our bibliometric analysis coincides with intensified research interest in personalized nanomedicine, where nanocarriers are designed

with surface modifications to target specific biomarkers overexpressed in individual patient tumors, potentially offering tailored therapies with optimized benefit-risk profiles [35]. As this research field continues to mature, interdisciplinary collaboration between materials scientists, pharmacologists, and clinical oncologists will be essential to overcome remaining challenges and realize the full potential of nanoparticle-based approaches in mitigating adverse drug reactions while maintaining therapeutic efficacy in oral cancer treatment.

Despite the comprehensive nature of this bibliometric analysis, several limitations should be acknowledged. First, our reliance on Web of Science and Scopus databases may have excluded relevant literature from non-indexed journals, particularly those published in languages other than English, potentially limiting the global representation of research in this field. Second, the accuracy of our analysis is inherently dependent on the consistency and completeness of metadata in the source databases, including potential variations in author names, institutional affiliations, and keyword assignments. Third, while the study period extends to 2025, data for this final year is inherently incomplete, representing only publications registered through the early months of 2025, which may skew trend analyses for the most recent period. Fourth, citation metrics used as indicators of research impact may not fully reflect the clinical relevance or quality of published works, as publications with longer presence in the literature naturally accumulate more citations. Fifth, the focus on adverse drug reactions in oral cancer may overlook important related research categorized under broader or adjacent terms not captured by our search strategy. Sixth, our analysis primarily examines quantitative aspects of the literature rather than qualitative assessment of research methodology or findings, which would require different analytical approaches.

The findings of this bibliometric analysis offer several important implications for future research in the field of oral cancer drug adverse reactions. Our analysis highlights the need for more integrated research approaches that combine clinical observations with laboratory investigations, particularly in emerging areas such as immunotherapy and nanoparticle-based drug delivery systems where adverse reaction profiles remain incompletely characterized. Future studies should prioritize longitudinal investigations that track adverse reactions over extended treatment periods, as our keyword burst analysis revealed growing interest in recurrent disease management but limited attention to long-term toxicities. The geographical imbalance in research contributions suggests opportunities for expanded multicenter international collaborations, especially between high-publishing countries and regions with high oral cancer prevalence but limited research output. Additionally, the identified research clusters point toward promising directions for targeted investigations, including the integration of artificial intelligence for adverse reaction prediction, personalized medicine approaches based on genetic profiling, and the development of novel strategies to mitigate chemotherapy and radiotherapy-induced toxicities while maintaining therapeutic efficacy. As research evolves toward more sophisticated treatment modalities, interdisciplinary collaboration between clinical oncologists, pharmacologists, and basic scientists will be increasingly essential to comprehensively address the complex challenges of managing adverse drug reactions in oral cancer treatment.

5. Conclusion

This comprehensive bibliometric analysis provides valuable insights into the evolution of research on adverse drug reactions in oral cancer treatment from 1995 to 2025. Our findings reveal a significant upward trajectory in publication volume, particularly after 2010, reflecting growing recognition of the importance of managing treatment-related toxicities in oral cancer care. The research landscape is characterized by distinct shifts in focus—from basic understanding of risk factors to increasingly sophisticated therapeutic approaches including immunotherapy and nanoparticle-based drug delivery systems. The identification of 12 major research clusters with varying temporal distributions highlights the multidisciplinary nature of this field and points to promising areas for future investigation. As international collaboration continues to strengthen, particularly between established research hubs in Asia, North America, and Europe, opportunities emerge for developing more effective strategies to mitigate adverse reactions while maintaining therapeutic efficacy, ultimately improving quality of life and clinical outcomes for patients with oral cancer.

Ethics Approval and Consent to Participate

Not applicable, as this study involved analysis of publicly available bibliometric data.

Consent to Publish Declaration

Not applicable.

Consent to Participate Declaration

Not applicable.

Clinical Trial Number

Not applicable.

Availability of Data and Materials

The data generated and analyzed during the current study are available from the Web of Science Core Collection and Scopus database. The search strategy and criteria used to generate the dataset are detailed in the Methods section of this paper.

Conflict of Interest

The authors declare that they have no competing interests.

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