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Dentistry Section

Role of ARNT2 in Cancer with Specific Emphasis on Oral Squamous Cell Carcinoma: A Bibliometric Review

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ABSTRACT

Introduction: Oral Squamous Cell Carcinoma (OSCC) remains a significant public health issue worldwide, given its rising incidence and unfavourable survival rates, even with treatment advances. Owing to its bivalent function in cancer biology as an oncogene or tumour suppressor, depending on the cellular environment, Aryl Hydrocarbon Receptor Nuclear Translocator 2 (ARNT2), a bHLH-PAS transcription factor, has emerged as a potential biomarker and therapeutic target.

Aim: This article reports an exhaustive bibliometric examination of worldwide research trends on ARNT2 with specific emphasis on its significance to OSCC.

Materials and Methods: The present bibliometric study employed targeted keyword approaches, articles between 1996 and 2025 were retrieved from PubMed and Scopus. Network mapping, co-authorship, citation analysis, and keyword clustering were all performed in R software (v4.5.1). Original, peer-reviewed articles and reviews only were included. The evaluated parameters comprised publication year, journal source, country of origin and citation counts.

Results: Analysis of 220 documents identified significant growth in ARNT2 over the last 20 years. The role of ARNT2 in hypoxic transcriptional control, its tumour-suppressive activity by regulation of cell growth and apoptosis, and its effect on reprogramming of the metabolism by the VHL-HIF1α-GLUT1 pathway were the three predominant thematic groups identified. The suppression of ARNT2 in OSCC and its potential as a marker for prognosis are emphasized in the highest cited publications. It has its greatest input from China, Japan, and the US, and global collaboration is expanding.

Conclusion: ARNT2 plays a critical role in the pathogenesis of OSCC, as per the bibliometric picture, and its diagnostic and therapeutic possibility is increasing. For maximizing the potential of ARNT2 in targeted interventions in oral cancer, there is a need for increased translational research.

Keywords: Aryl hydrocarbon receptor nuclear translocator 2, Biomarker, Cancer progression, Cell proliferation, Gene expression, Oncogene

INTRODUCTION

Head and neck cancers are a major health problem around the world. About 90% of them are Squamous Cell Carcinomas (SCCs) that originate from the epithelial lining of the mouth, larynx, and throat. Oral Squamous Cell Carcinoma (OSCC) is the seventh most frequent type of cancer in the world, making up around 4.5% of all cancer cases [1] and causing an estimated 450,000 deaths each year, according to GLOBOCAN 2020 estimates. OSCC mostly affects those over 50, and men are far more likely to get it than women [2]. The number of cases is very high in South and Southeast Asia, mostly because people there use a lot of cancer-causing substances like areca nut, tobacco, and alcohol [3]. Epidemiological forecasts show that the number of OSCC cases will climb by 30% by 2030, especially among younger people. Not only are lifestyle risk factors to blame for this rise, but so are the increasing effects of oropharyngeal malignancies linked to Human Papillomavirus (HPV) [2].

Even though treatments have gotten better, survival rates are still low, with five-year survival rates between 39% and 42% and ten-year survival rates at 38% [4]. Aryl Hydrocarbon Receptor Nuclear Translocator 2 (ARNT2) is one of the new molecular players in cancer biology that is getting more and more attention. ARNT2 is a basic Helix-Loop-Helix (bHLH)-PAS transcription factor that is known to control a wide range of normal and abnormal processes, including as neurodevelopment, circadian rhythm, and the body's response to low oxygen levels. ARNT2 can function as either an oncogene or a tumour suppressor in cancer, contingent upon the tumour microenvironment, the cellular context, and its dimerization partners, such as HIF-1α and AhR. It appears to facilitate tumour progression in cancers such as glioblastoma and breast carcinoma, while seemingly inhibiting tumour growth in kidney and lung cancers [5,6].

However, the role of ARNT2 in oral squamous cell cancer remains largely unexplored. This work provides a comprehensive bibliometric review of literature related to ARNT2 to address this gap. This investigation aimed to delineate the expansion of scientific interest, identify key contributors, and uncover emerging trends, particularly concerning the advancement of ARNT2-targeted antibodies and their prospective therapeutic applications in OSCC.

MATERIALS AND METHODS

The present bibliometric study was carried out from June 2024 to January 2025. The Scopus and PubMed databases were utilised as principal data sources. Scopus, created by Elsevier, was selected as primary database because to its indexing of scientific literature across several fields [7]. The uniform metadata and indexing terms of the database facilitated the systematic retrieval of ARNT2-related papers. PubMed was selected due to its specialisation in biomedical literature, particularly in clinical and translational research. Other databases, such as Web of Science, EBSCOhost, and Google Scholar, were also examined; nevertheless, Scopus and PubMed provided the most comprehensive coverage for the current study emphasis [6]. As this research did not include human or animal subjects, ethical approval was waived.

Inclusion and Exclusion criteria: The inclusion criteria encompassed peer-reviewed original and review works from 1996 to 2025,

focusing on ARNT2 in cancer, particularly OSCC. The exclusion criteria comprised conference abstracts, editorial correspondence, and withdrawn publications. A total of 220 qualifying papers were obtained.

Study Procedure

The included search keywords were "ARNT2," "oral cancer," "oral squamous cell carcinoma," and "transcription factor," which were utilised in conjunction with Boolean operators. These terms were searched in the title, abstract, and keyword fields to find all relevant publications. Some other added terms like 'ARNT2 gene', 'ARNT2 antibody', and variations of 'oral squamous cell carcinoma' were also used. The connectors like "AND","OR" were used to link similar terms. Two independent researchers reviewed titles first, then evaluated abstracts. Articles that seemed relevant went through full-text reading and assessment. A third researcher helped resolve any disagreements. Each included publication provided information about authors, journal, publication year, research focus, methodologies, results, conclusions, and future research directions.

The evaluated parameters comprised publication year, journal source, country of origin and citation counts.

STATISTICAL ANALYSIS

The R software (version 4.5.1) was utilised for network visualisation. This software generates maps utilising network data and provides distinct benefits for bibliometric analysis. R software facilitated the construction of diverse networks from bibliographic data, including co-authorship networks to analyse collaborative patterns among researchers, citation-based networks to identify influential publications, and keyword co-occurrence networks to delineate conceptual relationships in ARNT2 research. The software's sophisticated layout and clustering methods identified distinct research clusters and demonstrated relationships among various research themes. The natural language processing capabilities facilitated the construction of term co-occurrence networks from abstract data. Bibliographic information was exported from Scopus and PubMed in BibTeX format. The data underwent cleaning procedures utilising thesaurus files to standardise author names, institutional affiliations, and keywords. Three types of R software representations were utilised: network visualisation to illustrate connections between items, overlay visualisation to depict temporal progress, and density visualisation to indicate the concentration of research activity. Each type provided distinct insights into ARNT2 research [6]. This framework provided a comprehensive overview of ARNT2 research in oral cancer. Key contributors, evolving research themes, and emerging trends in this significant field were identified.

RESULTS

Annual publication trends demonstrate a consistent growth of ARNT2-related OSCC research, with major increase of publication observed in 2021 and 2024, correlating with new functional insights into ARNT2 in tumour growth regulation [Table/Fig-1].

The [Table/Fig-2]. shows that the vast majority of publications (180, or 81.4%) have received between 0 and 50 citations. This is in the foundational layer of the research ecosystem, comprising important but less transformative work such as preliminary studies, technical reports, case series, and confirmatory research. These papers were essential for incremental progress and provide the necessary data for meta-analyses.

A smaller, yet significant, cohort of papers (23, or 10.4%) falls into the 51-100 citation range. These represent high-quality, impactful research that has successfully influenced the field. These are typically robust functional studies that provide mechanistic insights into ARNT2's role in OSCC pathogenesis, or well-designed clinical studies with clear prognostic findings. The most elite group consists

Time period	Number of publications	Notable trends
1993-2000	3	Early exploratory studies
2001-2010	56	Focus on expression and gene regulation
2011-2020	123	Peak growth; role in OSCC pathogenesis clarified
2021	19	Spike after novel findings on ARNT2 and cancer growth
2022	1	Least number of papers
2023	1	Focus on definitive role
2024	15	Continued surge linked to cancer biology insights
2025 (till date)	3	Expanding interest in ARNT2 antibody development

[Table/Fig-1]: Annual growth of publications in ARNT2 and OSCC research (1993-2025).

Citation range	Number of publications	% of total	Notable examples
>100 citations	18	8.18%	Highly influential reviews and cohort studies
51-00 citations	23	10.4%	Functional studies with wide clinical impact
0-50 citations	180	81.4%	Smaller experimental or descriptive studies

[Table/Fig-2]: Citation Metrics of ARNT2-Related Research

of 18 papers (8.18%) that have each accrued over 100 citations. This small fraction of the literature has had an outsized impact on shaping the direction of OSCC research. ARNT2 regulates tumoural growth in oral squamous cell carcinoma, study by Kimura et al. [6] is the most-cited ARNT2 article with specific relation to oral squamous cell carcinoma, whereas broader studies relating only to ARNT2 studies in cancer biology achieved citations exceeding 218 [Table/Fig-3]. [Table/Fig-3] provides the most influential research concerning the ARNT2 gene, highlighting two key publications that have significantly shaped the field. The disparity in citation counts between the two primary academic databases, Scopus and Google Scholar, is a notable feature of this data and reflects their different indexing methodologies. [Table/Fig-4] provides a critical analysis through which to view the dissemination and impact of ARNT2 research, revealing distinct patterns about where the field's knowledge is produced and which venues have published its most influential work.

Author(s)	Year	Journal	Citations (scopus)	Citations (google scholar)
Kimura et al., (OSCC)	2016	Journal of cancer	31	51
Maltepe E et al., (Broader studies)	2000	Biochemical and biophysical research communications	83	135

[Table/Fig-3]: Top-cited ARNT2 publications [6,8].

Journal name	Articles	Citations
Biochemical and biophysical research communications	9	562
Toxicological sciences	8	632
PLoS ONE	6	114
Journal of biological chemistry	5	159
Mechanisms of development	4	538
Journal of cancer	1 (notable)	33

[Table/Fig-4]: Journal-wise publication and citation distribution.

Biochemical and Biophysical Research Communications (BBRC) leads in article count [9]. This aligns with its reputation as a premier rapid communication journal for groundbreaking preliminary findings in molecular biology. The high citation count (562) suggests several of these papers were among the first to report key functions or interactions of ARNT2, making them foundational references.

Toxicological Sciences has the second-highest number of articles [10] and the highest total citation count (632). This strongly indicates that a significant and highly influential strand of ARNT2 research is rooted in toxicology, specifically its role in the Aryl Hydrocarbon Receptor (AhR) pathway. Mechanisms of Development, despite a moderate number of articles [4], boasts an exceptionally high citation count (538). This points to the existence of seminal, early papers that established ARNT2's critical role in embryonic development. PLoS ONE and Journal of Biological Chemistry (JBC) host a number of solid, impactful studies. JBC, a discipline-specific heavyweight, publishes mechanistic studies that become standard references in the field. PLoS ONE's presence reflects its role as a platform for sound, reproducible research that may be more specialised or incremental. Wang Z, Whitelaw ML, and Hahn ME are the top contributors whose works significantly shaped ARNT2 research in oral cancer [10] [Table/Fig-5].

Author	Publications	Citations
Wang Z	8	230
Whitelaw ML	7	231
Hahn ME	5	275

[Table/Fig-5]: Leading authors in ARNT2 research.

The USA leads in citation impact with 3021 cited papers, China excels in antibody development with 465 citations, and Japan pioneered early ARNT2-OSCC studies with 875 citations [Table/Fig-6].

Country	Research strengths	Notable focus
USA	Genomics, large cohort studies, therapeutics	Treatment-oriented
China	High-throughput screening, antibody development	Translational research
Japan	Early mechanistic studies, expression profiling	Molecular biology

[Table/Fig-6]: Country-wise contributions to ARNT2-OSCC research.

DISCUSSION

This bibliometric analysis provides a detailed analysis of research activities of ARNT2 in various cancer types, with emphasis on OSCC. Notably, the volume of ARNT2-related publications and citations has steadily increased since the early 2000s, with significant surges observed following pivotal functional studies. For instance, the demonstration of ARNT2's involvement in OSCC proliferation, hypoxia signaling, and metabolic regulation has likely served as a catalyst for growing interest in the field.

Data support a contextual doubleness in ARNT2's function where in describe a situation where two contrasting elements are present and their manifestation depends on the specific circumstances like in glioblastoma, ARNT2 appears to promote tumourigenicity, whereas in OSCC and other epithelial tumours, it acts as a tumour suppressor. In glioblastoma, ARNT2 knockdown in tumour stem–like cells inhibits tumourigenic properties and reduces the expression of key transcription factors such as SOX9, POU3F2, and OLIG2, thereby indicating its role in maintaining aggressiveness (glioma stemness) [11]. Conversely, in OSCC, ARNT2 mRNA and protein are significantly downregulated compared to normal oral tissues, and ARNT2 overexpression suppresses proliferation while modulating the VHL-HIF1α-GLUT1 metabolic axis [6].

Apart from oral squamous cell carcinoma, ARNT2 exerts a tumour-suppressive role in other epithelial cancers. In Non-small Cell Lung Cancer (NSCLC), higher intratumoural ARNT2 expression correlates with improved Overall Survival (OS), and functional assays demonstrate that ARNT2 overexpression induces apoptosis and inhibits tumour growth both in vitro and in-vivo [12]. Also, in hepatocellular carcinoma, ARNT2 downregulation promotes cell proliferation, invasion, and migration, whereas its overexpression attenuates these malignant features and improves survival outcomes in animal models [13]. These findings reinforce ARNT2's tumour-suppressive potential across diverse epithelial malignancies, particularly via mechanisms involving altered proliferation, metabolic suppression, and apoptosis. In OSCC, the involvement of VHL-mediated HIF1α degradation and reduced GLUT1 expression establishes a plausible metabolic basis for this suppression [5]. Geographically, research contributions are led by US institutions, with pronounced influence from Japanese and Chinese groups. Japan laid the groundwork with mechanistic and expression studies in OSCC, while the US has spearheaded translational genomics and potential therapeutic explorations. Chinese institutions increasingly contribute through screening efforts and antibody development emphasising ARNT2's integration with AhR biology and molecular regulation [10].

This analysis highlights ARNT2's potential as both a biomarker and therapeutic target in OSCC. Future research should prioritize standardised validation across labs for antibodies, establish large, prospectively collected multicentre OSCC cohorts with transcriptomic/proteomic data and clinical outcomes, ARNT2's dimerisation partnerships using cellular and molecular tools, advance to organoid systems, orthotopic xenografts, and OSCC patient-derived models, and investigate ARNT2-modulating agents, assessing effects on metabolism, hypoxia, and immune interactions [6].

Limitation(s)

Despite the insights, several limitations of ARNT2 in the present study is that the most OSCC studies involve small, single centre cohorts, limiting statistical power for survival or prognostic modelling. Discrepancies in ARNT2 detection methods like antibody clones, Immunohistochemistry (IHC) scoring thresholds also hinder synthesis across studies. OSCC research relies primarily on cell lines; advanced models such as organoids, co-cultures, and in-vivo tumour systems remain underutilised. However, few studies assess ARNT2's prognostic or predictive utility in patient cohorts or its interaction with immune infiltrate data. Also, the keyword-driven bibliometric methods may overlook relevant studies outside indexed journals or those using alternative nomenclature.

CONCLUSION(S)

In summary, the current bibliometric analysis underscores the growing significance of ARNT2 in oral cancer research, revealing its emerging role as a key regulator of tumour biology. From transcriptional control under hypoxia to metabolic regulation and apoptosis, ARNT2 influences multiple cancer-related pathways. Its consistent downregulation in OSCC and association with tumour progression highlight its potential as a diagnostic biomarker and therapeutic target. Continued research into ARNT2's mechanisms and clinical applications could pave the way for novel strategies in oral cancer management.

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