BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, Issue 12

DOI: 10.58240/1829006X-2025.21.12-227

ORIGINAL RESEARCH

HISTAMINE RECEPTORS IN ORAL CANCER: MECHANISMS, CARCINOGENESIS, AND THERAPEUTIC POSSIBILITIES – A SYSTEMATIC REVIEW

Harshkant Gharote[1], Anuroop Singhai[2], Arati Panchbhai[3],
[1]Professor, Basic and Preventive Sciences Department, General Dentistry Program, Batterjee Medical College, Jeddah - 21442, Saudi Arabia. ORCID:0000-0002-3306-4962 Email: harshkantgharote@gmail.com
[2]Associate Professor, Clinical Sciences Department, General Dentistry Program, Batterjee Medical College, Jeddah -21442, Saudi Arabia. ORCID: 0000-0002-8806-1283 Email: anuroopsinghai@gmail.com
[3]Professor, Department of Oral Medicine and Radiology, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Higher Education and Research, Sawangi, Wardha 442004, India. ORCID: 0000-0001-8871-8794
Corresponding author Dr. Anuroop Singhai, Associate Professor, Clinical Sciences Department, General Dentistry Program, Batterjee Medical College, Jeddah - 21442, Saudi Arabia. Email: anuroopsinghai@gmail.com
Received: Nov 29. 2025; **Accepted:** Dec 27, 2025; **Published:** Jan. 5, 2026

Abstract

Mast cells and their degranulation products play a key role in the pathogenesis of cancer, with histamine, being a key factor in carcinogenesis through its four distinct receptors. Research has shown that the expression of these receptors in malignant tissues triggers a variety of effects that modulate cancer cell behavior. However, there is lack of definitive evidence elucidating the precise mechanisms behind their involvement. This review aims to provide an overview of the current understanding of histamine receptors in oral carcinogenesis and highlight potential directions for future research in this field.

A literature search in Medline provided 27 articles for key terms, histamine receptors and oral cancer. Eight articles relevant to the search terms conducted studies on expression of histamine receptors in oral cancer.

The present review indicated a strong role of histamine receptors in oral carcinogenesis and suggests to generate new evidence on high scales. Therapeutic interventions employed in the form of inhibitors for these receptors may provide a promising breakthrough in cancer management.

Key words: Histamine receptors, oral cancer, carcinogenesis, therapeutic outcome

INTRODUCTION

Oral cancer, the most common form in the head and neck region, has high mortality and early metastasis due to late detection and diagnosis. Younger population being at higher risk of oral cancer, it has become a serious public health concern ranking at number six in global cancer burden. The percentage of 5-year survival varies from 40-50% in oral malignancies. Currently, it is revealed that not only tumor cell itself, but also the tumor microenvironment plays a role in growth and survival of cancer cells. Immune cells like mast cells and macrophages found in tumor microenvironment, can secrete several cytokines, chemokines, growth factors and enzymes.[1,2]

Expressions of mast cells in the tumor microenvironment of oral cancer have underlined their role as a principal player in the pathogenesis of oral cancer.[3,4] Various enzymes and bioactive molecules in mast cells are found to be participating in the pathophysiology of oral cancer. Histamine, one of the active cellular molecules, has been studied over a few decades for its role in various physiological and pathological processes, including immune responses, inflammation, and regulation of gastric acid secretion. It can modulate cell proliferation and modulation of different normal and tumorous tissues.[5,6] Its effects are mediated through four distinct receptors labelled as H1R through H4R, each playing a role in different cellular and tissue responses. Moreover, histamine has highly drawn the attention due to its implications in cancer development and metastasis. Recent studies have highlighted the significance of histamine and its receptors in carcinogenesis of various cancers including oral squamous cell carcinoma (OSCC).[7,8]

The literature reveals that the H1 receptor has been associated with advanced stages of tumor and may be implicated in the promotion of oral carcinogenesis while H2 receptor shows overexpression.[9] Nonetheless, little is known about the role of histamine and its receptors in

OSCC, although few studies with limited sample sizes and a lack of animal studies to generate evidence for expression of histamine receptors in oral cancer.[8, 10] This review explores the literature contemplating objectives like molecular mechanisms of histamine receptor signaling, their interactions with carcinogens, and potential therapeutic implications, elucidating the findings from the published data on oral cancer.

MATERIAL AND METHODS

This systematic review refers to PRISMA guideline following searches from Medline/PubMed, ScienceDirect, and EBSCOhost using advanced search features with keywords based on Medical Subject Headings (MeSH) guideline with predetermined screening and eligibility criteria.

Search strategy

A research question was formulated as follows: do histamine receptors play potential role in the pathogenesis of oral cancer? To address the research question, an extensive search was conducted on Medline/PubMed, ScienceDirect and EBSCOhost using the terms “histamine receptors” and “oral cancer.” The search, guided by MeSH terms, revealed a comprehensive set of search words: ("receptors, histamine"[MeSH Terms] OR ("receptors"[All Fields] AND "histamine"[All Fields]) OR "histamine receptors"[All Fields] OR ("histamine"[All Fields] AND "receptors"[All Fields])) AND ("mouth neoplasms"[MeSH Terms] OR ("mouth"[All Fields] AND "neoplasms"[All Fields]) OR "mouth neoplasms"[All Fields] OR ("oral"[All Fields] AND "cancer"[All Fields]) OR "oral cancer"[All Fields]). A total of 27 articles were initially identified in Medline while two articles appeared in EBSCOhost.

Screening process

All the 27 articles were read carefully for language, full-text availability and specific for the research question. After thoroughly reviewing the abstracts to recognize the relevance of the search terms, eight articles were ultimately selected for inclusion in the review. The excluded articles comprised of three reviews, 16 studies were regarding other malignancies (e. g. colorectal, bladder and pancreatic cancers) and on allergic and inflammatory responses towards the histamine receptors (Figure 1).

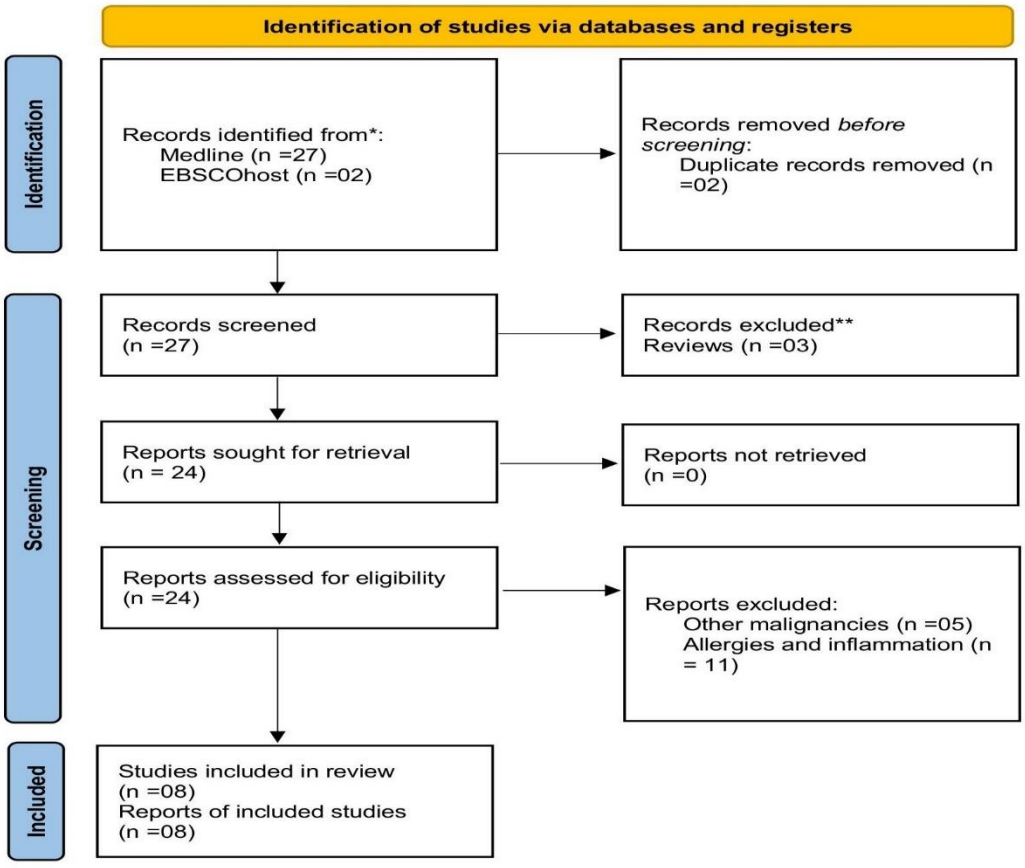

Figure 1 Flowchart illustrating the sequence of article selections for the review

RESULTS

The selected eight articles were read carefully to identify the details about the studies conducted on various histamine receptors in oral cancer. Five studies included oral squamous cell carcinoma [11-15] while one study was particularly about OSCC involving tongue.[16] Two studies were conducted on evaluation of photodynamic treatment in context to histamine receptors. [17, 18] The main objectives, findings, and inferences from each study to provide a clear overview of the Histamine receptors related oral cancer research and/or treatment were summarized (Table 1).

Table 1: Summary of the key inferences from the studies included in the review

Author	Key Findings	Inference
Ding et al. (2022)[11]	H1R gene polymorphism is associated with lower risk of developing advanced tumor stages in betel-quid-chewing patients.	H1R genetic variants may influence tumor progression, with gene morphism linked to the tumor size and clinical staging.
Kimura et al. (2022)[12]	Histamine receptors co-expressed with chemokine ligands. Tumor depth invasion affected histamine expression	Histamine influenced tongue SCC through histamine receptors and chemokines affecting tumor microenvironment.
Kon et al. (2022)[13]	Effect of epigallocatechin gallate on histamine receptors in four oral cancer cell lines.	There was stimulation of histamine production and decreased H1R expression in those cell line.
Salem et al. (2017)[16]	H4R expression was reduced in tongue SCC and oral epithelial dysplasia.	Possible association between HR and oral carcinogenesis through histamine-mediated factors in the regulation of oncogenes.
Parihar et al. (2013)[18]	Confirmation of histamine receptor over-expression in tumor mass. Photodynamic treatment led to regression of tumors up to 1000 mm^3.	Conjugating histamine to chlorin can improve tumor targeting and enhance Photodynamic treatment efficacy in oral cancer.
Grimm et al. (2013)[14]	H1R expression was rare in OSCC but associated with advanced tumor stages. Patients with H1R expression had poorer disease-free survival.	H1R may serve as a prognostic marker for OSCC, with higher expression linked to poorer survival outcomes. Activation of H1R may promote carcinogenesis in OSCC.
Parihar et al. (2011)[17]	Cp6-histamine showed 10x higher cellular uptake than Cp6, with higher phototoxicity in oral cancer cell lines.	Conjugating Cp6 with histamine enhances its uptake and phototoxicity, making it a promising approach for improving PDT in oral cancer.
Arai et al. (2002)[15]	Both bradykinin and histamine enhanced calcium ion influx, but only histamine's effect was inhibited by H1 receptor antagonists.	Histamine activates calcium influx in oral cancer cells through H1 receptors, which may play a role in tumor progression.

DISCUSSION

Histamine is a biogenic amine that plays a crucial role in various physiological processes, including immune responses, allergic reactions, and neurotransmission. It exerts its effects through binding to four types of receptors: H1, H2, H3, and H4. These receptors are G protein-coupled receptors found on various cell types, including those within the oral cavity. Recent research highlights the involvement of histamine receptors in the pathophysiology of oral cancer, especially OSCC, with significant implications for cancer development, progression, and potential therapeutic strategies.[6,8,9]

Molecular Mechanisms of Histamine Receptor Signalling:

The key aspects of molecular mechanisms of these receptors in cancer, specifically in relevance to OSCC, are as following:

H1 Receptor is principally involved in mediating allergic responses but also plays a significant role in cell proliferation, migration, and inflammation in cancer. Histamine activation of the H1 receptor has been linked to the regulation of signaling pathways such as PI3K/Akt and MAPK, both of which are involved in promoting tumor growth and metastasis.[14] H1 receptor activation has been associated with increased vascular permeability and immune cell infiltration, which can facilitate tumor progression.[8,16] In OSCC, H1 receptor expression has been correlated with poor prognosis, suggesting its potential as a prognostic marker.[14]

H2 Receptor is known for its role in gastric acid secretion, but in cancer, it has been implicated in immune modulation and cell survival. Histamine

signaling through the H2 receptor can inhibit apoptosis and promote tumor cell survival through activation of the cAMP-PKA pathway.[8,10] Studies suggest that the H2 receptor contributes to immune evasion by modulating the activity of immune cells, such as T-cells and macrophages, within the tumor microenvironment.[12]

H3 Receptors are primarily involved in the regulation of neurotransmitter release and regulates the synthesis and release of histamine, have also been found to play a role in tumor biology. Although not studied in the context of OSCC, evidences suggest that H3 receptor is expressed in numerous types of tumors and is associated with tumor cell proliferation, migration and invasion. [19,20]

H4 Receptor is expressed on immune cells, has emerged as a critical regulator in inflammation and immune responses within the tumor microenvironment. In OSCC, H4 receptor signaling has been shown to promote tumor progression by facilitating immune cell recruitment and influencing angiogenesis. To be precise, H4R signaling enhances the inflammatory milieu, which may facilitate the development and progression of OSCC.[16]

Interactions Between Histamine Receptors and Carcinogens

Histamine receptors, especially the H1 and H4 subtypes, are involved in the cellular response to carcinogenic agents, particularly environmental and chemical carcinogens. One of the key factors influencing oral carcinogenesis is the exposure to environmental carcinogens, such as tobacco smoke, alcohol, and certain occupational chemicals.

Histamine and Environmental Carcinogens*:* Ding et al.[11] examined the combined effects of histamine receptor H1 gene polymorphisms and exposure to environmental carcinogens on OSCC susceptibility. Their findings indicate that genetic variations in the H1 receptor may modulate the response to carcinogen exposure, thereby influencing tumor development. This suggests that histamine receptor genetic polymorphisms may serve as potential biomarkers for OSCC risk and progression, particularly in individuals exposed to carcinogens.[11]

Histamine and Tumor Microenvironment*:* Kimura et al.[12] explored the role of histamine in modulating the chemokine balance in the tumor microenvironment of squamous cell carcinoma of the tongue. Histamine released in response to tumor-induced inflammation may alter the immune cell composition within the tumor, enhancing tumor cell survival and metastasis. Histamine's ability to influence chemokine production and immune responses underscores its potential as a therapeutic target in managing OSCC progression.[12]

Epigallocatechin Gallate (EGCG) and Histamine: Kon et al.[13] studied the effects of EGCG, a compound found in green tea, on histamine production and histamine receptor expression in oral cancer cell lines. EGCG was found to stimulate histamine production and downregulate the H1 receptor, which could alter the response of OSCC cells to external stimuli. This finding suggests that dietary compounds such as EGCG might modulate histamine receptor expression and contribute to oral cancer prevention or therapy.[13]

Therapeutic Implications of Histamine Receptor Modulation

The involvement of histamine receptors in OSCC may provide novel opportunities for therapeutic interventions. Both receptor antagonists and agonists have potential roles in the treatment of OSCC.

Histamine Receptor Antagonists*:* Targeting histamine receptors with specific antagonists could mitigate tumor growth and metastasis. For instance, H1 receptor antagonists could reduce tumor-associated inflammation and prevent immune cell infiltration, potentially improving the therapeutic outcomes in OSCC patients. H2 receptor antagonists, commonly used for gastric acid disorders, might be repurposed to target immune modulation in the tumor microenvironment, enhancing anti-tumor immunity.[8,16]

Photodynamic Therapy with Histamine Conjugates: Parihar et al. explored the use of chlorin p6-histamine conjugates in photodynamic therapy (PDT) for OSCC. By enhancing cellular uptake and phototoxicity, these conjugates may offer a novel therapeutic strategy. The conjugation of histamine to a photosensitizer could increase the selectivity and efficacy of PDT, particularly in targeting cancer cells that overexpress histamine receptors.[17,18]

Histamine and Immune Modulation*:* The potential of histamine receptor modulation in enhancing anti-cancer immune responses is another promising avenue for OSCC therapy. Perhaps, H4 receptor antagonists may offer a strategy for controlling inflammation and modulating the tumor immune scenario, making it more responsive to immunotherapies.[16]

In summary, histamine receptors, predominantly H1, H2, and H4, play multifaceted roles in oral cancer progression. They influence tumor cell behavior, immune cell modulation, and therapeutic efficacy. Genetic variations in histamine receptor genes, histamine receptor expression in the tumor microenvironment, and receptor-targeted therapies offer promising strategies for improving the management of oral cancers, highlighting the importance of histamine signaling in the pathogenesis and treatment of OSCC and possibly head and neck related malignancies.

CONCLUSION

Histamine receptors play a crucial role in the molecular mechanisms in pathogenesis of OSCC, particularly in the regulation of tumor growth, immune and environmental carcinogenic responses. It was found that H1, H2, and H4 receptors are involved in various signaling pathways that influence tumor progression,

making them potential therapeutic targets. Further research into histamine receptor genetics, their interactions with various carcinogens, and the development of receptor-specific therapies will be essential in advancing the treatment and prevention of OSCC. The modulation of histamine receptors, either through their antagonists, agonists, or coupled therapies, embraces promise for improvement in patient outcomes and providing novel treatment opportunities in the fight against oral cancer.

DECLARATIOM

Conflict of interest:

Authors declare that there is no conflict of interest

Source of funding:

There are no funds procured

Author Contribution:

All authors have contributed substantially to the manuscript and all have reviewed the final manuscript

REFERENCES

1. Afriza D, Bakar A, Pratiwi Y, Surya LS. Distribution of Oral Cancer Types in West Sumatra, Indonesia: a Cross-sectional Study. (J Int Dent Med Res 2024; 17(3): 1214-1221.
2. Pugdee K, Wongpattaraworakul W, Hitakomate E. Role of Tumor-Associated Macrophages on Cathepsin-B, Cathepsin-D, MMP-2, and MMP-9 in HSC-3 Oral Cancer Cells. J Int Dent Med Res 2021; 14(1): 156-162.
3. Tranby EP, Heaton LJ, Tomar SL, et al. Oral Cancer Prevalence, Mortality, and Costs in Medicaid and Commercial Insurance Claims Data. Cancer Epidemiol Biomarkers Prev. 2022;31(9):1849-1857.
4. Hasan NR, Dehuri P, Jena A, Kanungo S. A Correlation of Serum Histamine and Mast Cell Count with the Established Prognosticators in Oral Cancer. J Microsc Ultrastruct. 2023;11(2):97-102. doi:10.4103/jmau.jmau_138_20
5. Gudiseva S, Santosh ABR, Chitturi R, Anumula V, Poosarla C, Baddam VRR. The Role of Mast Cells in Oral Squamous Cell Carcinoma. Contemp Oncol (Pozn). 2017;21(1):21-29. doi:10.5114/wo.2017.65157
6. Sarasola MP, Táquez Delgado MA, Nicoud MB, Medina VA. Histamine in cancer immunology and immunotherapy. Current status and new perspectives. Pharmacol Res Perspect. 2021;9(5):e00778. doi:10.1002/prp2.778
7. Nguyen PL, Cho J. Pathophysiological Roles of Histamine Receptors in Cancer Progression: Implications and Perspectives as Potential Molecular Targets. Biomolecules. 2021;11(8):1232. doi:10.3390/biom11081232
8. Salem A, Salo T. Nothing to sneeze at: Histamine and Histamine Receptors in Oral Carcinogenesis. Oral Dis. 2021;27(5):1090-1096. doi:10.1111/odi.13411
9. Massari NA, Nicoud MB, Medina VA. Histamine receptors and cancer pharmacology: an update. Br J Pharmacol. 2020;177(3):516-538. doi:10.1111/bph.14535
10. Salem A, Salo T. Commentary: Pathophysiological Role of Histamine H4 Receptor in Cancer: Therapeutic Implications. Front Pharmacol. 2020;11:874. doi:10.3389/fphar.2020.00874
11. Ding YF, Lin YW, Chiu WK, et al. Combined impacts of histamine receptor H1 gene polymorphisms and an environmental carcinogen on the susceptibility to and progression of oral squamous cell carcinoma. Aging (Albany NY). 2022;14(10):4500-4512.
12. Kimura S, Noguchi H, Yoshida K, et al. Relationship of histamine expression with chemokine balance in the tumor microenvironment of squamous cell carcinoma of the tongue. Head Neck. 2022;44(7):1554-1562. doi:10.1002/hed.27056
13. Kon M, Ishikawa T, Ohashi Y, Yamada H, Ogasawara M. Epigallocatechin gallate stimulated histamine production and downregulated histamine H1 receptor in oral cancer cell lines expressing histidine decarboxylase. J Oral Biosci. 2022;64(1):120-130. doi:10.1016/j.job.2022.01.003
14. Grimm M, Krimmel M, Alexander D, et al. Prognostic value of histamine H1 receptor expression in oral squamous cell carcinoma. Clin Oral Investig. 2013;17(3):949-955.
15. Arai T, Matsumoto H, Akimoto Y, Nishimura H, Ono M, Fujii A. Behavior of HO-1-N-1, buccal mucosa carcinoma derived cells, on [Ca2+]i responses to stimulants. J Oral Sci. 2002;44(2):103-108. doi:10.2334/josnusd.44.103
16. Salem A, Almahmoudi R, Listyarifah D, et al. Histamine H_4 receptor signalling in tongue cancer and its potential role in oral carcinogenesis - a short report. Cell Oncol (Dordr). 2017;40(6):621-630.
17. Parihar A, Dube A, Gupta PK. Conjugation of chlorin p(6) to histamine enhances its cellular uptake and phototoxicity in oral cancer cells. Cancer Chemother Pharmacol. 2011;68(2):359-369.
18. Parihar A, Dube A, Gupta PK. Photodynamic treatment of oral squamous cell carcinoma in hamster cheek pouch model using chlorin p6-histamine conjugate. Photodiagnosis Photodyn Ther. 2013;10(1):79-86.
19. Lin JJ, Zhao TZ, Cai WK, et al. Inhibition of histamine receptor 3 suppresses glioblastoma tumor growth, invasion, and epithelial-to-mesenchymal transition. Oncotarget. 2015;6(19):17107-17120.
20. Chen J, Hu XY. Inhibition of histamine receptor H3R suppresses prostate cancer growth, invasion and increases apoptosis via the AR pathway. Oncol Lett.2018;16(4):4921-4928. doi:10.3892/ol.2018.9310