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Histamine H_1 Receptor Antagonists in Cancer: Mechanisms, Clinical Evidence, and Therapeutic Potential

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Abstract

Histamine signaling through the histamine H_1 receptor (H_1R) plays a significant role in cancer biology. H_1R is often overexpressed various malignancies and contributes to proliferation, invasion, angiogenesis and evasion of the immune system. Given the widespread use of H_1 antihistamines in the treatment of allergic diseases, there is a growing interest in incorporating these agents as anticancer therapy. Preclinical studies have demonstrated a role for H_1- antagonists in apoptosis, pyroptosis, lysosomal destabilization, and reversal of multidrug resistance, as well as in enhancing chemotherapy and immunotherapy efficacy. Specific agents such as loratadine, desloratadine, and cyproheptadine have demonstrated survival benefits in breast, ovarian, lung, and hepatocellular cancers but the evidence is inconsistent. This inconsistency could be attributed to dosing, drug class, target tumor and study design. First-generation antihistamines show strong mechanistic activity but limited tolerability. In contrast second- and third-generation drugs are safer but require higher doses than usual therapeutic ranges. Although H_1 antihistamines have demonstrated several mechanisms that can be utilized for therapeutic purposes in oncology, sufficient randomized clinical trials and clinical evidence have yet to emerge. Crucial questions for clinical application such as defining optimal agents, dosing strategies, and synergistic combinations with chemotherapy or immunotherapy, are not yet fully answered.

Key Words: Antihistamines, Cancer therapy, Drug repurposing, Histamine H_1 receptor.

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1- INTRODUCTION

Histamine and its receptors, particularly the histamine H1 receptor (H1R), have been detected in cancer progression. Clinical studies indicate that not only is H1R expressed in a variety of malignancies such as breast, ovarian, pancreatic, and liver cancers, but it also appears to correlate with poorer prognosis and reduced survival (1-4). These results have sparked interest in H1-antihistamines as potential novel therapies in oncology (5).

Blocking H1R has been reported to have antitumor properties in several experimental studies. Preclinical studies suggest that drugs such as Loratadine and Astemizole can destabilize lysosomes, reverse multidrug resistance, and sensitize tumors to chemotherapy (5). Loratadine has also been shown to induce apoptosis and pyroptosis in lung cancer cells (6). In hepatocellular carcinoma, the simultaneous use of Cyproheptadine with Sorafenib has significantly increased survival (7). These findings suggest the possibility that H1-antagonists may act not only on tumor cells but also on the tumor microenvironment, inducing angiogenesis and immune responses (8, 9).

Clinical evidence, however, remains inconsistent. Some large cohort studies suggest that the use of Loratadine and Desloratadine after cancer diagnosis is related to improved survival in breast, ovarian, and lung cancers (1, 3), and Cyproheptadine use has been associated with favorable outcomes in hepatocellular carcinoma (7). Contrary to these studies, others report inconsistent results, depending on tumor type and the specific H1-antagonist used (4). Differences in study design, exposure definitions, and adjustments for confounding factors further contribute to heterogeneity. For instance, Cetirizine appears to improve immunotherapy efficacy in melanoma (8), though such effects were not consistently observed in other studies (4).

Despite promising preclinical data and suggestive biological pathways, the clinical evidence remains incomplete. Therefore, in this review we seek to summarize mechanistic insights, evaluate both preclinical and clinical evidence, discuss current challenges, and consider how H1-antihistamines might eventually be incorporated into clinical practical guidelines.

2-1. H1 Receptors and Cancer Biology

H1R is a G-protein–coupled receptor traditionally recognized for its role in allergic responses and inflammation. Recent evidence, however, points to a significant role in cancer biology. Upon activation, H1R triggers multiple signaling cascades that can promote tumor progression, both through direct effects on cancer cells and by modulating the tumor microenvironment (TME) (10, 11).

As shown in Table 1, H1R expression varies significantly across different cancer types, with consistent upregulation observed in several malignancies.

2-1-2. Molecular Mechanisms of H1R in Tumor Growth

Activation of H1R causes tumor growth via cellular mechanisms that depend on proliferation, survival, and invasion. For instance, in hepatocellular carcinoma, H1R signaling drives cell cycle progression through the cyclic AMP-dependent protein kinase A (cAMP–PKA) pathway. This not only suppresses apoptosis and increases pro-survival signaling but also facilitates invasive behaviors, including lamellipodia formation and increased matrix metalloproteinase-2 (MMP2) production, thereby promoting tumor cell invasion (12).

In oral squamous cell carcinoma, H_1R has been implicated in epithelial-to-mesenchymal transition (EMT). Specifically, a cyclic HRH1/ADAM9/Snail axis promotes EMT and metastasis. Interestingly, compensatory activation of STAT3 signaling can limit the efficacy of H_1R blockade alone, whereas combined inhibition of H_1R and STAT3 appears to produce synergistic antitumor effects, highlighting the importance of pathway crosstalk in H_1R-driven tumor progression (13).

Furthermore, H_1R activates several canonical signaling modules-including protein kinase C, MAPK/ERK, and NF-κB pathways. Although the downstream effects vary depending on cellular context, they consistently contribute to tumor proliferation, invasion, and remodeling of the microenvironment (9, 15). Altogether, these findings indicate that H_1R functions as a critical promoter of tumor progression through multiple proliferative and survival pathways, posing as a potential therapeutic target across various malignancies.

H_1R also appears to promote angiogenesis. In endothelial cells, H_1R activates the PKC–ERK1/2 cascade, upregulating c-Fos/AP-1 and cyclin D1 to stimulate proliferation and neovascular growth (16). Additionally, it improves vascular remodeling in the tumor microenvironment by increasing VEGF and MMP release (11, 17). These processes integrate with tumor metabolic reprogramming to further support angiogenesis.

Given this preclinical evidence of H_1R's pro-angiogenic and tumor-promoting roles, investigating H_1R antagonists as potential anticancer agents is a logical next step (12). This leads us to examine retrospective and epidemiologic studies that assess the impact of H_1-antihistamines on tumor growth and patient survival, providing clinical context to the mechanistic findings.

Table-1. Cancer Type-Specific H_1R Expression.

Cancer Type	Expression Pattern	Clinical Correlation
Hepatocellular Carcinoma (HCC)	Frequently upregulated in tumor cells	Associated with shorter recurrence-free and overall survival (12)
Oral Squamous Cell Carcinoma (OSCC)	Elevated in tumor cells with regional spread	Correlates with lymph node metastasis and poor prognosis (13)
Glioblastoma (GBM)	Increased in tumors and TME	Associated with worse overall and progression-free survival (11)
Pancreatic Ductal Adenocarcinoma (PDAC)	Expressed in cancer cells and TME	Negatively correlates with MHC-I and CD8+ T cell infiltration (14)

2-2. H_1R Antagonist Drugs and Their Effects on Tumor Growth

Several H_1-antihistamines have been studied for their anticancer properties. Large retrospective and epidemiologic analyses have identified commonly studied agents and their signaling impacts in cancer cohorts. In a cohort study by Olsson et al., Cetirizine, Clemastine, Desloratadine, Ebastine, Fexofenadine, and Loratadine, with peri-diagnostic use of Desloratadine and Ebastine, showed a favorable survival rate in breast cancer, while outcomes for other drugs indicated mixed results (18). Further studies have focused particularly on Loratadine and Desloratadine and also note Cetirizine, Fexofenadine, Terfenadine and Diphenhydramine in preclinical settings (18, 19). These reports are summarized in Table 2.

Table-2. Overview of first-, second-, and third-generation H_1-antihistamines evaluated for anticancer activity, highlighting key preclinical mechanisms (e.g., apoptosis induction, lysosomal disruption, receptor blockade) and available clinical or epidemiologic signals related to cancer outcomes.

Drug	Key preclinical mechanism(s)	Clinical/epidemiologic signal
Cetirizine	Mast-cell stabilization, H1 blockade (in vitro)	Included in national cohort analyses; mixed signals across tumor types (18, 20)
Loratadine	Induces apoptosis/pyroptosis via PPARγ / caspase-8 / GSDMD (in vitro & in vivo)	Associated with improved survival in several cancer cohorts and dose-dependent signal in lung cancer analyses (6, 19)
Desloratadine	H1 blockade (active metabolite family)	Positive survival association in breast-cancer registry analysis (18)
Diphenhydramine (DPH)	Inhibits Hv1 proton channels; downregulates STAT3→MCL-1; proapoptotic in melanoma models (in vitro & in vivo)	Preclinical antitumor efficacy; repurposing interest (10, 21)
Terfenadine	Induces apoptosis via caspase-8/Bid; suppressed tumor growth in xenografts (in vitro & in vivo)	Strong preclinical cytotoxicity but clinical cardiotoxicity historically limits use; repurposing discussed in reviews (12, 22)
Fexofenadine	Studied epidemiologically; limited positive associations reported	No consistent survival signal in some analyses (18)

Population-based studies and small clinical cohorts suggest that H_1-antagonist use may be associated with improved survival outcomes. In Danish registry data, Loratadine use significantly lowered all-cause mortality among patients with non-localized NSCLC and other cancers. Astemizole showed a similar effect, while Ebastine demonstrated a weaker but consistent trend. Interestingly, the benefit appeared most prominent in patients receiving concurrent chemotherapy, supporting preclinical findings of chemosensitization (5). In ovarian cancer, the use of cationic amphiphilic (CAD) antihistamines was associated with reduced cancer-related mortality (HR 0.63, 95% CI 0.40–0.99) compared with non-CAD users, with some evidence of a dose-response relationship. Complementary in vitro studies further demonstrated consistent, dose-dependent cytotoxicity across ovarian cancer cell lines treated with CAD, however not with non-CAD antihistamines (23). In hepatocellular carcinoma, a hospital-based cohort showed that simultaneous cyproheptadine and sorafenib nearly doubled median overall survival (11.0 vs. 4.8 months) and quadrupled progression-free survival (7.5 vs. 1.7 months), with multivariate analysis confirming significantly reduced risks of mortality (HR=0.24) and progression (HR=0.18) (7).

2-2-1. Mechanisms of H_1 Blockade

Blocking HRH_1 can affect both tumor cells and the tumor microenvironment through receptor-related and receptor-unrelated mechanisms. H_1R is frequently upregulated in several cancers and contributes to tumor proliferation, migration, and survival by activating intracellular signaling pathways such as cAMP–PKA, as well as regulating MMPs and cell-cycle progression. Pharmacologic H_1R blockade has been shown to reverse these tumorigenic effects in experimental

models (12). In hepatocellular carcinoma, H_1R overexpression promoted cell growth, lamellipodia formation, MMP-2 production, cell-cycle progression, and apoptosis suppression; inhibition with Terfenadine reduced tumor growth in xenograft models (12). In both preclinical and clinical contexts, CAD drugs with H_1-antagonist activity sensitized tumor cells to chemotherapy and breached multidrug resistance. Sub-micromolar concentrations of Loratadine, Astemizole, and Ebastine enhanced chemotherapy efficacy in NSCLC, breast, and prostate cancer, reinforcing the notion that H_1R antagonists can act synergistically with cytotoxic therapies to overcome resistance mechanisms (5).

Molecular mechanisms also include suppression of the STAT3–MCL-1 survival axis. Diphenhydramine attenuated phospho-STAT3 (Tyr705), downregulated anti-apoptotic MCL-1, and induced apoptosis in melanoma cells, thereby impeding B16-F10 tumor growth in mice (10).

H1 inhibition has also been shown to affect ion transport, as Diphenhydramine inhibited Hv1 proton channel currents in leukemic Jurkat cells, causing intracellular acidification and apoptosis through an H1-independent pathway (21). Similarly, Terfenadine activated the caspase-8/Bid cascade, leading to downstream caspase-3 and PARP cleavage in oral cancer cells (22). Furthermore, Loratadine provided a distinct mechanism in lung cancer, where it upregulated PPARγ, promoted gasdermin D transcription, and enhanced caspase-8 activation, inducing apoptosis and pyroptosis dose-dependently (6).

Beyond direct tumor cell effects, H1 antagonists can relieve histamine-mediated immunosuppression in the tumor microenvironment, specifically by reversing CD8+ T-cell inhibition, suggesting potential synergy with checkpoint blockade immunotherapies (15, 24). Overall, these studies highlight the diverse mechanisms through which H1 antagonists apply antitumor activity, spanning direct cytotoxicity, apoptosis, metabolic disruption, and immune modulation (6, 10, 12, 15, 21, 22, 24).

2-2-2. Dosing Considerations and Safety

Clinical dosing of H1 antagonists is not established in randomized trials for oncological use, and safety remains guided by standard antihistamine pharmacology. First-generation agents such as Diphenhydramine have broad CNS and off-label effects, while second- and third-generation drugs (Cetirizine, Loratadine, Desloratadine, Fexofenadine) affect more peripherally and are better tolerated, making them more suitable for chronic adjunctive use in oncology (25). Terfenadine shows strong preclinical antitumor activity but its cardiotoxicity (QT prolongation) limits chronic use unless safer analogues are developed (12, 22). Human anticancer dosing remains undefined, as effective concentrations suggested in the preclinical settings often exceeded standard doses, precluding off-label recommendations (6, 10, 21, 22). Potential interactions with chemotherapy, QT-prolongation in specific drugs, and immunotherapies require exhaustive evaluation, and the current reviews stresses the need for randomized clinical trials to establish efficacy and safe dosing (4, 24). Inclusion in clinical guidelines will depend on early-phase studies evaluating cardiac effects.

3- LIMITATIONS

The current evidence supporting the anticancer role of H_1-antihistamines is limited due to the lack of randomized clinical trials and the predominance of retrospective or observational studies. The heterogeneity across study designs, variable patient sample sizes, cancer types, dosing strategies, and outcome measures

further complicates interpretation. Additionally, many preclinical studies rely on concentrations that exceed standard therapeutic ranges, raising questions about clinical translatability. These factors collectively limit the strength of current conclusions and underscore the need for more rigorous, controlled investigations.

4- FUTURE DIRECTIONS

Future research should focus on reaffirming the therapeutic potential of H1-antihistamines in oncology through well-designed clinical trials. Comparative studies are needed to determine which agents have the greatest anticancer efficacy and to establish dosing strategies that balance safety with therapeutic benefit. Preclinical work should continue dissecting receptor-related and receptor-unrelated mechanisms, identifying biomarkers that predict response based on H1R expression, tumor type, and molecular profile. Given promising evidence of synergy with chemotherapy and immunotherapy, upcoming trials should prioritize rational combination strategies. Additionally, the development of novel analogues or safer derivatives of potent but cardiotoxic agents may broaden therapeutic options. Collectively, these efforts will clarify whether H1-antihistamines can be repurposed as cost-effective and accessible adjuncts in cancer therapy.

5- CONCLUSION

H1R signaling promotes tumor progression by driving cell proliferation, angiogenesis, and immune suppression. This makes H1-antagonists (antihistamines) promising candidates for cancer drug repurposing, supported by strong preclinical data and some clinical associations. However, the evidence remains inconsistent. While the desire for drug repurposing is justified by their accessibility and established safety in allergy treatment, incorporation into oncology requires further validation. Evaluating optimal drugs, dosing regimens, and combination strategies will be essential to unlock the potential of H1-antagonists as adjunctive therapies in cancer therapy.

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