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Antihistamines: Beyond just allergy treatment

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Abstract:

Histamine and its receptors (H1R-H4R) are involved in several significant physiological processes and pathogenic conditions. Antihistamines, widely recognised as drugs for treating allergies, belong to the H1 antihistamine group, which targets H1R on endothelial cells, smooth muscle cells, and immune cells to alleviate allergic symptoms. Less well-known are H2 antihistamines and H3 antihistamines, which have been developed and approved for treating gastric acid diseases and narcolepsy, respectively. Preclinical and clinical studies have demonstrated the efficacy of numerous H1 and H2 antihistamines, which have been approved for clinical use with specific indications, in addressing viral infectious diseases, cancer, and multiple sclerosis. The low prices and established safety profiles of these antihistamines over the past decades position them as promising candidates for addressing these conditions, which still lack effective and affordable treatments. Accelerating clinical trials and licensing procedures is essential to introduce antihistamines with their novel applications to the market. This review emphasises the critical roles of histamine and its receptors in various biological processes, discusses the current clinical uses of antihistamines, and explores repurposing antihistamines for novel medical indications.

Keywords: **antihistamine, cancer, histamine, histamine receptor, infection, multiple sclerosis.**

Classification numbers: **3.2, 3.6**

1. Introduction

Histamine, a biogenic amine, is primarily produced and secreted by mast cells, basophils, gastric enterochromaffin-like cells, and histaminergic neurons via exocytosis [1]. This molecule plays a pivotal role in regulating various physiological and pathophysiological processes by engaging four distinct receptors known as H1R, H2R, H3R, and H4R (histamine receptors 1-4) [1]. Targeting histamine receptors to modulate cellular activities in pathogenic conditions has been applied for several decades. Several antihistamines have received clinical authorisation, with H1R antihistamines used for treating allergies, H2R antihistamines for acid peptic diseases, and H3R antihistamines for narcolepsy with and without cataplexy.

Drug discovery is a lengthy process with a significantly high cost and a meagre success rate of less than 1%. Drug repurposing, which involves finding new clinical uses for FDA-approved drugs, is highlighted as a shortcut path to replace conventional high-risk drug development [2]. The prolonged historical use of antihistamines in clinics since 1946, coupled with their low cost and excellent safety profiles, makes them outstanding candidates for repurposing to treat pathological conditions in need of effective and accessible treatments. Recent studies have shown that numerous H1 and H2 antihistamines could be repurposed to address other diseases, including cancer, viral infectious diseases, and multiple sclerosis [3-6]. In this review, we provide comprehensive insights into the biology of histamine and its receptors, delve into the approved indications of antihistamines, and explore their promising potential for novel clinical applications beyond their conventional uses. We also discuss the underlying mechanisms by which antihistamines drive their therapeutic effects and their potential to be approved for treating cancer, viral infectious diseases, and multiple sclerosis.

2. Histamine

Histamine (2-(1H-imidazol-4-yl)ethanamine) was first chemically synthesised by A. Windaus, et al. (1907) [1], derived from the amino acid histidine through a decarboxylation reaction. Three years later, H.H. Dale, et al. (1910) [2] revealed its biological function as an autocoid causing smooth muscle contraction. In 1920, a researcher reported another function of histamine in promoting gastric acid secretion. Histamine has only been considered a natural constituent of the body since it was isolated from lung and liver tissues in 1927 [7]. Over the past century, extensive research has demonstrated the pivotal roles of histamine in regulating numerous physiological and pathophysiological processes. In the body, histamine is synthesised with the catalysis of the L-histidine decarboxylase (HDC) enzyme. It is primarily produced by mast cells, basophils, gastric enterochromaffin-like cells in the gastric mucosa, and

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histaminergic neurons in the posterior hypothalamus, known as professional histamine-producing cells [3]. Histamine is also produced by nonprofessional histamine-producing cells, such as dendritic cells, T cells, macrophages, neutrophils, and epithelial cells, in response to external allergic or nonallergic inflammatory stimuli [3-5].

Histamine plays a vital role as a mediator, modulating numerous physiological processes in the body. First, it actively contributes to the immune system's defence against pathogens through various mechanisms. Histamine stimulates mucus secretion in the human airway, providing a protective barrier against pathogen invasion [6]. Additionally, it induces smooth muscle contraction, promoting pathogen expulsion from the gastrointestinal or respiratory tract through actions such as vomiting or coughing [7]. Histamine also enhances vascular permeability and vasodilation, facilitating the recruitment of immune cells to the infected site for effective pathogen elimination [7]. Moreover, histamine regulates the maturation, activation, polarisation, effector function, and migration of various immune cells [8]. Second, histamine acts as an essential contributor to gastric acid secretion by parietal cells in response to gastrin stimulation, facilitating effective food digestion in the stomach [9]. Third, histamine plays an essential role in the neurotransmission of the central nervous system, acting both as a neurotransmitter itself and as a modulator of other neurotransmitters, thereby regulating various brain functions [10]. Conversely, histamine also mediates multiple pathophysiological conditions. For instance, histamine serves as a crucial mediator in several allergic diseases, including asthma, atopic dermatitis, chronic urticaria, allergic rhinitis, and chronic pruritus. Excessive histamine release in the stomach can lead to increased acid secretion, resulting in gastric ulcers. Abnormal histamine levels in the brain have been associated with neurological and psychiatric diseases. Overall, histamine's intricate and multifaceted role in both physiological regulation and the pathogenesis of various conditions underscores its importance as a key player in numerous biological processes.

3. Histamine receptors and their signalling pathways

Histamine exerts its pleiotropic effects by binding to various histamine receptors (HRs) on different cell types. The four identified subtypes of histamine receptors are named in the order of their discovery: H1R, H2R, H3R, and H4R, and all of them belong to the rhodopsin-like family of the G protein-coupled receptor (GPCR) superfamily [11]. Upon the binding of histamines to the extracellular region of HRs, a conformational change occurs, facilitating the recruitment and activation of nearby guanine nucleotide-binding protein (G protein) to the receptor's intracellular region. In its inactive form, the G protein is a heterotrimeric protein consisting of three subunits: Gα, Gβ, and Gγ. Upon activation, the G protein dissociates into a functional Gα subunit and a Gβγ dimer to modulate various downstream effector proteins [12]. The G protein α subunits fall into four families ($G\alpha_q$, $G\alpha_s$, $G\alpha_i$, and $G\alpha_{12/13}$), with the first three families being associated with HRs.

Active $G\alpha_q$ activates phospholipase C (PLC), which hydrolyses phosphatidylinositol-4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP_3) (Fig. 1). IP_3 diffuses in the cytosol, binds to its receptor on the endoplasmic reticulum lumen, and causes the release of Ca^{2+} into the cytosol [13]. DAG also contributes to the elevated intracellular Ca^{2+} level by promoting calcium influx via voltage-gated Ca^{2+} channels on the plasma membrane. The elevated intracellular Ca^{2+} concentration activates nitric oxide synthase and triggers calcineurin-nuclear factor of activated T cells (NFAT) and nuclear factor-κB (NF-κB) pathways, thereby regulating cellular responses [14]. In addition, DAG recruits protein kinase C (PKC) to the membrane and activates it in the presence of Ca^{2+}. Activated PKC modulates cell proliferation and functions via the mitogen-activated protein kinase (MAPK) signalling pathway [15]. Both $G\alpha_s$ and $G\alpha_i$ exert their functions by targeting adenyl cyclase to regulate cyclic adenosine monophosphate (cAMP) concentration through opposing mechanisms. Specifically, active $G\alpha_s$ activates adenyl cyclase (AC), leading to an elevation of cAMP levels in the cytosol, whereas $G\alpha_i$ suppresses adenyl cyclase activity to reduce intracellular cAMP levels (Fig. 1). A high level of cAMP leads to protein kinase A (PKA) activation, subsequently triggering the cAMP response element-binding protein (CREB) and MAPK pathways to modulate cell survival, proliferation, differentiation, and functions by controlling gene transcription. Furthermore, the Gβγ dimer not only serves as a negative regulator of Gα signalling in the absence of receptor stimulation but also contributes to signal transduction. It directly interacts with and regulates various effectors, including potassium channels, phospholipase Cβ, adenylyl cyclase isoforms, PIP3 isoforms, and voltage-gated calcium channels [16, 17].

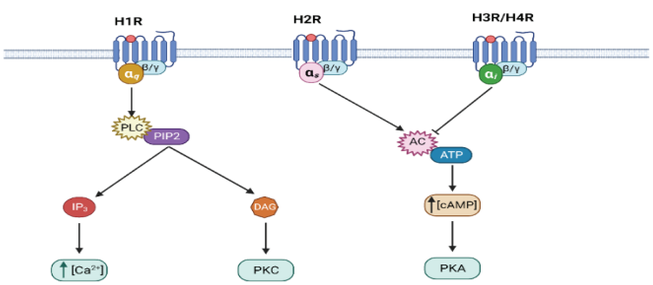

Fig. 1. Histamine receptors and their major signalling pathways. Histamine mediates its physiological and pathological effects through four distinct GPCRs, each differing in the Gα subunit. Upon histamine binding, H1R regulates cellular activities by increasing the intracellular Ca^{2+} concentration and activating PKC. On the other hand, H2R induces the accumulation of cAMP in the cytosol by activating its synthesising enzyme AC, subsequently leading to PKA activation. H3R and H4R act by inhibiting adenyl cyclase (AC) function, decreasing intracellular cAMP levels.

4. Antihistamines: Common drugs in clinical use

As discussed earlier, histamine is involved in several pathological conditions, including allergies, excessive gastric acid release-related diseases, and neurological disorders. Inhibiting histamine signalling is a practical therapeutic approach for treating these pathological conditions. Since histamine is a vital mediator in many physiological processes, targeting the specific histamine receptor is preferable to systematically blocking histamine ligands or their synthesis process. The term "antihistamine" used in this review refers to pharmacological substances inhibiting the proper histamine signalling through histamine receptors, irrespective of their classification as either inverse agonists or antagonists. H1, H2, H3, and H4 antihistamines denote the specific category of antihistamines tailored to target the activity of H1R, H2R, H3R, and H4R, respectively.

4.1. Antihistamines for treating allergic diseases

Allergies are unusually exaggerated responses of the immune system against nonmicrobial environmental antigens in certain individuals who are usually harmless to others [18]. These antigens, known as allergens, might be encountered through inhalation, ingestion, and skin contact and subsequently trigger allergic responses. Several types of allergic diseases, including asthma, allergic rhinitis, food allergies, urticaria, and atopic dermatitis, differ in causes, route of allergen exposure, manifested tissues, and symptoms. These symptoms can vary from mild to severe and might appear instantly or hours after allergen exposure. Systemic anaphylaxis is the most severe and potentially life-threatening allergic reaction with widespread inflammation.

Allergy is driven by a complex interplay of multiple inflammatory immune cells and their mediators. Histamines, the primary mediators of the allergic response, bind to their receptors, mainly through H1Rs on smooth muscle cells, endothelial cells, and immune cells, facilitating many pathological reactions, including increased vascular permeability, itching, smooth muscle contraction-induced bronchoconstriction, and mucus production. In conjunction with other cytokines and chemokines, histamine recruits and regulates the activation, differentiation, and function of other inflammatory immune cells, provoking allergic inflammation and leading to tissue damage [18].

H1 antihistamines, commonly used for allergic disease treatment, were first discovered in the 1930s [19]. Mechanistically, H1 antihistamines specifically bind to H1Rs and block or significantly decrease the basal activity of the receptors to alleviate allergic responses. Current clinically approved indications for allergic disease include rhinitis, urticaria, conjunctivitis, dermatoses, atopic dermatitis, and angioedema, as well as other general symptoms mediated by histamines such as nausea, vomiting, motion sickness, bronchitis, and sinusitis. There are six major chemical groups of H1 antihistamines: alkylamines, ethanolamines, ethylenediamines, piperidines, piperazines, and phenothiazines, with three developing generations. First-generation antihistamines are generally effective at treating allergic symptoms; however, they may give rise to detrimental side effects, such as drowsiness, sedation, somnolence, fatigue, and impaired cognitive function and memory due to their ability to cross the blood-brain barrier [20]. However, some are still commonly used in many countries and can be purchased over-the-counter. Second-generation antihistamines developed in the 1980s with none or fewer sedative effects and higher selectivity to H1R have currently gained widespread popularity in the market. Several third-generation antihistamines have been developed in recent years, characterised by minimal side effects and extended durations of action. Notably, levocetirizine, fexofenadine, and desloratadine represent three third-generation antihistamines accessible not only within the United States but also in various other nations. Popular antihistamines on the market, both over-the-counter and by prescription, include cetirizine, loratadine, fexofenadine, diphenhydramine, desloratadine, and levocetirizine. Most belong to the second or third antihistamine generation, except for diphenhydramine, a first-generation antihistamine with sedating effects.

H4 antihistamines have been investigated for treating several allergic diseases. Preclinical studies have shown that H4 antihistamines can modulate Th2 cytokine production and reduce allergic inflammation, even superior to traditional H1 antihistamines. JNJ 39758979, the most studied H4 antihistamine, is being evaluated for its safety and efficacy in multiple clinical studies. Seven phase I or phase II clinical trials have been registered, four of which target one particular type of allergic response or disease (https://clinicaltrials.gov/). JNJ 39758979 was reported to alleviate pruritus in people with atopic dermatitis and healthy people with histamine intradermal injection-induced pruritus [21, 22]. However, the study of atopic dermatitis was terminated due to two cases of agranulocytosis [23]. Subsequently, two additional registered studies on asthma and rheumatoid arthritis were withdrawn due to this adverse effect. This result implies that the specific compound JNJ 39758979, as well as other H4 antihistamines in a broader context, necessitates further development prior to their prospective investigation and utilisation in clinical settings.

4.2. Antihistamines for treating acid peptic diseases

Acid peptic diseases, including gastric ulcers, duodenal ulcers, and gastroesophageal reflux disease, are characterised by an imbalance between the secretion of gastric juice and mucosal defence. Hydrochloric acid and pepsin are two significant components of gastric juice responsible for food digestion in the stomach but are also critical mediators in acid peptic diseases. Upon stimulation by gastric transmitters, primarily histamine, parietal cells carrying H^+/K^+-ATPases pump H^+ into the gastric lumen, where they combine with Cl^- ions to form gastric acid - hydrochloric acid (HCl) [24]. Pharmaceutical therapeutic approaches for treating acid peptic diseases mainly focus on improving mucosal defence with mucosal protective agents and controlling gastric acid secretion and pepsin activity using H2

antihistamines, proton pump inhibitors, and antacids [25]. Since *Helicobacter pylori* (*H. pylori*) infection has been demonstrated as a significant risk factor contributing to the destruction of the mucosal barrier [26], eradication regimens with antibiotics are frequently included for treating patients who have tested positive for this pathogenic bacteria.

H2 antihistamines were developed early for treating acid peptic diseases in the 1970s by Sir James Black [27]. Compared to antacids, which have been widely used for neutralising gastric acid and inhibiting pepsin since 1928, H2 antihistamines offer several beneficial effects with a distinct mode of action [27]. Unlike antacids that work by neutralising acid, H2 antihistamines directly suppress acid production, thereby reducing the amount of gastric acid and alleviating gastric acid-mediated symptoms. Although H2 antihistamines do not relieve symptoms as quickly as antacids, they are more effective in inhibiting acid secretion and have a longer duration of action, lasting up to 24 hours compared to 2 hours for antacids. Moreover, H2 antihistamines, with their gastric acid level-lowering ability, accelerate ulcer healing and effectively control symptoms of gastroesophageal reflux disease, for which antacids show modest improvement [25]. Four H2 antihistamines clinically approved in the US and other nations, with their popular commercial brand names, are cimetidine, ranitidine, famotidine, and nizatidine. With excellent safety, efficacy, and cost advantages, these drugs were widely used as the first-line treatment for acid peptic diseases until the appearance of proton pump inhibitors, which are superior in inhibiting gastric acid secretion and duration of action. However, long-term use of proton pump inhibitors is reported to be associated with a reduced bone mineral density risk, which is not observed in H2 antihistamines [28, 29]. Additionally, H2 antihistamines show comparable effectiveness with proton pump inhibitors in certain conditions [30, 31]. Hence, choosing either of them in a distinct scenario should be thoroughly considered to ensure efficacy and limit the risk of side effects.

4.3. Antihistamines for treating narcolepsy and other neurological disorders

Narcolepsy is a chronic neurological disorder caused by a disrupted sleep-wake cycle. A typical symptom of narcolepsy is excessive daytime sleepiness. People with narcolepsy experience sudden and uncontrollable episodes of falling asleep, even during activities such as working and driving, known as sleep attacks. In addition, three other common symptoms are cataplexy, sleep paralysis, and hallucinations. The causes of narcolepsy are not fully understood, with the most well-known being the deficiency of hypocretin (also known as orexin), a chemical that plays a pivotal role in regulating wakefulness in the brain. Although no cure is available for narcolepsy, its symptoms could be significantly controlled by medicines and lifestyle changes. The pharmacotherapeutic approach primarily targets reducing daytime sleepiness, although certain medications are also used for alleviating the symptoms of cataplexy, sleep paralysis, and hallucinations.

As mentioned above, histamine regulates various brain physiological functions primarily through interactions with H1R and H3R, which are broadly expressed in the central nervous system. While H1R mediates histamine signalling in the brain to modulate the sleep-wake cycle, cognition, arousal, aggressive behaviour, and memory, H3R functions as either an autoreceptor or a heteroreceptor to suppress the release of histamine and other neurotransmitters [32]. Together with hypocretin, histamine contributes to the regulation of the sleep-wake cycle. During sleep, a low histamine level is observed in the hypothalamus, while a high one is present during wakefulness [33]. Blocking H3R to unleash brain histamine concentration and other wake-promoting neurotransmitters is a strategy currently applied for treating excessive daytime sleepiness and cataplexy in narcolepsy. Pitolisant (WAKIX) is the first-in-class H3 antihistamine clinically approved in 2019 for narcolepsy patients with and without cataplexy. At the recommended dose, pitolisant shows comparable efficacy in reducing excessive daytime sleepiness and cataplexy but exhibits fewer and shorter-lasting side effects than modafinil, a widely used medication in narcolepsy treatment [34, 35]. Additionally, pitolisant is currently being evaluated in numerous clinical trials for other excessive sleep-related disorders, including idiopathic hypersomnia, myotonic dystrophy type 1, obstructive sleep apnoea, Prader-Willi syndrome, and other conditions, such as Parkinson's disease, drug or alcohol abuse (https://clinicaltrials.gov/). Several other H3 antihistamines are being investigated in various stages of clinical development for cognitive disorders, including Alzheimer's disease, schizophrenia, neuropathic pain, and attention deficit hyperactivity disorder [34, 36].

5. Repurposing antihistamines for treating other diseases

De novo drug discovery is typically laborious, expensive, and time-consuming, with a high failure rate. Generally, a drug development process from bench to bedside consists of five critical steps: discovery and development, preclinical research, clinical research, FDA drug review, and FDA post market drug safety monitoring. Developing a brand-new drug is estimated to take approximately US $2-3 billion and requires 14 years of research and approval. According to a report by the Biotechnology Innovation Organization, from 2006 to 2015, only approximately 10% of tested drugs passed clinical trials and were released to the market [37].

Drug repurposing, also known as drug repositioning, reprofiling, retasking, or therapeutic switching, involves finding new uses for approved drugs beyond their original medical indications. This approach has gained the scientific community's attention as an alternative strategy to traditional drug discovery with many advantages. All repurposing drug candidates have undergone formulation and extensive evaluation of pharmacodynamics, pharmacokinetics, safety, and toxicity in preclinical and clinical studies. As a result, developing them for other clinical purposes will be significantly faster, with lower costs and higher success rates.

Table 1. Antihistamines repurposed for treating various viral infections.

No.	Drugs	Class of antihistamines	Type of viral infection	Experimental model	Mode of action	Ref.
1	Carbinoxamine maleate Chlorpheniramine maleate	H1	Influenza A virus	*In vitro and in vivo*	Block virus entry	[38]
2	Diphenhydramine Chlorcyclizine	H1	Ebola and Marburg virus	*In vitro*	Block virus entry	[39]
3	Clemastine Benztropine Maprotiline	H1	Ebola virus	*In vitro*	Block virus entry	[40]
4	Chlorcyclizine HCl (CCZ)	H1	Hepatitis C virus (HCV)	*In vitro and in vivo*	Block virus entry	[41]
5	Chlorcyclizine	H1	Hepatitis C virus (HCV)	*In vitro*	Block virus entry	[42]
6	Doxepin	H1	COVID-19	*In vitro*	Block virus entry	[43]
7	Loratadine Desloratadine	H1	COVID-19	*In vitro*	Block virus entry	[44]
8	Deptropine	H1	Hepatitis E virus (HEV)	*In vitro*	Inhibit viral replication	[45]
9	Mebhydrolin napadisylate*	H1	Zika virus (ZIKV)	*In vitro*	Block viral RNA synthesis	[46]
10	Antazoline Hydrochloride	H1	Hepatitis B virus	*In vitro*	Inhibit viral replication	[47]
11	Azelastine	H1	SARS-CoV-2 virus	*In vitro*	Block virus entry	[48]
12	Famotidine	H2	SARS-CoV-2 virus	*In vitro*	Reduce inflammation by activating vagus nerve inflammatory reflex	[49]
13	Famotidine	H2	SARS-CoV-2 virus	*In vitro*	Reduce inflammation by inhibiting toll-like receptor 3 signalling, which activates IRF3 and NF-κB pathways	[50]
14	Famotidine	H2	SARS-CoV-2 virus	Retrospective cohort study	N/A	[51]
15	A combination of Loratadine (H1R) or fexofenadine (H1R) and famotidine (H2R)	H1 and H2	SARS-CoV-2 virus	Prospective observational study	N/A	[52]

*This antihistamine is unavailable in the U.S.

The results from drug repurposing studies have shown that antihistamines, which are widely clinically used for treating allergies, gastric ulcers, and other degenerative diseases, are highly potent in treating certain conditions. The accessibility and cost-effectiveness of antihistamines, particularly H1 and H2 antihistamines, signify that they could serve as more convenient and affordable therapeutic options for diseases that currently lack effective treatments. This section will discuss three new potential clinical applications of antihistamines: viral infections, cancer, and autoimmune diseases.

5.1. Viral infections

Viral infections can cause a broad spectrum of illnesses, ranging from asymptomatic to mild, moderate, severe, and life-threatening. The pathogenesis of viral infections involves a complex interaction between the viruses and the host. Once they successfully enter host cells, viruses can cause disease by disrupting cell functions and leading to tissue damage during replication. Viral infection triggers acute inflammation, a host defence mechanism involving the activation and recruitment of immune cells and their inflammatory molecules to eliminate pathogens. However, excessive and prolonged inflammation could also exert detrimental effects by causing damage to healthy tissues and organs, mediating many symptoms, such as fever, fatigue, and muscle aches, and increasing the disease severity.

Pharmaceutical treatments for most viral infections are limited and predominantly geared towards symptom relief. Despite the tremendous efforts of the scientific community, there has been modest progress in treating viral infections due to the lengthy drug discovery process and the rise in antiviral drug resistance. Moreover, the outbreak of many emerging and reemerging dangerous viruses in recent decades necessitates a quicker and superior strategy for drug development. Drug repurposing is a fantastic alternative to traditional drug discovery to catch up on finding effective treatments within a limited time in such scenarios. It has been shown that several H1R or H2 antihistamines are potential repurposed drugs for treating dangerous viral infectious diseases (Table 1).

The beneficial effects of antihistamines in treating viral infectious diseases could be mediated by directly inhibiting viral replication in the host or indirectly balancing antiviral immune responses and harmful inflammation. Several H1 antihistamines have potential in treating many dangerous viral infectious diseases, such as influenza, COVID-19, hepatitis, Ebola, Zika, and Marburg virus disease (Table 1). Antiviral effects are primarily mediated by interfering with viral attachment [43, 44, 48] or endocytosis [38, 39, 41, 42], thereby blocking the entry of viruses into host cells. Additionally, mebhydrolin napadisylate, an H1R antihistamine that is licensed for treating allergic symptoms in many countries but not the U.S., could limit the replication of the Zika virus by inhibiting RNA synthesis [46]. Deptropine and antazoline hydrochloride also suppress the replication of hepatitis E virus and hepatitis B virus, respectively, but the mechanisms remain elusive [45, 47].

Famotidine, an H2 antihistamine, is also highly potent in treating COVID-19. It was shown in a retrospective cohort study that the administration of famotidine was associated with improved clinical outcomes in COVID-19 patients [51]. However, a subsequent mechanistic study ruled out the direct inhibition of famotidine on the replication of the SARS-CoV-2 virus, suggesting an indirect beneficial effect on controlling immune responses [53]. Undoubtedly, Mukherjee et al. proved that famotidine downregulated the expression of Toll-like receptors on infected cells to reduce inflammatory responses via the interferon signalling factor 3 (IRF3) and NF-κB pathways [50]. More intriguingly, Yang and his colleagues showed that famotidine activated the vagus nerve inflammatory reflex to attenuate severe inflammation in a COVID-19 mouse model [49]. Furthermore, two other H2 antihistamines, nizatidine and cimetidine, were suggested to be used as adjuvants in manufacturing influenza and hepatitis B virus vaccines, respectively, because of their ability to activate dendritic cells and enhance both antibody- and T-cell-mediated immune responses [54, 55]. Famotidine, an H2 antihistamine, is also highly potent in treating COVID-19. It was shown in a retrospective cohort study that the administration of famotidine was associated with improved clinical outcomes in COVID-19 patients [51]. However, a subsequent mechanistic study ruled out the direct inhibition of famotidine on the replication of the SARS-CoV-2 virus, suggesting an indirect beneficial effect on controlling immune responses [53]. Undoubtedly, R. Mukherjee, et al. (2021) [50] proved that famotidine downregulated the expression of Toll-like receptors on infected cells to reduce inflammatory responses via the interferon signalling factor 3 (IRF3) and NF-κB pathways. More intriguingly, H. Yang, et al. (2022) [49] showed that famotidine activated the vagus nerve inflammatory reflex to attenuate severe inflammation in a COVID-19 mouse model. Furthermore, two other H2 antihistamines, nizatidine and cimetidine, were suggested to be used as adjuvants in manufacturing influenza and hepatitis B virus vaccines, respectively, because of their ability to activate dendritic cells and enhance both antibody- and T-cell-mediated immune responses [54, 55].

Overall, several clinically used H1 and H2 antihistamines exhibit the potential to treat viral infectious diseases through different mechanisms (Figs. 2 and 3). All investigated H1 antihistamines mediate their antiviral effects by directly targeting viral replication by blocking viral entry or inhibiting genetic material replication. In contrast, H2 antihistamines seem to indirectly alleviate viral infectious diseases by mitigating excessive inflammation and potentially enhancing T- and B-cell antiviral immune responses. To obtain a comprehensive perspective on applying H1 and H2 antihistamines in treating viral infections, more mechanistic studies, preclinical studies, and clinical trials are imperative.

The recent global COVID-19 pandemic has accelerated clinical studies searching for effective treatments. Notably, several clinical trials investigating the potential of antihistamines, specifically famotidine, have been registered on the website https://clinicaltrials.gov/ (Table 2). Both positive and negative therapeutic effects of famotidine have been reported. Several

Table 2. Clinical trials of antihistamines for treating COVID-19.

Drug	Phase	Clinical trial identifier
Cyproheptadine hydrochloride (H1R)	Phase 2	NCT04876573
Famotidine (H2R)	Phase 2	NCT04724720
Famotidine (H2R) and others	Phase 2	NCT04488081
Famotidine (H2R)	Phase 3	NCT04370262
Famotidine (H2R)	Phase 3	NCT04504240

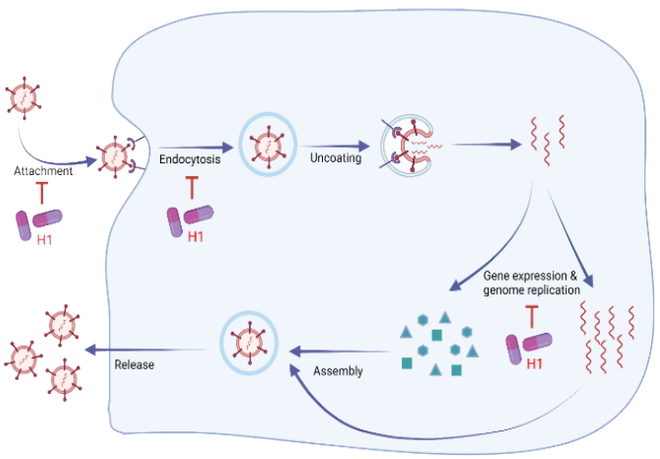

Fig. 2. H1 antihistamines mediate antiviral effects by directly targeting viral entry, gene expression, and genome expression.

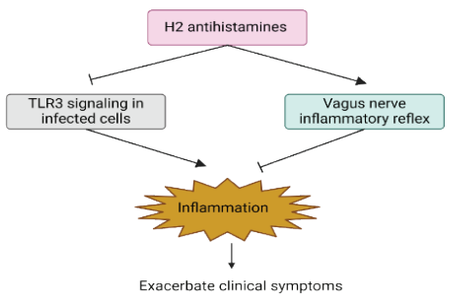

Fig. 3. H2 antihistamines alleviate viral infectious diseases by dampening inflammation to ameliorate clinical symptoms.

retrospective cohort studies showed that famotidine use in COVID-19 patients was associated with lower odds of mortality as well as clinical signs and symptoms compared to the control group [56-59]. Furthermore, randomised controlled clinical trials showed that COVID-19 patients with famotidine treatment showed faster inflammation and symptom resolution [60] and recovered more quickly with a shorter hospitalisation duration [61, 62]. These were further confirmed by a randomised controlled phase III clinical trial (Identifier No. NCT04504240). However, no difference in survival rate was observed in this trial, which is consistent with what was previously indicated in the other trial [61, 63]. On the other hand, a few retrospective cohort studies demonstrated that famotidine use was not associated with better therapeutic outcomes in COVID-19 patients. A meta-analysis including results from three prospective

clinical trials and seven retrospective cohort studies also indicated no efficacy of famotidine in COVID-19 treatments [64]. It is noted that all three randomised clinical trials included in this meta-analysis showed famotidine is beneficial in treating COVID-19. Given that the retrospective cohort study is less accurate than the randomised controlled clinical trial due to the existing bias in subject selection and great variations among selected subjects, we believe that famotidine mediates beneficial effects in treating COVID-19. More randomised controlled clinical trials and well-designed meta-analyses are required to confirm the efficacy of famotidine in treating COVID-19.

5.2. Cancer

Cancer is a leading cause of death worldwide, with millions of new cases diagnosed yearly. Cancer treatments include chemotherapy, surgery, radiation therapy, immunotherapy, targeted therapy, hormone therapy, and stem cell transplant, which could be used as a single therapy or a combination of two or more types to enhance efficacy. It has been shown that L-histidine decarboxylase, the enzyme synthesising histamine, is upregulated in cancerous tissue simultaneously with the elevated levels of histamine detected in various types of malignancies, implying an essential role of histamine in tumour immunity [65-67].

Early in the 1990s, several studies showed that histamine functions as a growth factor to promote cancer development in *in vitro* and *in vivo* models, suggesting that it could be a novel target for cancer treatment [65, 68, 69]. However, a few other studies reported the antitumour effect of histamine, which raised controversy regarding the role of histamine in cancer and delayed the development of cancer therapies targeting histamine [70-72]. This finding could be explained by histamine's involvement with various cell types and its complex signalling pathways through four different receptors. With increasing evidence published recently, disturbing histamine signalling and its biological effects by clinically approved antihistamines has received significant attention again and appears to be a potential therapeutic approach in cancer treatment. This section will discuss the antitumour effects of some antihistamines available on the market and the mechanisms driving these beneficial effects.

H1R is upregulated in several types of cancer cells [73, 74]. The high expression of H1R is associated with tumour progression and poor survival in patients with hepatocellular carcinoma, breast cancer, lung adenocarcinoma, and melanoma [74, 75]. J. Zhao, et al. (2020) [74] demonstrated that H1R activation promotes the proliferation, migration, and invasion of hepatocellular carcinoma via PKA-mediated pathways. Terfenadine, an H1R antihistamine used for treating allergic conditions, demonstrated therapeutic effects by inhibiting tumour growth and metastasis of hepatocellular carcinoma cells in both *in vitro* and animal models. These beneficial effects of terfenadine have also been confirmed in other cancers, including prostate cancer [76], colorectal adenocarcinoma [77], melanoma [78], and non-small cell lung cancer [79]. Although terfenadine was withdrawn from the U.S. market due to cardiovascular toxicity in 1997, several derivatives have been developed and have shown their potential to replace terfenadine in treating cancer [80]. A study conducted by H. Li, et al. (2022) [75] indicated that fexofenadine, a hydrochloride salt of terfenadine available in the U.S. and other nations for treating allergies, inhibited tumour growth and metastasis in many tumour models. Additionally, this study revealed a novel mechanism by which H1R promotes cancer development by disrupting the balance of M1 pro-inflammatory/M2 anti-inflammatory polarisation. The binding of histamine to H1R on macrophages polarises towards the immunosuppressive M2-like phenotype, leading to impaired T cell antitumour function. The use of fexofenadine in tumour-bearing mouse models resulted in a significant reduction in tumour volume and a better survival rate. This study also emphasised the ability of H1 antihistamines to be combined with immunotherapies and exhibited more potent therapeutic effects. The retrospective clinical study conducted by this research team indicated a positive correlation between the use of H1R antihistamines and better clinical outcomes in patients receiving immune checkpoint blockade therapies. Furthermore, a meta-analysis of 429,198 cancer patients demonstrated that using H1 antihistamines, specifically desloratadine or loratadine, is associated with improved survival across diverse cancer types [81].

H2 antihistamines are also potential repurposed drugs for treating cancers. Cimetidine has been studied the most among four clinically approved H2 antihistamines. Since the late 20th century, numerous clinical studies have been conducted to investigate the antitumour ability of cimetidine in several types of cancers, including colorectal cancer, melanoma, gastric cancer, and renal carcinoma [82]. Most of these studies showed that using cimetidine as a monotherapy or combined with others was beneficial in cancer treatment, as indicated by the overall survival rate or the response rate [83-85]. Specifically, it was noted in a study with colorectal cancer patients whose cimetidine treatment increased the 10-year survival rate by more than 30% compared to the control [84]. However, some studies demonstrated that cimetidine treatment exerted modest or no effects compared with control groups [86, 87]. Ranitidine, another H2 antihistamine, has reached the clinical trial stage, but the results were not very promising. In a randomised, placebo-controlled clinical study with colorectal cancer patients, ranitidine treatment showed an improved survival rate in patients who did not receive perioperative blood transfusion but not in transfused patients and patients who underwent curative resection [88]. In another prospective randomised clinical trial of 222 patients with gastric cancer, the administration of ranitidine increased the median survival days from 187 in the placebo group to 331 in the treatment group. Still, this difference was not statistically significant [89]. Clinical studies evaluating the clinical outcomes of two other H2 antihistamines, including famotidine and nizatidine, have yet to be conducted. Only two studies were

performed to investigate tumour lymphocyte infiltration in breast cancer patients [90, 91]. Both showed that famotidine treatments significantly increased the percentages of lymphocyte infiltration compared to the control treatments. It appears that nizatidine is not investigated for cancer treatment, as none of the studies have been found, either in *in vitro* or *in vivo* models.

Several mechanisms of action drive the beneficial effects of using antihistamines in cancer treatment. First, H2 antihistamines inhibit cancer cell growth by antagonising the cell proliferation-promoting ability of histamine via H2R [92, 93] or its additional H2R-independent off-target effect [94, 95]. Second, treatments with H2 antihistamines boost antitumour immune responses by increasing lymphocyte infiltration into the tumour [83, 96], enhancing the antigen-presenting ability of dendritic cells [97], or reversing the immunosuppression caused by regulatory T cells [98] and myeloid-derived suppressors [99]. Third, H2 antihistamines can suppress cancer cell metastasis by inhibiting cell adhesion to endothelial cells [100]. Finally, H2 antihistamines inhibit tumour neoangiogenesis [101], a critical mechanism driving cancer growth and metastasis.

To sum up, the apprehension of histamine's intricate effects for treating cancer, encompassing both tumour-promoting and tumour-inhibiting properties, in the last century has been allayed by the discovery of four distinct histamine receptors and the growing understanding of their various downstream signalling pathways, opening a new era in utilising antihistamines for cancer therapy. In essence, H1 and H2 antihistamines have demonstrated remarkable efficacy in cancer treatment, manifested by directly inhibiting tumour growth, metastasis, and angiogenesis or indirectly boosting antitumour immune responses.

5.3. Multiple sclerosis

Multiple sclerosis (MS) is a common disabling chronic neurological disorder that affects the central nervous system. It is characterised by the destruction of myelin, the insulating substance surrounding neurons that enables the quick and efficient transmission of electrical signals along nerve cells. MS is classified as an autoimmune disease in which the immune system mistakenly recognises myelin sheaths as non-self and destroys them. The underlying mechanism of this abnormal process is not fully understood. Like other autoimmune diseases, MS development is believed to stem from the interaction between disrupted self-tolerance caused by genetic susceptibility and the activation and recruitment of autoreactive lymphocytes by environmental triggers such as infections and other inflammatory stimuli [102]. Currently, there is no cure for MS. Treatments typically focus on managing symptoms, slowing disease progression, and reducing the frequency and severity of relapses.

There is increasing evidence of the link between histamine signalling via H1R and the development of MS [103, 104]. It was reported that H1R is upregulated in human MS lesion samples. Histamines and other mediators of mast cells were detected at the sites of demyelination in MS or its animal model, experimental autoimmune encephalomyelitis (EAE) [105]. An mRNA analysis of multiple MS lesions showed the upregulation of several genes related to allergic responses, including H1R, platelet-activating factor receptor, Ig Fc ε receptor 1 (FcεRI), and tryptase [103]. The deficiency of mast cells significantly reduced the incidence rate and severity of EAE [106]. These findings highlight the crucial role of mast cells and their mediators in the pathogenesis of multiple sclerosis.

Mechanistically, proteins from the damaged myelin sheath can trigger mast cell degranulation, releasing histamines and other inflammatory mediators to recruit more immune cells [107]. Histamine itself also disrupts the blood-brain barrier, allowing immune cells to enter the central nervous system to mediate neuroinflammation [107]. These allergic immune responses significantly contribute to exacerbating clinical symptoms and increasing the mortality rate. It was shown in a mouse model with EAE that myelin could trigger severe allergic reactions, including fatal anaphylaxis, following EAE recovery [105]. These findings suggest the beneficial effects of using antihistamines to complement multiple sclerosis treatments. Indeed, using sedating H1 antihistamines, including cyproheptadine, hydroxyzine, or pyrilamine, ameliorated EAE severity in mice [103, 105]. A pilot clinical trial in twenty MS patients demonstrated that hydroxyzine could stabilise or even improve the patients' health [108]. It was also shown in a randomised, placebo-controlled phase II clinical trial that the administration of clemastine, a first-generation sedating antihistamine, promoted myelin repair in MS patients [109]. Additionally, several clinical studies investigating the effects of H1 antihistamines in MS registered on the website https://clinicaltrials.gov/ are still awaiting their results. With solid scientific evidence, it is optimistic that H1 antihistamines could be a promising medication for treating MS. Despite receiving less attention, antihistamines have been investigated and shown potential in treating other autoimmune diseases, including arthritis [110] and autoimmune myocarditis [111]. In addition to H1, H4 antihistamines are also promising in treating autoimmune diseases due to their ability to block inflammation caused by H4R in various immune cell types, such as mast cells, dendritic cells, and T cells [112, 113].

6. Conclusions and perspectives

H1, H2, and H3 antihistamines have been authorised for treating allergies, acid peptic diseases, and narcolepsy, respectively. Advantages in the low cost and availability of these antihistamines make them potential drug candidates for repurposing in treating other challenging conditions. Our literature review shows antihistamines are highly potent for treating other diseases, including viral infectious diseases, cancers, and multiple sclerosis (Fig. 4). Off-label use of these drugs for other indications is legal and allowed in certain circumstances; however, obtaining approval by the FDA is necessary for convenient and widespread use in the new indications. Depending on the specific type of studied

antihistamine and disease, these investigations are in different stages of drug development, from screening *in vitro* to evaluating in clinical trials. Nevertheless, they have not been FDA-approved due to the limited results from objective randomised and controlled clinical trials. Clinical studies and licensing processes should be sped up to launch antihistamines in the market with their new uses.

However, the use of antihistamines should be more closely monitored, especially sedating H1 antihistamines. The convenience of over-the-counter antihistamines contributes to their misuse, either overdose or unnecessary long-term use [114]. Individuals misusing antihistamines might build up drug tolerance in which they need higher doses to get the therapeutic effects or have withdrawal symptoms after discontinuing the use of antihistamines. Given the current widespread clinical indications of antihistamines and their potential novel therapeutic applications, stricter management in their distribution and usage is necessary to prevent possible serious side effects and incidences.

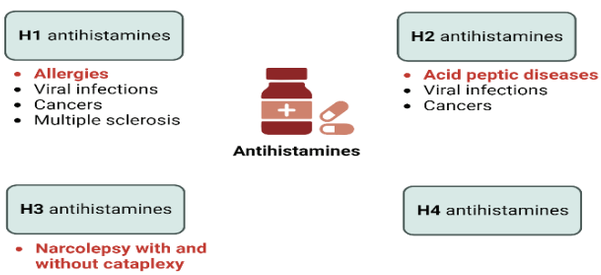

Fig. 4. Antihistamines in clinical applications. Beyond some specific indications approved by the FDA (red colour), antihistamines have been investigated and have potential in other pathological conditions including viral infections, cancers, and multiple sclerosis (black colour).

CRediT author statement

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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