Review

Bilastine Beyond H1-Receptor Antagonism: Molecular Pharmacology, Anti-Inflammatory Actions, and Emerging Tissue-Protective Effects

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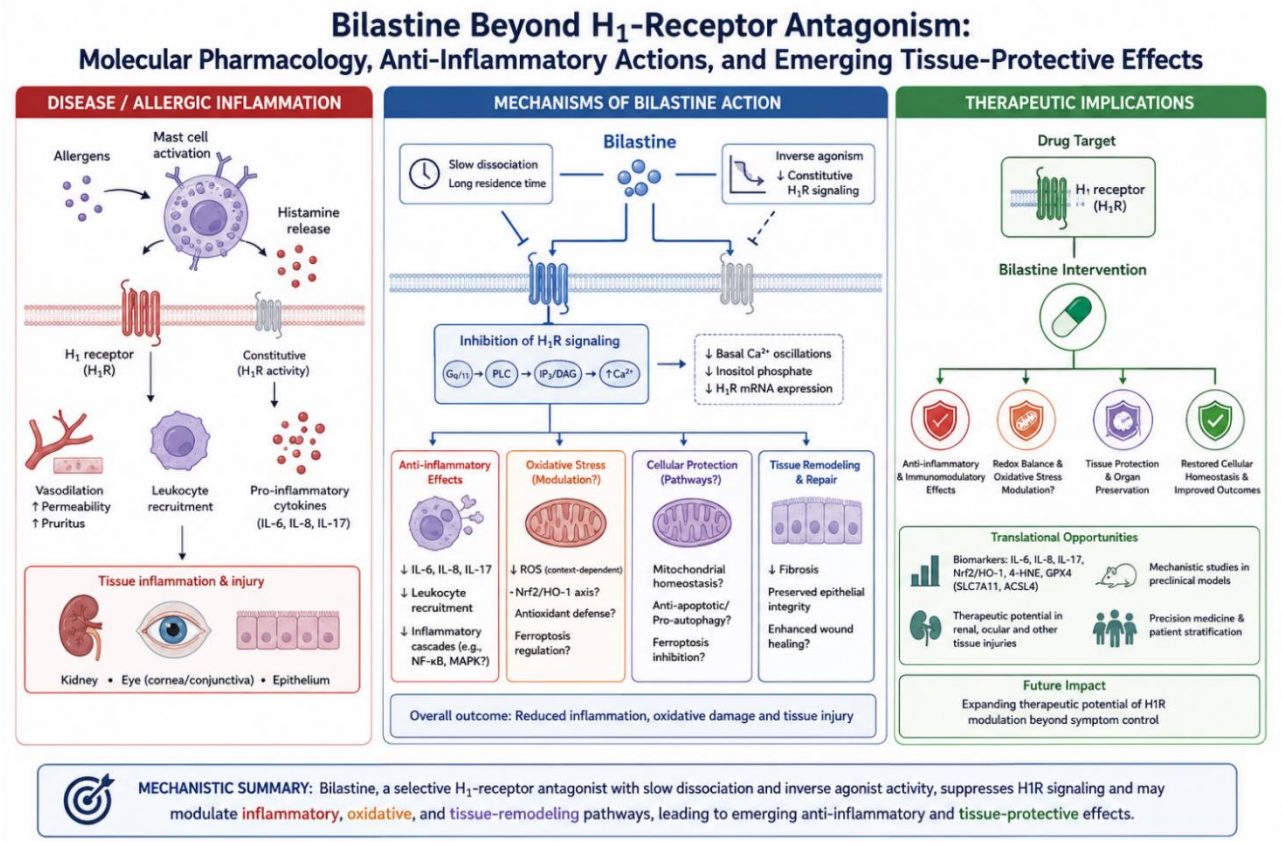
Abstract:

Bilastine is a second-generation, highly selective H1-receptor antagonist widely used for the treatment of allergic disorders. Beyond conventional antihistaminic activity, its pharmacological profile includes slow H1-receptor dissociation, prolonged receptor residence, and inverse agonism, raising the possibility that H1R modulation may influence inflammatory and tissue responses beyond acute histamine blockade. This review critically evaluates the molecular pharmacology of bilastine and examines emerging evidence for anti-inflammatory and tissue-protective effects, with particular emphasis on the strength and mechanistic limitations of the available evidence. Bilastine has demonstrated suppression of constitutive H1R signaling and attenuation of histamine-dependent responses, while clinical observations suggest reductions in selected inflammatory mediators, including IL-6, IL-8, and IL-17. Experimental evidence further indicates potential renal protection in diabetic nephropathy and favorable epithelial compatibility and wound-repair effects associated with preservative-free bilastine-containing ophthalmic formulations. However, the latter findings cannot yet be attributed specifically to bilastine because formulation components, particularly sodium hyaluronate and the absence of benzalkonium chloride, may substantially contribute to the observed effects. Importantly, direct evidence that bilastine acts as an antioxidant or modulates Nrf2/HO-1, NF-κB, MAPK, mitochondrial homeostasis, or ferroptosis remains insufficient. These pathways therefore represent mechanistic hypotheses rather than established pharmacological actions. Future studies using pathway-specific pharmacological and genetic approaches are needed to determine whether H1R modulation by bilastine causally influences redox homeostasis, inflammation, mitochondrial function, and regulated cell death. Clarifying these mechanisms may define new pharmacological dimensions of H1R antagonism and inform future tissue-protective and translational applications of bilastine.

Keywords: Bilastine; Histamine H1 Receptor; H1R Inverse Agonism; Antihistamines; Inflammation; Tissue Protection



Graphical Abstract: Bilastine Beyond H1-Receptor Antagonism: Molecular Pharmacology, Anti-Inflammatory Actions, and Emerging Tissue-Protective Effects. The figure illustrates how selective H1-receptor modulation by bilastine may extend beyond classical histamine blockade. Its slow receptor dissociation may support sustained inhibition of histamine-driven H1R signaling, while inverse agonism suppresses constitutive H1R activity, providing a plausible basis for downstream inflammatory modulation. Reduced IL-6, IL-8, and IL-17 levels, together with experimental renal protection and favorable epithelial responses, suggest potential effects on inflammation and tissue remodeling. However, involvement of Nrf2/HO-1, NF-κB, MAPK, mitochondrial pathways, or ferroptosis remains unestablished. These findings highlight bilastine as a useful model for investigating tissue-protective consequences of H1R modulation beyond symptomatic antihistaminic control.

Introduction

Histamine plays a key role in allergic inflammatory conditions, and its inflammatory effects have traditionally been attributed largely to activation of the histamine H1 receptor (H1R). Accordingly, H1-receptor antagonists, commonly known as antihistamines, have long been used in the treatment of allergic diseases (1). Bilastine is a selective H1-receptor antagonist characterized by high specificity for H1 receptors and minimal interaction with other receptor systems (2). Its pharmacological profile extends beyond conventional competitive antagonism, as bilastine exhibits slow dissociation from H1R and a relatively long receptor residence time, potentially contributing to sustained antihistaminic activity (3). In addition, experimental studies have demonstrated inverse agonist activity of bilastine, with bilastine reducing constitutive H1R activity and downstream basal intracellular signaling, including Ca^{2+} oscillations and inositol phosphate formation (4). Emerging evidence suggests that these pharmacological properties may be accompanied by effects on inflammatory and tissue responses. Clinical studies have reported reductions in inflammatory mediators such as IL-6, IL-8, and IL-17 following bilastine treatment (5, 6), while experimental work has demonstrated protective effects in diabetic nephropathy, including

improved renal function and reduced inflammatory and fibrotic changes (7). More recent in vitro studies have also suggested favorable effects of bilastine-containing ophthalmic formulations on epithelial integrity and corneal wound repair (8, 9). However, the mechanistic basis of these emerging effects remains incompletely defined. Therefore, this review critically examines the pharmacology of bilastine beyond classical H1R antagonism, with particular emphasis on its anti-inflammatory and emerging tissue-protective effects and the molecular mechanisms that remain to be established.

Pharmacological Profile and H1-Receptor Biology

- H1-receptor selectivity and receptor binding

Bilastine is a highly selective second-generation H1-receptor antagonist. Pharmacological profiling across a 30-target receptor panel indicated a pronounced preference of bilastine for H1 receptors, with minimal activity detected at several other clinically relevant receptor and ion-channel targets, including H2/H3, M3 muscarinic, α1- and β2-adrenergic, serotonergic, bradykinin, and leukotriene D4 receptors, as well as calcium channels (2). Functional studies in guinea-pig and rat tissues further confirmed that its antihistaminic activity was predominantly mediated through H1-receptor antagonism (2). This high receptor selectivity distinguishes bilastine from antihistamines with broader receptor activity and provides a pharmacological basis for its relatively favorable tolerability profile (10, 11). Importantly, H1R pharmacology cannot be described solely by ligand affinity. The H1 receptor is a constitutively active G-protein-coupled receptor, such that ligands can differentially modulate basal receptor activity; inverse agonists reduce constitutive activity, whereas neutral antagonists do not alter basal activity (12). This distinction becomes particularly relevant for bilastine because subsequent functional studies have demonstrated activity beyond simple prevention of histamine binding.

- Receptor kinetics and residence time

Drug–receptor binding kinetics provides an additional dimension of H1R pharmacology. Kinetic analyses indicate that bilastine remains associated with the human H1 receptor for substantially longer than rapidly dissociating first-generation antihistamines, with a measured residence time of 73 ± 5 min, versus 60 ± 20 min for fexofenadine and only 0.41 ± 0.10 min for diphenhydramine (3). After washout of extracellular bilastine, histamine-induced Ca^{2+} signaling remained suppressed in H1R-expressing cells, consistent with persistent receptor blockade associated with the drug's slow dissociation kinetics (3). Pharmacokinetic/pharmacodynamic modeling provides complementary evidence that the antihistaminic effects of bilastine persist beyond the period predicted solely from plasma concentrations. Pharmacokinetic–pharmacodynamic simulations indicated that once-daily bilastine at 20 mg-maintained plasma exposures above the modeled IC50 throughout the simulated interval for the flare response and for up to 20 hours for wheal inhibition (13). Similar pharmacokinetic and pharmacodynamic characteristics were subsequently observed in healthy Japanese subjects, in whom bilastine 20 and 50 mg produced significant inhibition of wheal and flare responses that persisted for 24 h (14). Thus, both receptor kinetics and systemic pharmacodynamics contribute to the prolonged duration of action of bilastine.

- Inverse agonism and constitutive H1R signaling

An important mechanistic feature of bilastine is its ability to suppress constitutive H1R activity. In H1R-expressing HeLa cells, basal intracellular Ca^{2+} oscillations were observed under resting conditions, consistent with constitutive receptor activity. Bilastine dampened this spontaneous Ca^{2+} oscillatory activity and produced a concentration-

dependent reduction in basal inositol phosphate formation (4). In parallel, bilastine decreased basal H1R mRNA expression, providing additional support for its inverse agonist activity beyond blockade of histamine-induced H1R signaling (4). Collectively, these findings support the classification of bilastine as an inverse agonist, although the extent to which this receptor-level activity translates into biological effects in human tissues remains incompletely defined (4). From a mechanistic perspective, suppression of constitutive H1R signaling provides a plausible receptor-level basis for effects beyond simple histamine blockade; however, direct evidence linking bilastine-induced inverse agonism to downstream inflammatory or tissue-protective pathways remains limited.

- Pharmacokinetic and Safety Profile

Bilastine is rapidly absorbed after oral administration, reaching peak plasma concentrations within approximately 1–1.5 h, with an absolute oral bioavailability of about 60% following a 20-mg dose (15). Population pharmacokinetic analyses demonstrated linear pharmacokinetics across a broad dose range, while PK/PD simulations supported a 24-hour dosing interval for bilastine 20 mg (13). In Japanese volunteers, single doses of 10–50 mg produced dose-proportional increases in Cmax and AUC, with no substantial accumulation after 14 days of once-daily administration (14). Bilastine undergoes minimal metabolic transformation in humans and is predominantly eliminated as unchanged drug, with renal excretion constituting a major elimination pathway (14, 16). Transporter studies indicate that bilastine is a substrate of P-glycoprotein (P-gp), while clinically relevant inhibition of major human drug transporters by bilastine appears unlikely at clinically relevant exposure levels (16, 17). Renal impairment increases systemic exposure to bilastine, consistent with the major contribution of renal clearance to its elimination; nevertheless, a 20-mg dose was well tolerated and remained within the established safety margin in a dedicated renal-impairment study (16). The limited penetration of bilastine into the central nervous system is another important component of its pharmacological profile. Consistent with its limited central effects, psychomotor and clinical studies have demonstrated minimal CNS-related impairment at therapeutic doses (18). In controlled highway-driving studies, bilastine at doses of 20 and 40 mg did not impair driving performance relative to placebo, whereas hydroxyzine significantly increased Standard Deviation of Lateral Position (SDLP), indicating substantial driving impairment (18). Moreover, at the therapeutic dose, bilastine did not increase the magnitude of alcohol-associated psychomotor impairment compared with alcohol alone (19). Together, these findings support the characterization of bilastine as a predominantly peripheral, non-sedating H1-receptor antagonist with a favorable CNS safety profile.

Anti-Inflammatory Effects and Cytokine Modulation

- Modulation of histamine-driven inflammation

Histamine contributes to allergic inflammation through H1R-mediated activation of vascular, epithelial, sensory, and immune-cell responses. H1R activation can promote vasodilation, vascular permeability, leukocyte recruitment, and production of inflammatory mediators, thereby amplifying local tissue inflammation (20, 21). Bilastine suppresses H1R-mediated signaling, attenuating histamine-induced responses and reducing downstream signaling associated with constitutive H1R activity (4). Importantly, the anti-inflammatory effects associated with H1-receptor antagonism may extend beyond simple inhibition of acute histamine-induced vascular responses. H1R signaling can influence the expression and release of inflammatory mediators, and second-generation antihistamines have been reported to modify several cellular processes involved in allergic inflammation (22). For bilastine, however, the strongest evidence

remains linked to modulation of histamine-dependent inflammatory responses rather than demonstration of a completely histamine-independent anti-inflammatory mechanism.

- Effects on inflammatory cytokines

Clinical and experimental observations suggest that bilastine may influence inflammatory cytokine networks. In patients with cold contact urticaria, bilastine treatment was associated with reductions in locally measured inflammatory mediators, including IL-6 and IL-8, following cold challenge (5). Similarly, in a prospective study of refractory chronic spontaneous urticaria, bilastine treatment was associated with reductions in circulating IL-6 and IL-17 together with improvement in disease activity (6). These findings suggest that H1R modulation may influence cytokine-associated inflammatory responses in allergic disease. However, available evidence does not establish bilastine as a direct inhibitor of a specific cytokine-signaling pathway. Therefore, reductions in proinflammatory cytokines should be interpreted as potential downstream consequences of H1R-associated modulation of inflammatory signaling rather than, by themselves, as evidence of direct molecular inhibition of individual cytokines (23).

- Evidence from human studies

Human evidence for the anti-inflammatory effects of bilastine remains relatively limited but is biologically consistent with its established antihistaminic activity. In cold contact urticaria, bilastine attenuated histamine-mediated cutaneous responses, including wheal formation and pruritus, while higher-dose treatment (80 mg/day) was accompanied by significant reductions in dermal IL-6 and IL-8 (5). In chronic spontaneous urticaria, bilastine treatment was also associated with reductions in circulating IL-6 and IL-17, suggesting that its clinical effects may involve modulation of inflammatory cytokine profiles in addition to symptomatic control (6). Nevertheless, most available clinical studies were designed primarily to evaluate antihistaminic efficacy rather than mechanistic immunomodulation. Consequently, changes in cytokine concentrations cannot necessarily be interpreted as evidence of a direct pharmacological effect on cytokine-producing cells. Larger controlled studies incorporating mechanistic biomarkers are required to determine whether cytokine modulation represents a reproducible pharmacodynamic property of bilastine.

- Evidence from experimental models

Preclinical studies provide additional evidence that H1R modulation may influence inflammatory tissue responses. In a murine model of diabetic nephropathy, bilastine treatment reduced renal inflammatory infiltration and collagen deposition while improving renal functional parameters, suggesting that H1R blockade may attenuate inflammatory and tissue-remodeling processes in chronic metabolic injury (7). Notably, these effects occurred without a primary glucose-lowering action, supporting the possibility that the observed renal protection was related to pathways downstream of H1R modulation rather than correction of hyperglycemia. Consistent with its established H1-receptor pharmacology, bilastine has also demonstrated antihistaminic activity in experimental tissues and anti-inflammatory activity in the Schultz-Dale reaction using sensitized guinea-pig ileum (2). Collectively, these findings support an emerging anti-inflammatory phenotype for bilastine; however, the molecular events linking H1R inhibition to broader tissue protection remain incompletely characterized. In particular, direct involvement of pathways such as NF-κB, Nrf2, mitochondrial signaling, or ferroptosis has not yet been established and therefore remains a priority for future mechanistic investigation.

Emerging Tissue-Protective Effects

- Renal protection

The most direct evidence for a tissue-protective effect of bilastine comes from experimental diabetic nephropathy. In streptozotocin-induced diabetic DBA2/J mice, bilastine improved renal functional indices and attenuated glomerular injury, with preservation of the filtration barrier and podocyte-associated structural proteins, while also limiting inflammatory cell accumulation and renal collagen deposition (7). Importantly, these effects were observed without a primary correction of hyperglycemia, supporting the possibility that H1R blockade itself contributes to the renal phenotype (7). Although this study provides an important proof of concept, the evidence remains restricted to a single experimental disease model and has not yet been independently reproduced in other forms of kidney injury. The broader biological plausibility of this observation is supported by recent evidence that H1R antagonism can influence systemic tissue injury. In a 2023 experimental burn model, H1-receptor antagonism attenuated catecholamine responses and reduced organ injury, suggesting that excessive histaminergic signaling may contribute to tissue damage beyond classical allergic disease (24). However, because this study used promethazine rather than bilastine, it should be considered supportive evidence for the H1R target rather than direct evidence for bilastine.

- Epithelial and ocular protection

More recent evidence has emerged from ocular epithelial models. A 2024 comparative in vitro study evaluated a preservative-free bilastine 0.6% ophthalmic formulation in primary human conjunctival and corneal epithelial cells. The formulation showed high cellular survival, did not significantly activate caspase-3/7-mediated apoptosis, and was associated with only a modest increase in ROS, which substantially declined after an 18-h recovery period compared with several comparator ophthalmic preparations (8). Importantly, the investigators attributed the favorable epithelial viability observed with bilastine largely to the absence of preservatives in the formulation, emphasizing the contribution of benzalkonium chloride (BAC) to the cytotoxic effects observed with preserved preparations. Accordingly, these findings demonstrate favorable epithelial tolerability of the preservative-free bilastine formulation but do not establish an intrinsic cytoprotective effect of bilastine itself. This distinction is particularly important because formulation characteristics can substantially influence ocular surface toxicity. In the 2024 study, BAC-containing ophthalmic preparations produced greater cytotoxic, oxidative, and apoptotic effects than preservative-free formulations, whereas the bilastine formulation maintained relatively high epithelial viability and limited apoptosis (8). Thus, the available evidence supports ocular surface compatibility and preservation of epithelial integrity with the preservative-free bilastine formulation, but does not yet establish a receptor-mediated cytoprotective mechanism attributable specifically to bilastine.

- Tissue repair and wound healing

Recent evidence comes from a 2025 comparative study of a multidose, preservative-free bilastine 0.6% ophthalmic formulation containing sodium hyaluronate. In an ex vivo bovine cornea model, this formulation showed the numerically highest bioadhesion among the tested preparations, although its bioadhesion was not significantly different from that of two comparator formulations. In human primary conjunctival epithelial cells, the bilastine formulation did not exhibit significant cytotoxicity under the tested conditions. In scratch-wound assays using immortalized and primary human corneal epithelial cells, the formulation promoted corneal re-epithelialization over 72 h and showed greater wound-closure activity than several benzalkonium chloride (BAC)-preserved comparator formulations (9). However, attribution of these effects specifically to bilastine requires caution. The formulation contained sodium

hyaluronate, which can enhance precorneal retention, hydration, lubrication, and ocular-surface protection; notably, the authors attributed the strong protective effect against dehydration mainly to the presence of hyaluronic acid (9). In addition, comparisons between otherwise compositionally similar preserved and preservative-free formulations containing the same active ingredients suggest that BAC may have contributed substantially to the impaired wound-healing phenotype observed with preserved preparations (9). Thus, the available evidence supports an emerging epithelial-reparative phenotype associated with a bilastine-containing ophthalmic formulation, but does not establish that bilastine itself directly activates epithelial wound-healing pathways.

- Evidence strength and limitations

Taken together, the tissue-protective evidence for bilastine is promising but remains preliminary. The renal study provides direct in vivo evidence, whereas the newer ocular studies provide in vitro/ex vivo evidence of epithelial compatibility and wound repair. Additional literature demonstrating tissue effects of H1-receptor antagonism strengthens the biological rationale for this concept but cannot substitute for bilastine-specific mechanistic studies. Recent structural and pharmacological studies further demonstrate that H1-antihistamines can induce distinct receptor conformational states and inverse regulation of H1R, providing a mechanistic framework for investigating effects beyond simple histamine blockade (25). The principal limitations are therefore the small number of bilastine-specific studies, dependence on particular experimental models, absence of independent replication, and limited mechanistic interrogation. Most importantly, no study has yet demonstrated that bilastine directly promotes tissue repair through Nrf2, NF-κB, MAPK, mitochondrial, or ferroptosis-related pathways. Accordingly, these mechanisms remain unresolved and should be considered priorities for future mechanistic studies rather than established properties of the drug.

Bilastine and Oxidative Stress

Because oxidative stress is an important component of tissue injury and inflammatory signaling, the potential relationship between bilastine and redox regulation warrants consideration. Direct evidence linking bilastine to oxidative-stress regulation remains limited. In a 2024 in vitro study, a preservative-free bilastine 0.6% ophthalmic formulation produced a modest elevation in ROS in human corneal epithelial cells, with ROS levels largely returning toward control values after a recovery period. These findings suggest limited redox perturbation under the tested conditions but do not provide evidence of intrinsic antioxidant activity (8). Similarly, a 2024 in vitro study of 12 H1-receptor antagonists found no strong antiglycation activity, including for bilastine, and provided no clear evidence of substantial inhibition of glycoxidation attributable to the H1-antagonist class (26). Thus, bilastine should not currently be characterized as an antioxidant drug. The relationship between bilastine and oxidative stress is therefore best considered context-dependent and mechanistically unresolved. Nrf2/HO-1 and NF-κB signaling provide plausible mechanistic links between redox regulation and inflammation (27, 28), but direct activation or inhibition of these pathways by bilastine has not been demonstrated. Consequently, the available evidence supports investigation of redox signaling as a potential mediator of bilastine-associated tissue protection rather than an established pharmacological mechanism.

Unresolved Molecular Mechanisms

Despite the emerging tissue-protective profile of bilastine, the molecular pathways responsible for these effects remain largely unresolved. The Nrf2/HO-1 axis represents a plausible candidate because of its established role in antioxidant

defense, glutathione metabolism, and ferroptosis regulation (29, 30). Similarly, the oxidative stress–NF-κB signaling axis may provide a plausible mechanistic link between H1R modulation and inflammatory responses (27, 31). Recent structural and functional evidence indicates that distinct H1R ligands can stabilize different receptor conformational states with corresponding changes in receptor signaling, providing a mechanistic basis for examining downstream pathways such as MAPK as candidate mediators of H1R-dependent cellular response (25). Mitochondrial homeostasis and ferroptosis represent additional, currently untested possibilities. Ferroptosis is driven by iron-dependent lipid peroxidation and is strongly regulated by pathways involving SLC7A11, GPX4, ACSL4, NRF2, and mitochondrial redox signaling (32, 33). However, no direct evidence currently demonstrates that bilastine activates Nrf2/HO-1, inhibits NF-κB or MAPK signaling, preserves mitochondrial function, or suppresses ferroptosis. These pathways should therefore be considered mechanistic hypotheses and priorities for future experimental validation, rather than established actions of bilastine.

Experimental Priorities

Future studies should directly determine whether the emerging tissue-protective effects of bilastine involve redox and regulated cell-death pathways. Priority experiments should evaluate Nrf2/HO-1 activation, NF-κB and MAPK signaling, mitochondrial function, and ferroptosis-related markers, including SLC7A11, GPX4, ACSL4, 4-HNE, and iron accumulation. These mechanisms should be investigated in relevant models of renal ischemia-reperfusion, drug-induced nephrotoxicity, and epithelial injury, with pharmacological inhibition or genetic approaches used to establish causality. A particularly informative experimental design would determine whether bilastine-induced protection depends on H1R signaling by using receptor-dependence approaches such as H1R knockdown or genetic validation, together with pathway-specific inhibitors where appropriate. This strategy could help distinguish receptor-dependent effects from nonspecific redox-related activity. For ferroptosis, rescue experiments using ferrostatin-1 or liproxstatin-1 could help determine whether lipid-peroxidation-dependent cell death contributes to the observed phenotype. The recent ocular studies provide a useful starting point for such mechanistic work but remain largely formulation- and cell-based (9).

Limitations of Current Evidence

Current evidence regarding the potential tissue-protective and redox-related effects of bilastine remains limited, with available studies differing substantially in experimental context and formulation. Recent clinical evidence has demonstrated favorable ocular safety and tolerability of topical bilastine, while other experimental findings suggest potential tissue-protective effects. However, these observations should be interpreted cautiously, as most available studies were not specifically designed to establish direct molecular causality or to define the signaling pathways underlying such effects (34, 35). Importantly, direct evidence linking bilastine to Nrf2/HO-1, NF-κB, MAPK, mitochondrial homeostasis, or ferroptosis remains absent or insufficient. Consequently, these pathways should be considered mechanistic hypotheses rather than established pharmacological actions. In addition, some observed effects may be attributable to formulation characteristics rather than bilastine itself, particularly in ocular studies. Finally, available clinical studies of bilastine have largely focused on symptomatic efficacy, quality of life, and safety outcomes in allergic diseases, rather than tissue-protective effects or redox-related biomarkers, highlighting a persistent gap between the proposed mechanistic actions and their clinical validation (36, 37).

Conclusions

Bilastine is an established second-generation H1-receptor antagonist whose pharmacological profile extends beyond conventional symptom control to include emerging anti-inflammatory and tissue-protective signals. However, current evidence for effects on oxidative stress remains limited, and available studies do not establish bilastine as a direct antioxidant or antiglycoxidative agent. Recent ocular studies provide evidence of favorable epithelial tolerability and potential effects on wound repair, while experimental renal findings further support a possible tissue-protective phenotype. The molecular basis of these effects remains unresolved. Nrf2/HO-1, NF-κB, MAPK, mitochondrial homeostasis, and ferroptosis represent plausible mechanistic pathways, but should currently be regarded as testable hypotheses rather than established actions of bilastine. Future studies incorporating pathway-specific interventions and validated models of tissue injury are therefore needed to determine whether H1R modulation by bilastine can causally influence redox homeostasis and regulated cell death. This evidence gap provides a clear direction for future translational research.

Mechanistic and Translational Relevance

Bilastine provides an informative model for examining how selective H1-receptor pharmacology may extend beyond classical antagonism of histamine-mediated responses. Its prolonged receptor residence and inverse agonist activity provide a plausible pharmacological basis for sustained suppression of agonist-driven and constitutive H1R signaling, respectively, with potential consequences for downstream inflammatory responses. Clinical and experimental observations involving inflammatory mediators such as IL-6, IL-8, and IL-17, together with evidence of renal protection and favorable epithelial responses, suggest that H1R modulation may influence inflammatory and tissue-remodeling processes; however, the molecular mechanisms linking bilastine to these effects remain incompletely defined. In particular, direct regulation of Nrf2/HO-1, NF-κB, MAPK signaling, mitochondrial homeostasis, or ferroptosis by bilastine has not been established. These pathways should therefore be considered testable mechanistic hypotheses rather than demonstrated pharmacological actions. From a translational perspective, determining whether such pathways contribute causally to bilastine-associated tissue protection could identify pharmacodynamic biomarkers and clarify previously unrecognized therapeutic dimensions of H1R modulation. Such investigations may also distinguish effects intrinsic to bilastine from those attributable to formulation-specific factors, particularly in ophthalmic applications. Rigorous preclinical studies incorporating pathway-specific pharmacological inhibition, genetic validation, receptor-dependence testing, and clinically relevant animal models of tissue injury, including cardiac, hepatic, renal, central nervous system, and peripheral neural injury, will be essential to determine whether the emerging tissue-protective phenotype represents a reproducible pharmacological property of bilastine and whether it can ultimately support clinically meaningful therapeutic applications.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interests

The author declares that there is no conflict of interest.

Author Contributions

The author was solely responsible for the conception and design of the review, literature search and selection, data interpretation and synthesis, drafting of the manuscript, and critical revision of the article. The author approved the final

version of the manuscript and agrees to be accountable for all aspects of the work.

Ethics Statement

All ethical considerations, including plagiarism, data fabrication, and duplicate publication, have been fully observed by the authors.

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