

Review

Histamine Intolerance: Mechanisms, Dietary Approaches, Microbiota Modulation, and Supplementation Strategies

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Abstract

Introduction: It is estimated that about 20–35% of the Western population reports symptoms of food intolerances, which is a growing trend. Intolerance to histamine, a dose-dependent, non-allergic food hypersensitivity reaction, despite similar clinical manifestations, has mechanisms distinct from food allergies. **Objectives:** This narrative review aims to ascertain and synthesize the evidence on the role of nutrition, microbiota modulation, and food supplementation in histamine intolerance. **Methods:** The search was conducted between September and October 2025 in the PubMed and ScienceDirect databases, using terms related to “histamine intolerance” and considering the last 10 years. 43 scientific articles and 5 additional regulatory and guidance documents were included. **Results:** The clinical manifestations of histamine intolerance are heterogeneous and complex, and different responses may occur in the same individual with equal doses of histamine. In the literature, intestinal dysbiosis promotes a local and systemic increase in histamine, triggering symptoms in predisposed individuals. The low-histamine diet induced a significant reduction in cutaneous and gastrointestinal symptoms. The literature also shows that diamine oxidase enzyme supplementation is promising in the treatment of migraines and chronic urticaria, contributing to a reduction in the dose and frequency of drugs. In addition, vitamins C and B6, S-adenosylmethionine, and magnesium have been studied in therapy. **Conclusions:** Histamine intolerance represents a challenge in clinical practice due to its complexity, symptomatologic diversity, and the lack of consensus regarding diagnosis and treatment.



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1. Introduction

It is estimated that around 20–35% of the Western population reports symptoms associated with food intolerances, and the trend appears to be increasing [1]. Although clinical manifestations of histamine intolerance (HI) can mimic those of food allergies, such as urticaria, gastrointestinal symptoms, headache, rhinitis, or even anaphylaxis-like symptoms, the two conditions are entirely different entities [2,3]. Food allergies are immune-mediated

reactions, through immunoglobulin E or cellular mechanisms, triggered by proteins present in food [4,5]. Although less frequent, these reactions can range from mild symptoms to severe anaphylactic reactions [5]. In contrast, histamine intolerance, a food intolerance, is typically less severe and designated as a non-allergic food hypersensitivity reaction according to the World Allergy Organization and does not involve the immune system [4,6]. Food intolerances frequently follow a dose-dependent pattern and seem to affect women more than men [7]. This difference is often forgotten, leading to misdiagnosis and inadequate management. Moreover, histamine intolerance is often confused with irritable bowel syndrome (IBS) and other functional gastrointestinal disorders like functional dyspepsia and non-celiac gluten sensitivity (NCGS) due to overlapping symptoms [5]. In addition, growing evidence suggests that intestinal dysbiosis plays a central role in the pathophysiology of HIT, with an increase in histamine-producing bacteria and reduced microbial diversity contributing to elevated histamine levels and impaired barrier function [6,8].

Histamine (2-[4-imidazole]-ethylamine) is a bioactive amine that is synthesized from L-histidine (an essential amino acid) through a decarboxylation process by histidine decarboxylase [9,10]. In humans, two main enzymatic pathways of histamine are known: diamine oxidase (DAO) and histamine-N-methyltransferase (HNMT). DAO is a copper, vitamin C, and B6-dependent enzyme encoded by the AOC1 gene, located on chromosome 7 (7q34-36) [11–14]. It acts in the extracellular space and is found mainly in the intestines, placenta, and kidneys; its action leads to the formation of imidazole acetaldehyde, which is subsequently converted to imidazole acetic acid for excretion. HNMT is a cytosolic enzyme and therefore acts exclusively in the intracellular space; it is expressed in most tissues, particularly in the liver and kidney. Methylation of histamine by HNMT results in N-methylhistamine, which is subsequently degraded by the enzyme monoamine oxidase B (MAOB) [15]. Histamine plays essential physiological roles, mainly mediated by binding to four types of receptors (H1, H2, H3, and H4), which activate cells via autocrine or paracrine mechanisms [6,16,17].

This narrative review aims to examine and synthesize existing research on the role of nutrition and food supplementation, with special emphasis on the clinical application of DAO enzyme supplements and aims to fill the gap between the relationship of gut microbiota dysbiosis and histamine levels. It will also address various diagnostic approaches to raise awareness of this topic among healthcare professionals. Figure 1 summarizes the mechanisms of histamine production, the contributing factors, and the management strategies for histamine intolerance.

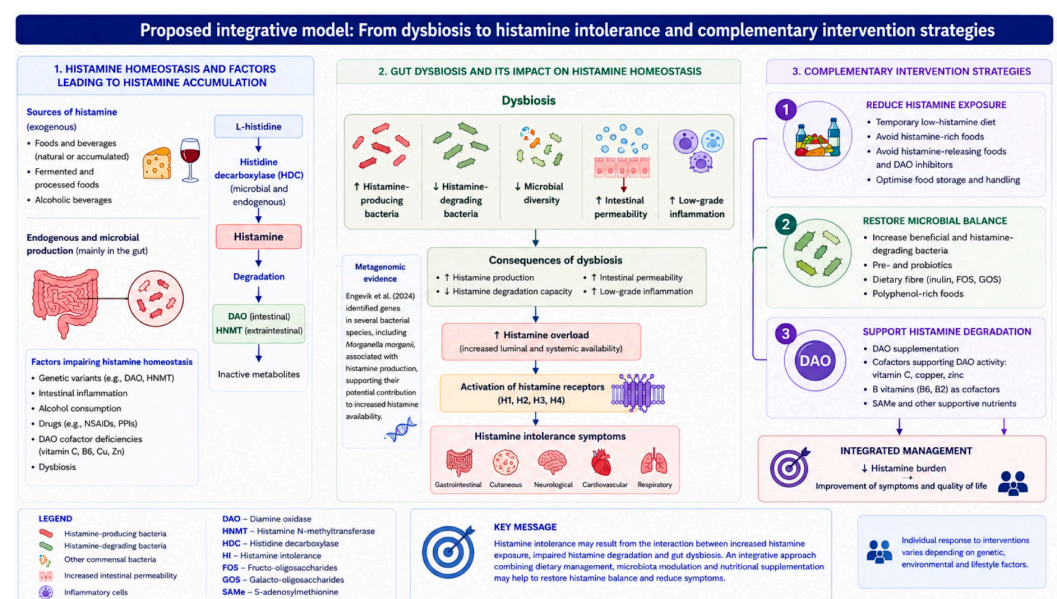


Figure 1. Towards an Integrative Model of Histamine Intolerance: From Increased Histamine Exposure to Complementary Management.

2. Materials and Methods

The bibliographic search for this review was conducted in PubMed (National Library of Medicine, Bethesda, MD, USA) and ScienceDirect (Elsevier B.V., Amsterdam, The Netherlands) between September and October 2025. The keywords “histamine intolerance”, “histamine sensitivity”, and “histamine metabolism disorder” were used together with the Boolean operators AND and OR.

The filters applied in the PubMed database included a time frame corresponding to the last 10 years (2015–2025), human studies involving individuals aged 19 years or older, and the following article types: Books and Documents, Case Reports, Classical Article, Clinical Conference, Clinical Study, Clinical Trial, Clinical Trial Protocol, Consensus Development Conference, NIH, Controlled Clinical Trial, Government Publication, Guideline, Legislation, Observational Study, Practice Guideline, and Randomized Controlled Trial.

However, two included studies employed murine microbiota models as complementary experimental approaches within research that also analyzed microbiota samples from human volunteers. Review articles and studies whose title and/or abstract were not aligned with the topic were also excluded.

Additionally, searches were conducted on the European Union platform EUR-Lex, the European Food Safety Authority (EFSA) website, and the book “Integrative and Functional Medical Nutrition Therapy”.

In total, 43 scientific articles, 3 regulatory guidance documents issued by the European Commission, 1 EFSA opinion, and 1 additional set of guidelines from medical specialty societies were included. All references were managed using EndNote software (Version 21; Clarivate Analytics, Philadelphia, PA, USA).

3. Histamine Intolerance

It is estimated that about 1% of the population is histamine intolerant [6,8,15]. However, its impact may be even greater than current estimates suggest [6,13]. HI arises in the gut, leading to an imbalance between histamine degradation and accumulation [18]. This imbalance may result from reduced activity of the main degrading enzymes—DAO in the extracellular space and HNMT intracellularly—or from excessive histamine production by gut bacteria [8,10,12,19,20]. This may be due to genetic or acquired causes such as certain drugs, alcohol consumption, or deficiencies in cofactors like vitamin B6, vitamin C, copper, and zinc [6,12,20]. Reduced DAO activity has also been observed in conditions such as chronic kidney disease, viral hepatitis, and liver cirrhosis [12]. Several small intestine pathologies, which impair mucosal integrity, result in compromised DAO activity, which correlates with the severity of mucosal destruction. Thus, DAO has been proposed as a biomarker of mucosal integrity [1,21]. Similarly, a dysbiotic gut microbiota can contribute to increased histamine levels [19]. Patients with HI often reveal an overgrowth of histamine-producing bacteria and decreased abundance of beneficial colonies, leading to increased luminal histamine production and impaired gut barrier function [8,19].

More than 50 single nucleotide polymorphisms that affect DAO enzyme activity have been identified [6,20]. These significantly influence DAO expression and activity but on their own may not be sufficient for the development of HI [12].

4. Clinical Manifestations and Diagnosis of Histamine Intolerance

4.1. Signs and Symptoms

Since histamine receptors are ubiquitous in the body, the clinical manifestations are heterogeneous and complex [8]. Substantial inter- and intra-individual variability exists in clinical presentation and intensity. The same individual may tolerate different amounts of histamine on different occasions, depending on factors such as gut microbiota

composition, DAO activity at the time, cofactor status, concurrent intake of other biogenic amines, alcohol consumption, and hormonal fluctuations (particularly in women). Sensitivity varies according to the menstrual cycle, being higher in the follicular phase and decreasing in the luteal phase, when DAO levels tend to be higher [12]. During pregnancy, placental DAO production can increase up to 500-fold, which often leads to the temporary disappearance of HI symptoms in pregnant women [15]. These variants explain why identical histamine loads can trigger significantly different patterns of symptoms even in the same person [12,13].

According to the reference [3], gastrointestinal symptoms are the most frequently reported, followed by cutaneous and neurological symptoms, such as headache [3,22].

Table 1 summarizes the symptoms described according to the affected organs and systems.

Table 1. Main signs and symptoms described, adapted from [2].

Organs and Systems	Symptoms
Gastrointestinal (H1, H2, H3, H4)	Bloating, flatulence, postprandial fullness, diarrhea, abdominal pain, constipation, nausea, vomiting
Respiratory (H1, H2, H3)	Rhinorrhea, rhinitis, nasal congestion, dyspnea, sneezing
Skin (H1, H2, H4)	Pruritus, flushing, urticaria, dermatitis, swelling
Cardiovascular (H1, H2)	Tachycardia, hypotonia, collapse
Nervous System (H2, H3)	Headache/migraine, dizziness

4.2. Diagnosis and Complementary Diagnostic Methods

In individuals presenting with nonspecific, non-allergic functional gastrointestinal complaints, the assessment of histamine intolerance should be considered as part of the diagnostic workup [21]. It should also be considered in the evaluation of patients with asthma, chronic urticaria, atopic dermatitis [2,13], fibromyalgia, attention deficit hyperactivity disorder [23], and migraine [22]. The diagnosis is mainly clinical, and a complete anamnesis is essential [2]. In a study by Rentzos et al., where serum DAO concentrations were measured at the baseline and during each phase of the diet (low histamine or mixed), including a control group that followed an unrestricted diet, although a significant reduction in gastrointestinal and cutaneous symptoms was observed, no consistent differences in DAO levels were identified among the different groups studied [13]. Elevated DAO values (above 16 U/mL) may be useful for ruling out HI; low values are relatively common and are not diagnostic [3]. Although a reference range for normal serum DAO has been proposed, clinical monitoring of symptom response to a histamine-restricted diet seems to be more reliable for the existence of HI [22]. Nevertheless, symptom assessment remains subjective, and symptoms are frequently reported in placebo groups [13]. Measurement of decreased urinary metabolite concentration, such as methylhistamine, could be a more objective, reliable, and non-invasive diagnostic biomarker [2].

The oral provocation test, performed in a single-blind, placebo-controlled study, has been proposed as a “gold standard” method for excluding the diagnosis. In individuals who experienced symptoms after histamine administration, such as diarrhea or facial flushing, but not after placebo, the diagnosis could be supported. However, the placebo group had a high rate of reactions (62.7%), which limits the ability to unequivocally confirm hypersensitivity, although the test may help exclude the diagnosis in many patients. Further double-blind, prospective studies with a larger and more diverse sample and a healthy control group are needed for diagnosis accuracy. Greater standardization is also required

regarding the dose of histamine administered, diet design, symptom assessment and other complementary diagnostic methods [3].

5. Histamine in Food

Dietary histamine and other amines are present at significant levels in various foods (Table 2). Other biogenic amines, produced by bacterial fermentation, such as cadaverine, tryptamine, tyramine, and serotonin, among others, and/or polyamines (putrescine, spermidine, and others), can also cause adverse reactions by affecting histamine metabolism [18,24]. Foods containing other amines, as well as histamine-releasing foods, are presented in Table 2. Furthermore, the level of histamine in foods naturally increases through storage and cooking methods and varies geographically; therefore, a diet may be low in histamine but is unlikely to be histamine-free [18,25]. The cleanliness of materials and the microbial composition also influence the amount of histamine contained in the food [18]. In general, biogenic amines are thermostable; therefore, if they are already present in the food, heat treatment does not significantly degrade them. However, boiling in water can reduce the content of bioactive amines in certain types of vegetables, probably transferring them from the food to the water [8].

Table 2. Classification of foods according to their contribution to dietary histamine exposure, reported histamine concentrations, and recommended elimination strategy during a low-histamine diet. Adapted from [8,14,20,26].

Food Category		Main Mechanism	Reported Histamine Concentration (mg/kg) *	Recommendation During Elimination Phase
Fish and seafood products				
Fermented and canned fish	Sardines, mackerel, canned tuna	High histamine content	14.4 (ND–657.1)	Avoid
Fresh fish	Fresh cod, hake, sole	Usually low histamine, but highly storage-dependent	0.8 (ND–36.6)	Fresh products generally tolerated; consume immediately after purchase or freezing
Shellfish	Shrimp, lobster, oysters, clams, mussels	Histamine-releasing foods	Low or negligible histamine	Individual assessment only
Meat and meat products				
Dry-fermented sausages	High histamine content	High histamine content	32.2 (ND–357.7)	Avoid
Cured meat products	High histamine content	High histamine content	13.0 (ND–150.0)	Avoid
Smoked meat products	Smoked ham, smoked sausages	High histamine content	Variable	Avoid
Pork	Considered histamine-releasing food	Histamine-releasing foods	Low or negligible histamine	Individual assessment only
Dairy products				
Raw milk cheeses	Parmesan, Grana Padano	High histamine content	59.4 (ND–389.9)	Avoid
Ripened cheeses	Camembert, Gouda, Cheddar, Feta	Variable histamine content depending on ripening	18.1 (ND–162.0)	Usually avoid

Table 2. Cont.

Food Category		Main Mechanism	Reported Histamine Concentration (mg/kg) *	Recommendation During Elimination Phase
Alcoholic beverages				
Wine	Especially red wine	Variable histamine content and alcohol may interfere with histamine metabolism	3.8 (0.09–55.0)	Frequently restricted
Beer	-	Variable histamine content	1.2 (ND–21.6)	Frequently restricted
Vegetables				
	Tomato, spinach, sauerkraut	Variable histamine content	2.8 (ND–69.7)	Assess individual tolerance
	Pumpkin, Zucchini	Rich in competing biogenic amines (mainly putrescine); low histamine content	Low or not detected	Assess individual tolerance
	Tomato, Spinach	Described as histamine releaser	Low	Assess individual tolerance
Fruits				
	Fresh fruits	Generally low histamine content	0.07 (ND–2.51)	Generally permitted
	Pineapple, Banana, Citrus fruits, Strawberries	Rich in competing biogenic amines (mainly putrescine)	Low or not detected	Assess individual tolerance
	Pineapple, Lime, Lemon, Papaya, Strawberries, Kiwi	Described as histamine releasers	Low	Assess individual tolerance
Others				
Egg white	-	Histamine-releasing foods	Low or negligible histamine	Individual assessment only
Fermented soy products	Soy sauce, miso, tempeh	High histamine and other biogenic amines	Variable	Avoid
Legumes	Lentils, chickpeas, soybeans	Rich in other biogenic amines	Low	Assess individual tolerance
Chocolate	-	Rich in other biogenic amines; low histamine content	0.58 **	Assess individual tolerance
Nuts	Walnuts, peanuts, pistachios, almonds, cashews	Rich in other biogenic amines	Low	Assess individual tolerance
Coffee, Tea	-	Considered histamine-releasing food	Negligible	Assess individual tolerance

ND, not detected. * Values are expressed as mean histamine concentration (reported range). Histamine concentrations vary substantially according to raw material quality, microbial contamination, fermentation, ripening, storage conditions and analytical methodology. ** The published data for chocolate reported by [14] show inconsistencies between the reported mean and range and should, therefore, be interpreted cautiously.

According to EFSA, bioactive amines present in food can pose a danger to human life, and it has been suggested that these amines could weaken the protective barrier against dietary histamine [9,15].

Histamine formation in foods depends on the availability of free amino acids, the presence of decarboxylase-producing microorganisms, and environmental conditions that

promote microbial growth and enzymatic activity [8]. Free amino acids may be naturally present in food matrices or released during storage and processing through proteolytic reactions [18]. Histamine is generated from the amino acid L-histidine by bacterial or yeast strains possessing histidine decarboxylase activity, which explains why particularly high concentrations are frequently found in fermented and matured products such as aged cheeses, fermented vegetables, alcoholic beverages, and processed meats [8].

In this context, it is important to distinguish between foods that naturally contain histamine as part of their intrinsic composition and those in which histamine accumulates as a consequence of storage, maturation, or fermentation processes [18]. Certain foods, including tomatoes and shrimp, may contain baseline amounts of histamine irrespective of microbial activity. In contrast, fermented, aged, or improperly stored foods can accumulate substantially higher concentrations due to progressive protein degradation. During these processes, proteolysis releases free amino acids, particularly L-histidine, which can subsequently be converted into histamine by microorganisms with decarboxylase activity [8]. As a result, histamine concentrations may increase considerably depending on storage conditions, microbial contamination, and production practices [8].

Overall, current evidence supports reducing the intake of histamine-rich foods as the cornerstone of dietary management in histamine intolerance. However, recommendations regarding other dietary restrictions remain less robust and should be individualized according to clinical response to minimize unnecessary dietary limitations while maintaining nutritional adequacy [8,15].

6. Strategies for Intervention in Histamine Intolerance

6.1. Gut Microbiota and Dysbiosis as Modulatory Factors in Histamine Intolerance

The microbiota is a community of microorganisms, such as bacteria, viruses, and fungi, that cohabit each individual symbiotically. There is no universal eubiosis profile; however, some bacterial groups, such as Clostridiales, Bacteroides, Prevotella, and Bifidobacteria, have been associated with health. Moreover, environmental and lifestyle factors can alter the microbiota throughout the lifespan [27,28].

This community performs several functions, including immunological maturation and synthesis of nutrients, neuroactive molecules, and bioactive metabolites, such as histamine produced via histidine decarboxylation [19,28–30].

When dysbiosis occurs, the intestinal environment is imbalanced towards inflammation and the augmentation of intestinal permeability, which facilitates the translocation of pro-inflammatory molecules. This imbalance has been studied and implicated as a potential contributing factor for HI, usually associated with the reduced activity of the DAO enzyme, which may be secondary to the intestinal inflammation [19,31]. Furthermore, intestinal dysbiosis may involve a reduction in beneficial bacterial strains (*Akkermansia muciniphila*, *Limosilactobacillus reuteri*), alongside an increase in histamine-producing bacteria (*Enterococcus faecalis*, *Bifidobacterium pseudocatenulatum*, *Lactobacillus gasseri*, *Escherichia coli*, *Morganella morganii* and *Proteus mirabilis*) and a decrease in histamine-degrading bacteria, such as some bacterial strains of *Escherichia coli* and *Klebsiella pneumoniae*. These alterations, either isolated or combined, increase both local and systemic histamine, leading to the characteristic symptoms of HI in predisposed individuals [29,32].

From a metagenomic perspective, Engevik et al. analyzed the genomes of several bacteria and identified genes associated with the production and transport of histamine precursor substrates, confirming the enhanced capacity of bacterial species such as *Morganella morganii* to produce histamine. Considering that *M. morganii* is a bacterium associated

with the intestinal environment and presents a two-fold superior capacity to produce this molecule when compared to other species, dysbiosis profiles can favor the increased abundance of this bacterium and, consequently, contribute to an elevated histamine production [29].

However, elevated histamine levels may be caused by other factors, including the ingestion of histamine- or histidine-rich foods, which may increase endogenous histamine either by being a source of this molecule or by stimulating its release by granulocytes and mast cells in the intestinal epithelium, acting, therefore, synergistically with dysbiosis and DAO's reduced activity [32]. It is also important to consider microbial metabolites, such as putrescine and cadaverine, as they can inhibit DAO's activity, which, in turn, aggravates the symptoms [30].

Having this under consideration, complementary tools have been studied, namely probiotic supplementation. In the study by Di Cesare et al., the authors tested the impact of administering a probiotic containing strains of *Lactiplantibacillus plantarum*, *Lactiacaseibacillus rhamnosus*, *Limosilactobacillus fermentum*, and *Bifidobacterium longum* in two phases over eight weeks. They found suggestive alterations of the improvement of both the microbiota's composition and richness, as found in the alterations in the urinary and serum microbiota's metabolites, for example, the reduction in the aminoacidic derivatives, typical of dysbiosis. These alterations were not associated with changes in microbial mass. Additionally, a reduction in histidine utilization and, consequently, in histamine formation and related symptoms was observed [28].

Nevertheless, most studies in the literature are conducted with reduced sample sizes, frequently within specific pathological conditions, such as inflammatory bowel disease, or, conversely, with healthy volunteers or using animal or in vitro models, which limits the extrapolation of results to different contexts. However, even with these limitations, the microbiota and its modulation have emerged as a potential route for the management of HI profiles. Thus, strategies that promote microbial diversity, either by increasing beneficial bacterial strains or limiting the presence of histamine-producing bacterial species, may contribute to a reduction in inflammation and, ultimately, the attenuation of the symptoms associated with HI. The temporary restriction of histamine- and histidine-rich foods and the supplementation with enzymatic cofactors or microbiota regulators are two examples of complementary strategies, with synergistic effects, that may support histamine degradation and help mitigate clinical symptoms.

6.2. Low-Histamine Diet: Principles and Clinical Application

The Low Histamine Diet (LHD) is considered the main therapeutic strategy for histamine intolerance. The response to a low-histamine diet and the reintroduction of histamine-rich foods, in addition to being a basis of clinical evaluation, is also a main form of diagnosis. Its main objective is a controlled reduction in histamine-rich foods that can raise systemic histamine levels [2]. Typically, the LHD is divided into phase 1, in which there is a 2-week dietary restriction of foods rich in histamine and other biogenic amines (Table 2); phase 2 involves the gradual reintroduction of foods excluded in phase 1, taking into account the individual's food preferences, and an assessment of individual sensitivity to ingested histamine is made; phase 3 is considered the long-term diet, in which individual nutritional recommendations are made based on individual sensitivity to ingested histamine, taking into account exogenous risk factors and quality of life [11]. The LHD should exclude several foods based on their histamine content. In Table 2, we present a list of foods that are most frequently recommended to be excluded in the LHD. The elimination diet should also include the exclusion of foods suspected of triggering histamine release and also foods rich in other biogenic amines, since these

act as competitive substrates for the DAO enzyme, compromising its ability to degrade histamine and, consequently, the effectiveness of the intestinal barrier (Table 2) [2].

The rationale for the LHD is supported by the considerable variability in histamine concentrations among foods and the mechanisms underlying its formation and accumulation [8]. While some foods naturally contain histamine as part of their intrinsic composition, others may develop substantially higher concentrations during storage, maturation, fermentation, or inadequate handling due to microbial decarboxylation of L-histidine [8]. Consequently, exposure to dietary histamine is influenced not only by food selection but also by factors such as freshness, processing methods, storage conditions, and microbial contamination [18]. This variability, together with the potential contribution of other biogenic amines that may interfere with histamine degradation, reinforces the need for an individualized dietary approach aimed at reducing the overall histamine burden while identifying each patient's specific tolerance threshold.

From a clinical perspective, the LHD should be implemented as a structured elimination–reintroduction strategy following a comprehensive clinical assessment and the exclusion of alternative diagnoses [11]. Rather than constituting a permanent restrictive diet, its primary purpose is to evaluate the relationship between dietary histamine exposure and symptom occurrence, allowing the identification of each patient's individual tolerance threshold [11]. Consequently, dietary management should be individualized and supervised by a qualified healthcare professional to ensure nutritional adequacy while minimizing unnecessary dietary restrictions [2].

Effects, Therapeutic Applications, and Limitations of LHD

Considering the available clinical evidence, adherence to an LHD has been reported as effective in reducing gastrointestinal, dermatological, and ear, nose, and throat symptoms [13,33–36]. A compilation of studies involving the application of LHD is presented in Table 3. LHD induced a significant reduction in cutaneous (urticaria, pruritus) and gastrointestinal symptoms compared to mixed diets [13]. In patients with Chronic Spontaneous Urticaria, LHD resulted in symptomatic improvement in 75% of individuals, with a reduction in the Urticaria Activity Score and improved quality of life [33]. A significant reduction in plasma histamine levels was observed after four weeks of LHD in patients with chronic urticaria, indicating that plasma histamine levels may be diet-dependent in these individuals [34]. In a case report, adherence to LHD significantly improved cough and throat clearing symptoms in a patient with persistent laryngopharyngeal reflux, with the Reflux Finding Score improving from 11 to 6 [36].

Despite the symptomatic benefits, LHD presents challenges and limitations to be considered. Among them are inconsistencies in serum DAO, symptomatic variability, and risks of long-term restriction. In the case of inconsistency in serum DAO, it was found that in prospective and crossover clinical trials, short-term LHD did not show a significant ability to alter or raise serum DAO levels, so this measurement is considered inconclusive as a diagnostic tool or biomarker of dietary fluctuations [13]. However, in retrospective studies, it was found that strict and long-term adherence to LHD may correlate with an increase in serum DAO values, although the data are inconsistent [34]. In individuals with HI, there were no significant differences in headache severity between the LHD period and the mixed diet, reflecting symptomatic variability [13].

Table 3. Studies evaluating the efficacy of Low-Histamine Diet (LHD) and Diamine Oxidase (DAO) supplementation in histamine intolerance.

Reference	Study Type	Sample and Duration	Objectives	Results	Limitations
Low-Histamine Diet					
[36]	Case report	1 individual; 6 months	Describe a case of persistent laryngopharyngeal reflux and associated symptoms, aggravated or initiated by histamine	LHD showed improvement in the Reflux Finding Score and resolution of cough and throat clearing	Single case; Generalization of the study is impossible
[13]	Prospective Randomized Controlled Study Crossover	18 individuals; 3 weeks on LHD + 3 weeks on Mixed Diet (MXD)	Evaluate the activity of DAO measured in serum and correlate it with the LHD to assess histamine hypersensitivity related to dietary intake during the intervention period.	Gastrointestinal and cutaneous symptoms improved with LHD. No significant differences were observed in headache pain severity. No differences were found between MXD and DAO activity. Ten individuals showed stable levels or decreases in DAO after LHD. DAO prevalence was elevated only in the LHD group compared with control during MXD.	Small sample size. DAO measurement in serum has proven inconclusive as a diagnostic tool for HI, since values fluctuate after meals. The commercial method used (Sciotec DAO-REA [®]) was only validated for diagnostic purposes, not for comparison with histamine as substrate.
[33]	Prospective intervention study	56 individuals; 3 weeks	Investigate the impact of LHD on symptoms and quality of life in patients with Chronic Spontaneous Urticaria (CSU).	≥1 point reduction in UAS4 (Urticaria Activity Score over 4 days) occurred in all individuals. 75% benefited from LHD. DAO activity remained stable after the diet.	No control group and was not double-blind. DAO was evaluated as a biomarker recommended in CSU patients, but enzyme activity remained stable.
[35]	Retrospective study of patient records and follow-up questionnaire to evaluate diet adherence and symptom evolution	101 individuals; median follow-up of 13 months (range: 2–44 months)	LHD improves symptoms of histamine intolerance and increases serum DAO values correlating with diet adherence.	Serum DAO levels increased significantly after starting LHD. A significant DAO increase occurred in individuals adhering strictly or occasionally to the diet. Overall, 79% reported symptom improvement (or symptom resolution). Among the 50 individuals with symptomatic improvement, there was a significant increase in DAO.	Retrospective analysis dependent on self-reported diet classification. The duration of follow-up varied widely (median 13 months).
[37]	Prospective observational study	78 individuals; 72 followed dietary recommendations	Investigate clinical and laboratory predictors (including serum DAO levels) of efficacy of treatments and a low-histamine diet in individuals with chronic urticaria.	76.4% reported symptom improvement with LHD. DAO < 5.4 U/mL and multiple food triggers were significantly associated with greater likelihood of responding to LHD.	DAO efficacy as a predictor of LHD response was based on a single cutoff value (5.4 U/mL) from the study cohort. Medication adherence was self-reported, which may introduce bias.

Table 3. Cont.

Reference	Study Type	Sample and Duration	Objectives	Results	Limitations
Low-Histamine Diet					
[34]	Prospective dietary intervention study	22 individuals; 4-week low-histamine diet	Evaluate the role of ingested histamine in adults with CSU and determine DAO activity and histamine levels before and after the diet.	USS and UAS significantly improved after 4 weeks of LHD. A significant reduction occurred in pruritus severity, number of days with urticaria, and distribution of lesions. No significant changes in plasma DAO activity were observed. No influence was found from changes in antihistamine or prednisone use.	Small sample size. Participants did not discontinue antihistamines, which could influence plasma DAO activity.
DAO Supplementation					
[38]	Experimental Randomized Clinical Trial Placebo-Controlled Double-blind Crossover	20 individuals; 105 days; Placebo or animal-based DAO	Test the hypothesis that DAO supplements may reduce the severity of CSU in individuals unresponsive to a single daily dose of antihistamine and on a low-histamine diet during 21 days.	Reduction in the 7-Day Urticaria Activity Score in all individuals with DAO deficiency compared to the placebo group ($p = 0.041$). Slight but significant reduction ($p = 0.049$) in antihistamine use during supplementation with DAO.	Small sample size. No dietary records available.
[22]	Experimental Randomized Clinical Trial Placebo-Controlled Double-blind	82 individuals; 1 month; Placebo or animal-based DAO	Test DAO supplementation as a preventive treatment for migraines in individuals diagnosed according to the criteria of the International Headache Society, with DAO deficiency (<80 HDU/mL)	Statistically significant reduction ($p = 0.0217$) in the DAO group regarding migraine duration. Reduction in triptan observed in the DAO group. Reduction in pain frequency and intensity observed in both groups.	Treatment duration. No dietary records available.
Low-Histamine Diet and DAO Supplementation					
[2]	Prospective Trial Protocol Randomized Placebo-Controlled Double-blind	400 individuals (8 groups of 50 individuals); Start: 06/2022 Expected conclusion: 05/2025; Placebo, animal-based DAO, or plant-based DAO	Test the efficacy of a LHD and/or food supplements containing DAO in improving symptoms of HI.	Results not yet published.	Smaller sample per group. Potential bias in dietary records.

Low-histamine diet (LHD); Mixed diet (MXD); Diamine oxidase (DAO); Chronic Spontaneous Urticaria (CSU); UAS/UAS4 = Urticaria Activity Score; Urticaria Severity Score (USS).

However, the strength of this evidence is tempered by substantial methodological limitations, including small sample sizes, a reliance on retrospective data, and the absence of standardized food lists, which complicates cross-study comparisons. In addition, the clinical utility of serum DAO as a biomarker for monitoring dietary response remains uncertain, reflecting the broader lack of validated diagnostic tools for histamine intolerance [13,35]. Furthermore, the lack of long-term randomized controlled trials leaves the optimal duration and the physiological impact of prolonged restriction largely unknown. In fact, prolonged dietary restriction, complexity and lack of concrete food lists can lead to risks including malnutrition, social isolation and a propensity for unbalanced eating patterns [26]. The long-term goal of dietary management is therefore to identify each individual's tolerance threshold and establish the least restrictive dietary pattern capable of controlling symptoms while maintaining nutritional adequacy and quality of life. Future research should prioritize large-scale, placebo-controlled provocation studies and the development of validated diagnostic tools to establish clear tolerance thresholds.

6.3. Role of Supplementation

6.3.1. Oral DAO Supplementation: Forms and Clinical Evidence

Currently, there are two types of DAO food supplements on the market: animal-based and plant-based. Animal-based products, which are more widely marketed, contain a protein extract obtained from pig kidneys, approved as a novel food under Commission Implementing Regulation (EU) 2017/2470 [39]. The maximum authorized amount of this extract is 12.6 mg with 7% DAO per day, 0.9 mg of DAO in total. This means that, to avoid exceeding the maximum permitted dose, the recommended dosage is 4.2 mg of porcine kidney protein extract with 0.3 mg of DAO per dose, administered three times a day [39–41].

Initially, Commission Implementing Regulation (EU) 2018/1023 only authorized the use of porcine kidney protein extract as a Food Supplement (FS) in the form of enteric-coated, encapsulated micro pellets [41]. Subsequently, Commission Implementing Regulation (EU) 2024/2048 amended this condition, establishing that the safety and efficacy of DAO supplements should be based on the amount of enzyme, regardless of the pharmaceutical form used [40].

Plant-based DAO supplements have been more recently introduced to the market and contain legume sprouts, especially green peas (*Pisum sativum*) [2].

As shown in Table 3, Refs. [22] and [38] used DAO enzyme in capsules, whereas Ref. [2] used tablets. In all three studies, DAO enzyme of animal origin was used; however, Ref. [2] also used DAO of plant origin, at doses of 4.2 and 8.4 mg per tablet [2,22,38].

According to the studies mentioned, food supplements with DAO show promise in the treatment of symptoms associated with HI, especially in cases of migraine and chronic urticaria. In addition, DAO supplementation may help reduce the dose and frequency of medications such as triptans and antihistamines. DAO food supplement is safe and well tolerated, with no significant reports of adverse effects [22,38]. However, these results should be interpreted with caution, given that the current scientific evidence is still limited. Larger randomized controlled trials with standardized methodologies are required to confirm the clinical effectiveness of DAO supplementation, determine the optimal dosage, and compare the effectiveness of supplements derived from different sources, thereby supporting a more evidence-based application of this strategy in the management of HI.

6.3.2. Other Food Supplements in the Therapy of HI

Scientific evidence on food supplementation as an adjunct therapy for histamine intolerance is limited [8]. The most frequently reported supplements include vitamin C, vitamin

B6, copper and zinc, as they may support histamine degradation and increase DAO [6,20]. Supplementation with probiotics has been proposed as a strategy to modulate the gut microbiota by reducing the production of the microbial enzyme L-histidine decarboxylase, i.e., by administering strains that do not produce this enzyme and, ideally, can simultaneously degrade histamine [8]. Positive effects have been reported with pancreatic enzyme supplementation, particularly in controlling gastrointestinal symptoms [20].

At the intracellular level, histamine is degraded by HNMT, which is predominantly expressed in the liver. Individuals with genetic variations that reduce HNMT activity may benefit from additional cofactor support to enhance this pathway. S-adenosylmethionine (S-AdoMet) plays a key role in this process, as HNMT uses S-AdoMet to convert histamine into N-methylhistamine, which is subsequently further degraded by MAOB.

If MAO-B activity is impaired due to insufficient cofactors or genetic polymorphisms, the degradation rate may decrease, potentially leading to histamine accumulation. In this context, riboflavin plays an important role, as it acts as a cofactor for MAO-B and supports the proper functioning of this enzymatic pathway.

Additionally, magnesium supplementation appears to exert protective effects by inducing relaxation of bronchial smooth muscle, reducing the histamine response through its anti-inflammatory effect, and decreasing susceptibility to developing anaphylactic reactions [42]. Current evidence suggests that food supplementation may represent a promising adjunct to dietary management of histamine intolerance [6,20]. However, clinical recommendations remain constrained by the limited number of high-quality intervention studies. Most proposed supplements are supported primarily by mechanistic evidence, with few trials specifically evaluating their effectiveness in patients with histamine intolerance. Therefore, further evidence is needed to validate the benefit, safety, and potential synergy of supplementation in the management of histamine intolerance, thereby supporting its integration into clinical practice.

Histamine intolerance (HI) is associated with an increase in histamine concentration that can result from two main sources: microbial dysbiosis, through alterations in histamine-producing and histamine-degrading bacterial strains or in overall microbial diversity, and dietary exposure, through the ingestion of histamine-rich foods, foods that potentiate histamine release, or histamine formed in food as a result of improper handling. Accordingly, complementary management strategies—including microbial modulation, dietary supplementation, and good food handling and culinary practices—may prevent or reduce this excess exposure and thereby alleviate the symptoms characteristic of HI.

7. Conclusions

HI represents a clinical challenge due to its complex nature, the diversity and non-specificity of signs and symptoms, and the lack of a validated diagnostic test and optimal management strategies [10,43]. Although genetic polymorphisms influence DAO enzyme expression, clinical heterogeneity also depends on environmental and nutritional factors, such as the histamine content in foods [12,18], and the microbiota modulation.

Unlike previous reviews, which have primarily addressed the pathophysiology or dietary management of histamine intolerance separately, this review critically examines how alterations in gut microbiota, histamine metabolism, and nutritional interventions—including DAO and other food supplement strategies—interact in the pathophysiology and management of this condition. By integrating these dimensions within a single framework, this review offers a broader and more comprehensive understanding of histamine intolerance as a multifactorial condition. Nevertheless, the available evidence remains limited by methodological heterogeneity, small sample sizes, and the lack of standardized diagnostic criteria. By identifying current evidence, limitations, and knowledge gaps, this

review provides an updated foundation to support future research and a more personalized approach to clinical management.

In conclusion, HI is a multifactorial condition in which genetic susceptibility, gut microbiota, and dietary factors interact to influence symptom development. Current evidence supports a personalized nutritional approach, with a low-histamine diet remaining the cornerstone of management, while gut microbiota modulation and targeted supplementation may represent promising adjunctive strategies.

8. Future Perspectives

Future research should therefore focus on validating reliable biomarkers, establishing internationally accepted diagnostic criteria, clarifying the interplay between gut microbiota and histamine metabolism, and conducting well-designed randomized controlled trials to determine the efficacy of dietary and nutraceutical interventions and to support evidence-based, personalized management of histamine intolerance.

A future multidisciplinary approach becomes fundamental to ensure a more accurate diagnosis and personalized treatment.

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Abbreviations

The following abbreviations are used in this manuscript:

HI	Histamine intolerance
DAO	Diamine oxidase
MAOB	Enzyme monoamine oxidase B
HNMT	Histamine-N-methyltransferase
EFSA	European Food Safety Authority
LHD	Low Histamine Diet
SAMe	S-adenosylmethionine

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