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Review

Diamine oxidase deficiency implications for health, current management, and future directions in the treatment of histamine intolerance: A review

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ABSTRACT

Diamine oxidase (DAO) is a key enzyme responsible for the metabolism of histamine, preventing its excessive accumulation and thereby maintaining physiological homeostasis. When DAO activity is insufficient, histamine intolerance (HIT) arises, manifesting as migraines, gastrointestinal disturbances, and allergy-like reactions, among other disorders. This review provides a comprehensive examination of DAO's biological role and its involvement in pathologies associated with impaired histamine degradation. Moreover, genetic and dietary factors influencing DAO activity are explored, emphasising their significance in histamine metabolism. In addition, it analyses clinical trials assessing the efficacy of DAO supplementation, shedding light on its therapeutic potential. Recent advancements in supplementation strategies are also highlighted, particularly those aimed at mitigating HIT symptoms. Furthermore, this review evaluates DAO-rich supplements in detail, focusing on the intrinsic differences arising from their diverse sources. Lastly, current challenges are discussed, including the lack of standardised diagnostic methods, limitations in supplementation efficacy, and gaps in the regulatory framework. By synthesising current evidence, this review aims to offer insights that guide future research and foster the development of innovative diagnostic and therapeutic strategies for the effective management of histamine intolerance caused by DAO deficiency.

0. Introduction

Diamine oxidase (DAO) is a critical enzyme in the regulation of histamine levels, particularly in the gastrointestinal tract, where it degrades exogenous histamine derived from food. DAO deficiency can disrupt this homeostatic mechanism, leading to histamine intolerance (HIT) and a range of clinical symptoms [1]. Histamine is produced endogenously from L-histidine by the enzyme histidine decarboxylase in mast cells, basophils, and several neuronal and immune lineages, whereas exogenous histamine chiefly enters the body through the consumption of fermented, aged, or microbially modified foods rich in biogenic amines [2]. The pleiotropic actions of this amine are transduced by four G-protein-coupled receptors (H_1–H_4) distributed across vascular, neural, immune, and gastrointestinal tissues, accounting for the heterogeneous clinical manifestations that arise when histamine homeostasis is perturbed [3]. Clearance of free histamine relies on two complementary catabolic routes—cytosolic histamine-*N*-methyltransferase (HNMT) and extracellular DAO.

Abbreviations: AD, *Atopic dermatitis*; ADHD, *Attention-deficit/hyperactivity disorder*; AMPP, *American Migraine Prevalence and Prevention* Study; AOC1, *Amine oxidase, copper-containing 1* (gene encoding DAO); CHO, *Chinese hamster ovary* (cell line); CNS, *Central nervous system*; CSU, *Chronic spontaneous urticaria*; DAO, *Diamine oxidase*; EC, *Enzyme Commission* number for enzyme classification (e.g., DAO [EC 1.4.3.22]); EFSA, *European Food Safety Authority*; EU, *European Union*; FL, *Fluorescence detection* (as in HPLC-FL); FM, *Fructose malabsorption*; H1, *Histamine H1 receptor*; H2, *Histamine H2 receptor*; H3, *Histamine H3 receptor*; H4, *Histamine H4 receptor*; HDC, *L-histidine decarboxylase*; HDU, *Histamine-degrading unit*; HIT, *Histamine intolerance*; HNMT, *Histamine N-methyltransferase*; HPLC, *High-performance liquid chromatography*; IBS, *Irritable bowel syndrome*; LI, *Lactose intolerance*; MS, *Mass spectrometry* (in HPLC-MS); OCT, *Organic cation transporter*; PMAT, *Plasma membrane monoamine transporter*; SIBO, *Small intestinal bacterial overgrowth*; TPQ, *Topaquinone* (copper amine-oxidase cofactor); UAS, *Urticaria Activity Score* (clinical severity scale).

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DAO is highly expressed in mature enterocytes and stored in vesicles on the basolateral membrane, forming a first-pass metabolic barrier that detoxifies luminal histamine before it reaches the portal circulation [2]. When factors that down-regulate intestinal DAO—whether genetic, pharmacological, or nutritional—override this barrier, histamine accumulates systemically, and it precipitates the clinical entity known as HIT [1], leading to a potential range of conditions, including migraines [4,5], skin disorders such as urticaria and atopic dermatitis [6], and fibromyalgia [7].

Given the broad spectrum of symptoms associated with HIT, management strategies are crucial to mitigate its impact on health. Recent research has highlighted the potential of DAO supplementation in alleviating symptoms by enhancing histamine degradation; particularly, in individuals with DAO deficiency [8,9] this could be a useful intervention alternative to dietary restriction of high-histamine foods.

1. Diamine oxidase and histamine metabolism

1.1. Histamine and histamine metabolism

Understanding the physiological role of DAO first requires an overview of histamine metabolism, including its sources, receptors, and regulatory pathways. Histamine is a multifunctional biogenic amine crucial in numerous physiological and pathological processes. It is synthesised from the amino acid histidine through the action of the enzyme histidine decarboxylase (HDC). This production occurs in various cell types, including mast cells, basophils and neurons (Fig. 1A). In addition to this endogenous histamine, this amine can also have exogenous origin, which is derived from dietary intake. Fermented products and improperly stored perishable foods such as fish and certain vegetables are rich in histamine, where it is synthesised by microorganism producing HDC that degrades food histidine [2].

Histamine normal range of serum levels is 0.3 to 1.0 ng/mL [10]. This amine can exert its effects either by activating extracellular membrane receptors or be taken up into cells by passive transport mediated by the plasma membrane monoamine transporter (PMAT) or via specific histamine transporters-organic cation transporters (OCT) [11]. Nevertheless, its effects are mainly mediated through four distinct histamine receptors (H_1, H_2, H_3, and H_4), each contributing to specific roles across different systems (Fig. 1B).

While H_1 and H_2 receptors have relatively low affinity (μM range), H_3 and H_4 receptors show high affinity for histamine (nM range). The H_1 receptor, mainly involved in allergic responses, is located in smooth muscle, endothelium, and the central nervous system (CNS). Its activation can cause vasodilation, bronchoconstriction, itching, and inflammation. H_2 receptors, concentrated in the gastric mucosa, regulate gastric acid secretion, affecting digestion and acid-base balance. In the CNS the H_3 receptor modulates neurotransmitter release, influencing sleep-wake cycles, appetite, and cognitive function, while the H_4 receptor, primarily found in bone marrow and immune cells, is associated with immune cell chemotaxis and inflammation, further linking histamine to immune regulation and inflammatory responses [3].

Therefore, histamine dysregulation, whether through excessive production, impaired enzymatic degradation, or increased intake from histamine-rich foods, can disrupt histamine homeostasis and lead to significant health complications. These complications manifest in a wide array of symptoms and conditions, including allergic reactions such as urticaria and anaphylaxis, gastrointestinal disturbances like bloating and diarrhoea, and chronic inflammatory conditions such as atopic dermatitis, and migraines [12]. The severity and range of these effects depend on both the level of histamine achieved and the sensitivity of affected histamine receptors across different organ systems [13].

Histamine degradation, key to preventing its accumulation and associated complications, primarily relies on two different enzymatic pathways, intracellular and an extracellular, each producing different metabolites (Fig. 1C). HNMT is an intracellular enzyme, which metabolises histamine in organs like liver, kidneys, and in systems like the CNS, catalysing the methylation of histamine [14]. In contrast to HNMT, DAO is responsible for extracellular histamine degradation in organs like the kidneys and the intestine, deaminating histamine into imidazole aldehyde [15]. Together, DAO and HNMT create a complementary system, with DAO managing extracellular histamine and HNMT

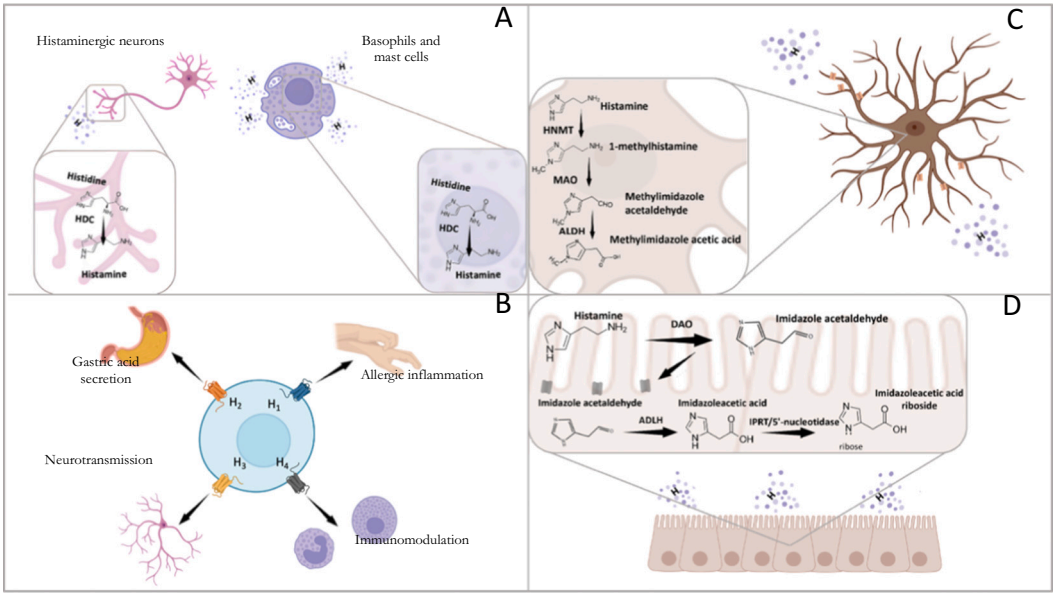

Fig. 1. Histamine metabolism. (A) Intracellular histamine production is mediated primarily by histaminergic neurons, basophils and mast cells, which convert histidine to histamine by the enzyme histidine decarboxylase (HDC). (B) Histamine mainly exerts its biological effects through four histamine receptor subtypes (H_1–H_4), which are distributed across diverse tissues, including smooth muscles, endothelium, gastrointestinal tract, the central nervous system, and immune cells, mediating functions such as gastric acid secretion, neurotransmission, and immune responses. (C) Intracellular histamine degradation is initiated by histamine-methyltransferase (HNMT) to generate 1-methylhistamine, which is further metabolized by monoamine oxidase (MAO) and aldehyde dehydrogenase (ALDH) until being converted to methylimidazole acetic acid. (D) In the intestinal epithelium, diamino oxidase (DAO) prevents histamine absorption from the gut lumen into the bloodstream, by converting dietary histamine to imidazole acetaldehyde, which in turn will continue being degraded to imidazoleacetic acid riboside.

addressing histamine within cells.

1.2. Diamine oxidase enzyme

The study of histamine metabolism has evolved significantly over the past century. In the early 20th century, histamine was first identified as a biologically active amine influencing several biological functions [16]. Subsequent research established the enzymatic pathways responsible for histamine degradation, notably identifying DAO as a critical enzyme involved in extracellular histamine breakdown [1]. The following years were characterised by an interest in DAO's clinical relevance, particularly concerning food histamine intolerance and gastrointestinal disorders [1,14]. More recently, advances in recombinant protein technology have enabled the production and characterisation of human DAO, fostering new therapeutic applications [17,18]. Emerging areas of research now explore plant-derived DAO sources, genetic polymorphisms affecting DAO activity, and the enzyme's potential as a biomarker and therapeutic agent in inflammatory and allergic diseases [19–21]. This historical trajectory underscores the growing recognition of DAO as a central figure in maintaining histamine homeostasis and its expanding role in clinical practice.

DAO [EC 1.4.3.22] belongs to the copper-containing amine oxidases family and is involved in the oxidative deamination of biogenic amines (primarily histamine), converting them to aldehydes while releasing ammonia and hydrogen peroxide as byproducts. The enzymatic activity of DAO is highly dependent on specific cofactors essential for its function. Copper ions (Cu^{2+}), calcium ions (Ca^{2+}), and topaquinone (TPQ) are recognised as the key cofactors of human DAO. These compounds act by facilitating the oxidation of amines, stabilising intermediate reaction states, and enhancing enzyme stability [15]. Structurally, DAO is an homodimeric enzyme, with each subunit containing a copper ion and a TPQ cofactor. The copper ion, coordinated by three histidine residues, is essential for catalysing the oxidative deamination of histamine and other biogenic amines [22,23]. Additionally, bioinformatics studies suggest the presence of calcium ions as additional cofactors, with two ions per subunit. These studies also indicate three glycosylation sites and three disulphide bonds, two of which stabilise each subunit individually, while the third forms an inter-subunit linkage, reinforcing the dimeric structure of the enzyme [24]. Furthermore, the precise positioning of its disulphide bridges likely contributes not only to the enzyme's stability but also to its substrate specificity, enabling high selectivity for histamine while showing no affinity for other amines, such as tyramine [25,26].

Regarding DAO's location, it is distributed in different tissues, mainly in intestine (in the brush-border) and in kidneys [27]. Intestinal DAO avoid excessive exogenous histamine absorption [1] (Fig. 1D) and renal DAO contributes to histamine reabsorption prevention [28]. Moreover, DAO activity is also very significant in placenta, avoiding the histamine circulation to the foetus [29], thus DAO potentially supports foetal development, as shown by elevated blood DAO activity during pregnancy [29,30].

While DAO is notably active in the gastrointestinal tract, it is also present in the blood at low concentrations. Serum DAO appears to originate from enterocytes, where it is stored in cytosolic vesicles and, upon stimulation, is released into the lamina propria, a connective tissue layer beneath the intestinal epithelium [1,31,32]. In this region, DAO may bind to extracellular matrix components or the basolateral membranes of enterocytes, facilitating its availability for further transport. From the lamina propria, DAO has been described to enter the lymphatic system, which transports interstitial fluid, enzymes, and other molecules. The lymphatic vessels would carry DAO to larger lymph nodes where it eventually drains into the bloodstream. Once in circulation, DAO can bind to endothelial cells lining blood vessels [33]. Although the exact mechanism of serum DAO origin needs further confirmation, its contribution to serum histamine regulation is better established [29,34]. According to this, it has been demonstrated a correlation between lower DAO serum levels and higher histamine concentrations, reinforcing the enzyme's role in maintaining histamine serum homeostasis [35].

Interestingly, plasma DAO levels are known to increase following heparin injection, [36]. One proposed explanation for this is a physiological mechanism during anaphylaxis, where mast cells degranulate and release heparin alongside histamine [37,38]. This simultaneous release may serve to enhance circulating DAO levels, facilitating the rapid degradation of blood histamine and mitigating histamine-mediated effects during severe allergic reactions. Furthermore, studies have confirmed the release of DAO during anaphylaxis, demonstrating its critical role in maintaining histamine homeostasis in the bloodstream under such conditions [39]. Moreover, an increasing number of studies show how individuals with lower levels of serum DAO activity have an increased risk of developing HIT [1].

Although the normal levels of DAO in the serum are not fully established yet, the ranges of DAO serum activity levels proposed by most researchers define distinct thresholds. Values equal to or above 10 U/mL (80 histamine degrading unit (HDU)/mL) are regarded as normal, levels between 3 and 10 U/mL (40–80 HDU/mL) are classified as moderately decreased, and values below 3 U/mL (40 HDU/mL) are considered significantly decreased. Therefore, subjects with serum DAO levels below 10 U/mL (80 HDU/mL) would be considered histamine-intolerant patients [40,41]. Nonetheless, it is important to note that the normal range of serum DAO levels, particularly for its use as a biomarker for HIT, remains a topic of ongoing discussion and debate [42,43]. The main advantages of measuring serum DAO as a biomarker are that it offers a non-invasive diagnostic option, as assessing DAO activity directly in the intestine would require biopsies, which are invasive and impractical for routine use. Current efforts are focused on validating serum DAO levels as a diagnostic tool.

While the correlation between intestinal and serum DAO levels remains to be fully established in humans [44], strong evidence from animal models and studies linking specific single nucleotide polymorphisms (SNPs) to reduced serum DAO activity suggests its potential as a biomarker for HIT [20]. The validation of this biomarker would offer significant benefits over the current reliance on dietary exclusion and histamine challenge methods, providing a more precise and objective approach to diagnosing and managing HIT [45,46]. Thus, developing accurate and accessible methods to measure DAO activity remains essential for both diagnostic and therapeutic purposes.

In mammals, DAO is coded by the AOC1 gene [47]. A few SNPs related to pathologies have been described in Caucasian and north Indian individuals, resulting in three amino acid substitutions, Thr16Met (rs10156191), Ser332Phe (rs1049742), and His645Asp (rs1049793), these variations could affect the functional enzyme structure, potentially preventing it from performing its intended biological function [5,48]. Furthermore, SNPs affecting the AOC1 promoter, which results in a decreased DAO expression, have also been described [4]. In addition, individuals who carry minor alleles of rs1049793, rs10156191, and rs2052129 in AOC1 have been observed to exhibit reduced serum DAO activity compared to those who do not carry these alleles, which can result in impaired histamine metabolism [4,5,49,50] (Fig. 2).

2. Disorders related to histamine intolerance

As previously mentioned, when histamine homeostasis is lost, HIT can occur, resulting in a spectrum of symptoms across multiple systems. This intolerance is often linked to DAO deficiency, which hinders the effective breakdown of histamine, allowing it to accumulate and affect various organs and systems [51]. The location and type of symptoms largely depend on which histamine receptor subtypes, H_1, H_2, H_3, or H_4, are activated, as each receptor is associated with distinct physiological effects in different tissues. Emerging evidence connects DAO deficiency with several pathologies, ranging from neurological to dermatological, gastrointestinal, and reproductive health issues [52]. Nevertheless, the presence of DAO deficiency does not necessarily equate to suffering from

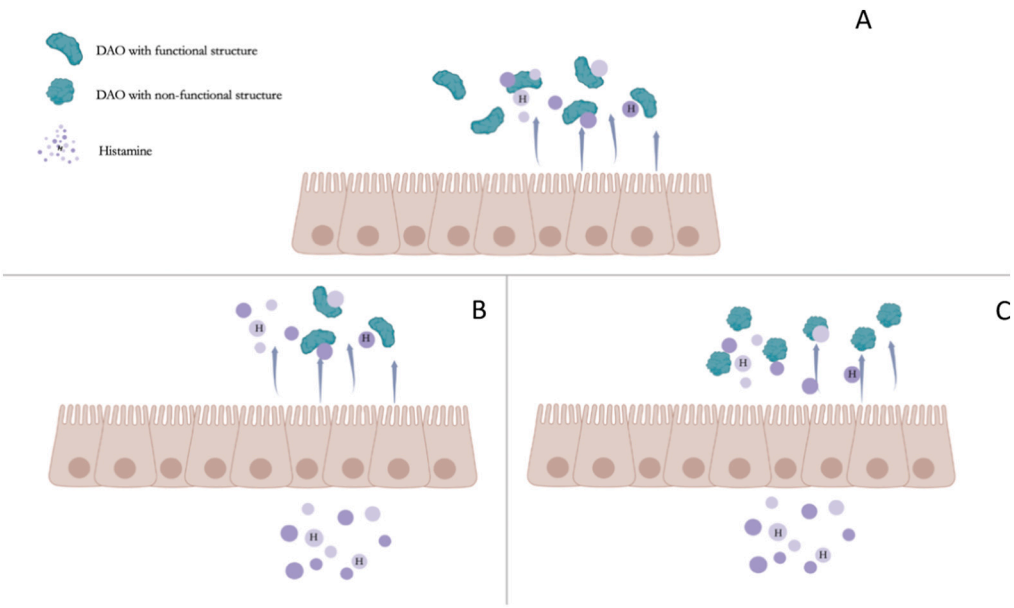

Fig. 2. Representation of diamine oxidase (DAO) enzyme in the intestinal tract of a healthy individual (A) and with DAO deficiency (B and C). Healthy individuals present higher amounts of the enzyme and with a functional structure to degrade histamine (A). On the contrary, individuals with DAO deficiency could either present lower levels of active DAO enzyme (B) or normal amounts of the enzyme with unfunctional structure (C)·H:Histame.

HIT [53]. Several mechanisms may account for this discrepancy, including the ability of specific strains of the microbiota to degrade histamine, variations in histamine load due to dietary differences, compensatory pathways for histamine degradation, and even polymorphisms in histamine receptors [54–57]. This phenomenon could be similar to what is observed in lactose intolerance, where not all individuals with lactose malabsorption experience the same severity of symptoms due to factors such as varying lactase activity levels and dietary habits [58]. However, this field remains in its early stages, and further research is needed to better understand these potential mitigating mechanisms. In this section, we explore the association of DAO deficiency and HIT with several common conditions, including migraines, skin disorders, intestinal problems, and reproductive health complications (Table 1).

As outlined in Table 1, the most frequently associated disorders include migraines, chronic spontaneous urticaria, atopic dermatitis [4,6,59]. Additionally, DAO deficiency has been linked to issues in female reproductive health [29] and food intolerances like lactose malabsorption [60]. These associations are supported by clinical and observational studies that report reduced serum DAO activity or improved symptoms following DAO supplementation in affected individuals [8,61]. The strength and nature of the association vary by condition, reflecting both direct enzymatic mechanisms and broader physiological factors such as intestinal integrity.

Table 1
Published studies investigating the prevalence of DAO deficiency and its association with several disorders.

Condition	Reference	Sample size (n)	Study design	Prevalence	Results
Allergy	[73]	53	Cross-sectional	55 %	Patients with IgE- or non-IgE-mediated allergy are likely to have low DAO blood activity and may concomitantly suffer from HIT.
Fibromyalgia	[7]	98	Epidemiology study	75 %	High prevalence of genetic DAO deficiency, specifically the presence of one or more alleles associated with low DAO activity in the four SNPs of the AOC1 gene, among Spanish women with fibromyalgia.
ADHD	[167]	40	Epidemiology study	82 %	82,1 % of the patients with attention deficit hyperactivity disorder (ADHD) presented reduced saliva DAO activity.
Skin related disorders	[6]	360	Observational study	19 %	19 % of patients with atopic eczema had lower levels of serum DAO. In addition, 20 % of HIT patients presented DAO deficiency as well, compared to 0 % in the control group.
	[61]	56	Prospective interventional study	56 %	The study found that a low-histamine diet is a useful tool to decrease symptoms and improve the quality of life in patients with CSU.
Chronic abdominal pain in the pediatric population	[168]	394	Observational study	8 %	Out of a total of 394, 31 of the patients who had recurring abdominal pain, had a typical history of HIT and lower serum DAO levels as well.
	[12]	16	Observational retrospective study	87 %	From a total of 16 patients, 14 of them had serum DAO levels that were less than 10 kU/L.
Migraine	[58]	198	Cross-sectional study	87 %	The prevalence of genetic DAO deficiency was found to be higher in the migraine group (87 %) compared to the control group.
Saccharides intolerance	[97]	439	Observational retrospective study	43 %	11.6 % of patients presenting GI discomfort and some sort of saccharide intolerance presented serum DAO levels lower than 3 kU/L and 31.4 % below 10 kU/L.
	[98]	279	Observational retrospective study	54 %	A total of 279 patients with lactose or lactose and fructose intolerance were studied, finding a 54.12 % overlap with low DAO serum levels.
	[60]	121	Observational retrospective study	36 %	Individuals with lactose malabsorption and a serum DAO activity level below 10 U/mL showed elevated end-expiratory hydrogen levels. From the entire cohort, 34.6 % of patients presented DAO deficiency.

2.1. Migraine

According to a study analysing data from the American migraine prevalence and prevention (AMPP) group, 43 % of women and 18 % of men report experiencing migraine at some point in their lifetime [62]. DAO deficiency could be involved in this condition since histamine is involved in various mechanisms associated with migraine pathogenesis, including inflammatory and allergic responses, gastric acid secretion, and neurotransmitter release [1]. Furthermore, DAO supplementation has been demonstrated to alleviate symptoms in migraine patients, further strengthening the association between DAO deficiency and migraine [61].

Indeed, García-Martín et al. investigated the association between four SNPs (rs2052129, rs10156191, rs1049742, and rs1049793) in the AOC1 gene, which are linked to decreased DAO activity, and the susceptibility to developing migraine in Caucasian Spanish cohort [5]. The study identified the rs10156191 SNP and gender as significant factors in migraine risk. Subgroup analysis revealed that male homozygotes with the rs2052129G allele and female carriers of the rs10156191T allele had a higher risk of developing migraine. Furthermore, the rs10156191T allele, which is associated with reduced DAO enzyme activity, was more prevalent among individuals with migraine, particularly in women.

DAO deficiency has also been evaluated in migraine sufferers. In a study by Izquierdo-Casas and colleagues, a high prevalence of DAO deficiency was observed in the migraine group, with 87 % of participants displaying this deficiency, compared to 44 % in the control group. Only 13 % of the migraine group exhibited normal DAO activity. While the study included more females than males, DAO deficiency rates were similar across genders (86 % in females and 90 % in males). The mean serum DAO activity in the migraine population was 64.5 ± 33.5 HDU/mL, which was significantly lower than that in the control group (91.9 ± 44.3 HDU/ml). Notably, the variability of DAO activity values among migraine patients was low, with 50 % of cases ranging between 49.5 and 67.1 HDU/mL [63].

Subsequently Izquierdo-Casas et al. conducted a double-blind trial to determine whether DAO supplementation could alleviate migraine episodes in migraine-affected population. The DAO-supplemented group showed a statistically significant reduction in pain duration after one month of treatment. Moreover, the mean duration of migraine attacks decreased by 1.4 h (from an initial mean of 6.1 h) with DAO supplementation. Additionally, there was a trend towards reduced triptan intake, family of drugs used to manage migraines, with some patients discontinuing use entirely. A decrease in the number of patients with low to moderate intake of triptans was also observed, indicating a potential reduction in pain intensity during migraine episodes. In contrast, the placebo group showed an increase in triptan intake compared to baseline levels [61].

2.2. Chronic spontaneous urticaria

Chronic spontaneous urticaria (CSU) is a skin disorder marked by recurrent wheals and/or angioedema persisting for over six weeks. Possible causes of CSU include chronic infections, autoreactivity, and intolerance to certain food components. Histamine, a primary mediator in CSU, plays a significant role in triggering wheals and angioedema [64]. Furthermore, HIT has been implicated as a potential cause of CSU, with some patients experiencing symptom exacerbation after consuming histamine-rich foods [59,65–67].

In a study by Siebenhaar and colleagues, the role of HIT in CSU was investigated by assessing symptom development after ingestion of histamine-rich foods, followed by a histamine-free diet and a double-blind, placebo-controlled histamine provocation. Findings showed that 17 % of patients responded to histamine provocation and experienced symptom relief with a histamine-free diet. Additionally, 46 % of patients reported significant improvement following a diet low in histamine, suggesting that, for some, symptom alleviation may stem from histamine avoidance. This research suggests that a subset of CSU patients may be affected by HIT [59].

In addition, Yacoub et al. examined the effects of DAO supplementation on CSU symptoms in a 30 day, double-blind, placebo-controlled, crossover trial involving CSU patients [9]. The results showed no significant correlation between baseline DAO levels and urticaria activity score (UAS-7) when considering the entire cohort. However, patients with low baseline DAO levels experienced a marked reduction in UAS-7 scores with DAO supplementation compared to placebo. Antihistamine drugs were evaluated, as they are routinary treatment for managing CSU when the person presents hives [68], showing a modest yet significant decrease in average daily antihistamine dosage during DAO supplementation. This study confirmed that DAO activity plays a role in CSU pathophysiology, and DAO supplementation could potentially aid in symptom control, particularly in patients with initially low DAO activity.

2.3. Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterised by pruritus, epidermal barrier dysfunction, dysregulated immune responses, and microbial dysbiosis [69]. The pathogenesis of AD is complex, involving both genetic predisposition and environmental triggers [70]. Nevertheless, AD presents across a spectrum of severity, ranging from moderate to severe, and affects both adolescents and adults. Current treatment options include topical corticosteroids and emollients for symptom management, as well as newer biologic therapies, such as lebrikizumab and tralokinumab [71,72].

In order to better understand the complexity of factors leading to this condition, the activity of DAO was studied in AD sufferers, as some research has proposed a possible histamine metabolism dysregulation in this condition [73,74]. In one study, a subgroup of AD patients exhibited an increased prevalence of HIT symptoms, potentially due to impaired histamine degradation [75]. Other studies have reported significantly lower DAO activity in the serum of AD patients relative to controls [6]. Notably, AD patients with HIT symptoms, low DAO activity, and elevated histamine levels also displayed a higher frequency of sensitisation to food allergens, headaches, and gastrointestinal symptoms [76]. These findings would imply that reduced DAO activity in AD patients may impair histamine degradation, thereby contributing to HIT symptoms and associated allergy.

2.4. Microbiota dysbiosis

The microbiota refers to the complex community of microorganisms, including bacteria, viruses, fungi, and other microscopic life forms, that inhabit a specific environment or ecosystem, being the most known the one within the gastrointestinal tract. This intricate ecosystem plays a fundamental role in maintaining human health by influencing numerous physiological processes [77].

One of the microbiota's critical functions is its role in immune system regulation, since it trains and modulates immune responses to maintain a balance between immune activation and tolerance [78]. Additionally, gut microbes are essential for nutrient metabolism, aiding in the breakdown and absorption of complex carbohydrates that human enzymes are unable to process [77]. Moreover, specific bacteria produce essential vitamins, including vitamin K and several B-complex vitamins, highlighting their contribution to host metabolism [79]. When the delicate balance of the microbiota is disrupted, a condition known as dysbiosis, these essential processes can become impaired. Dysbiosis, characterised by significant shifts in microbial populations, has been linked to various health issues due to the disruption of immune regulation, nutrient metabolism, and inflammation [80]. In addition to this, some studies have been performed to investigate the microbiota's relation with DAO deficiency and HIT.

In a recent investigation, Sánchez-Pérez et al. studied the potential

association between HIT symptoms and gut microbiota composition. Results showed dysbiosis in the gut microbiota of histamine-intolerant patients, characterised by a significantly lower proportion of beneficial gut bacteria and a higher abundance of histamine-secreting bacteria compared to healthy controls. Specifically, the HIT group exhibited a reduced abundance of Prevotellaceae, *Ruminococcus, Faecalibacterium* and *Faecablibacterium prausnitzii*, alongside an increased presence of histamine-secreting genera such as *Staphylococcus* and *Proteus,* which are linked to poor gut health. These findings suggested a potential role of gut microbiota in the development of HIT. The researchers proposed that a reduced abundance of Prevotellaceae may conclude in decreased mucin synthesis, which has been associated with increased gut permeability and mucosal inflammation, potentially impairing the functionality of DAO, which is involved in histamine metabolism [55].

In a follow-up study, the same research team further investigated and examined the effects of a 9-month dietary intervention for HIT on the intestinal microbiota composition in female patients. Using bacterial 16S rRNA gene sequencing, the study identified a significantly higher relative abundance of histamine-producing bacteria in histamine-intolerant sufferers compared to controls, specifically members of the Morganellaceae, Pseudomonadaceae, *Staphylococcus*, *Proteus, Proteus mirabilisis* and *Clostridium perfringens*. Additionally, a reduction in the relative abundance of the genus *Faecalibacterium,* a genus associated with a healthy gut, was observed within the HIT group. Notably, dietary treatment also increased the abundance of *Roseburia* spp., a bacterial group known for its positive impact on gut health, demonstrating that dietary management of histamine intolerance may beneficially alter gut microbiota composition [81].

The proposed mechanism of action suggests that the increase in beneficial microbial species may enhance competition for bacterial growth, thereby limiting the proliferation of histamine-producing bacteria, an already described phenomeon [82]. Additionally, the reduction in high-histamine foods and foods rich in histidine, the precursor to histamine would further limit, not only dietary histamine [83], but the availability of substrates required for bacterial histamine production [84–86]. Furthermore, the elimination of fermented foods, which are known to contain bacteria expressing histidine decarboxylase HDC, would reduce the ingestion of histamine-producing bacteria, thereby contributing to an overall reduction in histamine produced in the gut [85,86].

Overall, although the exact mechanism of how microbiota dysbiosis could be related to HIT needs further confirmation, current evident points towards the general gut health integrity, where a beneficial microbiota composition and consequently mucous status would contribute to normal DAO functioning.

2.5. Irritable bowel syndrome

Intestinal bowel syndrome (IBS) is a chronic gastrointestinal disorder affecting the large intestine, characterised by recurrent abdominal pain, bloating, and alterations in bowel habits, such as diarrhoea, constipation, or a combination of both [87]. Although the precise aetiology of IBS remains unclear, various factors, including stress, dietary triggers, and hormonal changes, have been implicated in modulating symptoms [87]. However, this condition frequently overlaps with related gastrointestinal disorders, such as functional dyspepsia and small intestine bacterial overgrowth (SIBO), which share symptoms like abdominal pain, bloating, and diarrhoea [88].

Emerging evidence suggests a significant role for histamine and its metabolism in IBS pathophysiology. Indeed, histamine has been shown to influence gut motility and sensory function, and its dysregulation may contribute to the hallmark symptoms of IBS [89]. Studies indicate that individuals with IBS frequently exhibit elevated histamine levels in the gut, as well as an increased sensitivity to histamine-rich or histamine-releasing foods [89]. It has been shown that over 50 % of IBS patients report gastrointestinal symptoms triggered by these foods, highlighting the potential involvement of histamine in symptom exacerbation [90]. Additionally, intestine biopsies from IBS patients revealed increased histamine production by activated mast cells and elevated histamine levels in intestinal tissues compared to healthy controls [91].

Further support for histamine's role in IBS comes from metabolomic and metagenomic analyses. Data from the Human Microbiome Project indicated that IBS patients exhibit higher levels of histamine and an increased prevalence of histamine-producing bacterial genes [89,92]. This finding aligns with alterations in the gut microbiome observed in HIT, which may amplify histamine production in the gastrointestinal tract. The expression of histamine receptors, particularly H_1, and H_2, is also upregulated in IBS patients, suggesting that histamine's signalling pathways are more active in this population [93].

Given the involvement of histamine in IBS symptomatology, DAO deficiency has been proposed as a contributing factor. Reduced DAO activity can lead to an accumulation of histamine in the gastrointestinal tract, intensifying symptoms such as abdominal pain and diarrhoea [89,94]. In addition, several studies have explored the relationship between histamine levels, DAO activity, and IBS symptom severity. For instance, research has shown that higher histamine levels correlate with increased abdominal pain and bloating in IBS patients, while food triggers commonly associated with histamine release exacerbate these symptoms [93]. In fact, DAO supplementation has been proposed as a strategy to mitigate histamine accumulation in the gut, thereby alleviating IBS-like symptoms. By enhancing histamine degradation, DAO supplementation could reduce the frequency and severity of symptoms, improving overall quality of life for affected individual [13].

2.6. Intolerance to lactose and other disaccharides

Lactose intolerance is a common condition characterised by the body's inability to properly digest lactose, the primary carbohydrate present in milk and dairy products. This results from a deficiency of lactase, an enzyme produced in the small intestine that breaks down lactose. When lactose remains undigested, it can lead to gastrointestinal symptoms such as abdominal pain, bloating, flatulence, and diarrhoea. There are several forms of lactose intolerance, each with distinct underlying causes. Congenital primary lactose intolerance is a rare genetic condition present from birth. Late-onset primary lactose intolerance, the most common form, develops gradually as lactase production declines with age. Secondary lactose intolerance arises from intestinal injury or illness, which temporarily reduces lactase production [95]. The common management of this intolerance typically results in the avoidance of milk and dairy products [95].

In 1984, Forget and colleagues examined the potential relationship between the disaccharidases maltase, sucrase, and lactase and DAO activities by measuring them in histologically normal small intestinal biopsies. Their findings revealed a significant association between the activities of the three disaccharidases and DAO activity, indicating that when there is intestine damage the levels of all these intestinal enzymes decrease [96].

The link between serum DAO activity levels and lactose maldigestion, as well as its symptomatic expression lactose intolerance (LI), was later investigated by Enko and colleagues. They demonstrated that serum DAO activity levels can distinguish between individuals with different hydrogen responses during the lactose hydrogen breath test. In particular, lactose maldigesters with serum DAO levels below 10 U/mL tended to exhibit more pronounced LI symptoms during the test. The same authors explored the association between carbohydrate malabsorption and HIT and their combined impact on gastrointestinal symptoms. The study highlighted that mucosal damage in the small intestine, reduced both DAO and lactase activities, confirming the explanation for the diagnostic overlap observed between LI and HIT [97].

In a more recent study, Schnedl and colleagues assessed the impact of additional food intolerances and malabsorption in patients with LI using hydrogen breath tests. They identified 106 persons with both LI and HIT,

and 45 persons with combined LI, HIT, and fructose malabsorption (FM) out of a total of 279 participants. More than 50 % of persons combined LI and FM and HIT. Therapeutic interventions, including a histamine-reduced diet and oral DAO supplementation, were reported to alleviate symptoms in HIT individuals, including functional non-gastrointestinal symptoms [98].

2.7. Women reproductive health

Studies have demonstrated that serum DAO levels are affected by the menstrual cycle in healthy women, with fluctuations that may influence histamine degradation capacity throughout the cycle [99]. Additionally, the crucial role of DAO during pregnancy has been well-documented [100]. Although blood histamine concentrations typically remain within the normal range during pregnancy, serum histamine degradation capacity significantly increases, due to the DAO production of the placenta [100]. This organ is a rich source of DAO, and it is thought to act as a metabolic barrier, preventing excess biologically active histamine from entering either the maternal or foetal circulation, thus maintaining a balance between histamine and DAO appears essential for a successful pregnancy. The rise in DAO activity begins in the second or third month, peaks with a 1000-fold increase around the fifth to seventh month and remains elevated until delivery. Postpartum, DAO activity returns to baseline levels within three to four days [101,102].

Moreover, research by Legge and Duff found that among women with threatened abortions, those with plasmatic DAO levels within the normal range were more likely to experience a continuing pregnancy, whereas low DAO levels were associated with an increased likelihood of miscarriage [103]. Another study evaluated plasma DAO during the first and second trimesters, finding that persistently low or decreasing DAO levels in early pregnancy correlated with increased foetal wastage. Although some of these pregnancies did result in term deliveries, these foetuses were considered high-risk. Reduced serum DAO activity has been documented in several pregnancy-related complications, including pre-eclampsia, eclampsia, diabetes, threatened and missed abortion, and trophoblastic disorders [100–102,104].

Although further studies are yet required to fully understand the role that DAO plays in healthy pregnancy development, nonetheless the high DAO expression that occurs during pregnancy as well as the pregnancy disorders correlated to low DAO levels indicate its key role during foetus development.

3. DAO supplementation to manage histamine intolerance

Elimination diets are commonly employed as an initial strategy to manage HIT caused by DAO deficiency. By reducing or avoiding the consumption of histamine-rich foods (such as aged cheeses, fermented products, alcohol, and certain fruits and vegetables) these diets aim to lower absorbed histamine levels by the body and mitigate related symptoms [65,67,105,106]. While often effective in the short term, elimination diets present notable challenges. Indeed, adherence to a restrictive diet can be difficult, particularly given the ubiquity of high-histamine foods and their cultural and culinary significance [107]. This rigidity may also lead to nutritional imbalances if essential nutrients from restricted foods are not adequately replaced [108]. Over time, the social and psychological burden of maintaining such a diet can negatively impact quality of life, underscoring the need for more sustainable and effective approaches.

In this context, enzyme-based supplements have gained considerable attention in recent years due to their potential to target specific biochemical pathways and offer a natural, and often well-tolerated means of supporting health [109,110]. These supplements, which provide active enzymes that facilitate various physiological processes, are particularly valuable for individuals with enzyme deficiencies or those who require enhanced enzymatic activity for optimal health [111]. For example, lactase supplements aid in lactose digestion, and digestive enzyme blends support overall digestive health [58]. Among these enzyme-based supplements, DAO supplementation has emerged as a promising approach to address histamine intolerance and related conditions [112].

Regarding to DAO deficiency, the aim of DAO supplementation is to alleviate symptoms associated with high histamine levels by enhancing intestinal DAO levels, particularly in the gut where DAO is predominantly active [1]. This increase in intestinal DAO facilitates the degradation of histamine, thus mitigating symptoms [1]. According to this, DAO supplementation has shown promise in reducing symptoms related to DAO deficiency and HIT, including conditions like migraines and CSU [8,9,61]. Clinical trials and intervention studies have demonstrated improvements in allergic rhinitis, gut health, and histamine regulation following DAO supplementation (Table 2) [8,81]. These effects result from supplemented DAO's ability to degrade excess histamine in the intestine, thereby reducing symptoms linked to histamine overload. DAO-rich supplements are currently available in various forms, such as tablets and capsules, and are derived from natural sources (e.g., porcine and leguminous plants) and biotechnological methods [8,113,114].

There are multiple natural sources of DAO, including animal-derived and plant-based sources, with porcine kidneys being the most common [113]. Different sources of DAO, however, can exhibit biochemical differences, such as variations in cofactor requirements and glycosylation patterns, which could explain stability, activity, and substrate affinity differences [18,115–118]. DAO can be extracted from pig kidneys and pea sprouts through homogenisation, followed by concentration or purification to remove other proteins and contaminants [1]. Recombinant sources are also used to produce DAO through genetic engineering [17,119]. This approach provides a consistent enzyme source and is suitable for large-scale commercial production [17].

3.1. Sources of DAO

3.1.1. Animal sources

Pig kidneys are a widely used animal source of DAO, often utilised in supplements aimed to alleviate symptoms related to DAO deficiency and HIT [1]. DAO extract from porcine kidneys is normally prepared by mincing and homogenising the tissue, followed by defatting and dehydration using acetone. An optional freeze-drying step is sometimes added to enhance DAO stability by reducing moisture content. To ensure microbial safety, biocidal treatments such as sodium hypochlorite or low-dose irradiation are commonly applied, yielding a stable, DAO-rich powder suitable for use in dietary supplements [117].

Importantly, DAO-rich pig kidney supplements are not purified isolated DAO but rather complex extracts, containing not only DAO but also other compounds that remained to be fully described [25].

3.1.2. Vegetal sources

For individuals who follow vegetarian or vegan diets or who have ethical or religious concerns about animal-derived products, plant-based sources of DAO offer an alternative. While most commercially available DAO supplements are porcine-based, some vegan options, primarily from pea sprouts, are also available [113].

Pea sprout-based DAO production often involves etiolated (dark-grown) pea sprouts, which show increased DAO expression [120]. Depending on the required purity level, processes such as lyophilisation and ultrafiltration can be applied [121]. Research on pea-derived DAO shows it has potential benefits for DAO deficiency and histamine-related conditions, including effects on histamine-induced contractions in colonic muscles, anaphylactic reactions, and inflammatory disorders [122,123]. Biochemically, pea DAO is also an homodimeric enzyme, with each subunit containing a copper ion and a TPQ cofactor, essential for its catalytic activity. The copper ion also plays a crucial role in the deamination reaction. However, in contrast to the porcine DAO, pea DAO contains a manganous ion instead of calcium [124]. Moreover, pea-sprouts DAO features two disulfide bridges and two glycosylation sites,

Table 2
Published interventions regarding DAO supplementation.

Reference	Indication	Sample size (n)	Supplement characteristics	Study design	Results
[169]	Histamine intolerance	56	Pig kidney-sourced Manufacturer: PelLind 0.25 mg of extract/capsule 10,000 HDUs/capsule 2 capsules/provocation test	Randomized, double-blinded and placebo-controlled	The DAO supplemented group showed a significant decrease severity of histamine intolerance symptoms after histamine provocation test
[6]	Histamine intolerance	14	Pig kidney-sourced Manufacturer: Daosin 2 capsules/ day (before lunch/dinner)	Retrospective study	13 of 14 participants improved in histamine intolerance symptoms
[9]	Chronic spontaneous urticaria	20	Pig kidney-sourced Manufacturer: Daosin 2 capsules/ day (before lunch/dinner)	Double-blinded, placebo-controlled crossover trial	There was a decrease in UAS-7 and a small but significant decrease in the amount of antihistamine medication taken per day in patients receiving DAO supplementation.
[61]	Migraine	100	Pig kidney-sourced Manufacturer: DR Healthcare 4.2 mg of extract/capsule (7 %DAO) 10,000 HDUs/capsule 2 capsules before each meal (breakfast, lunch and dinner)	Randomized, double-blinded and placebo-controlled	Migraine attacks lasted significantly less, as well as a reduced migraine drugs intake in the supplemented group
[8]	Histamine intolerance	28	Pig kidney-sourced Manufacturer: Daosin 4.2 mg of extract/capsule (0.3 mg of DAO) 1 capsule before each meal (breakfast, lunch and dinner)	Open-label interventional pilot study	An enhancement was observed in the frequency and severity of all histamine intolerance-related symptoms after DAO supplementation.

which potentially contribute to its distinct characteristics, such as its higher affinity for putrescine over histamine. Furthermore, the observed differences from pig-kidney DAO may underlie a key functional distinction between the enzymes- namely, the markedly lower stability exhibited by pea-sprout DAO [125]; this is one of the major challenges that supplements from this source face nowadays, thus some researchers have tried different approaches to try to better stabilise the enzyme [126]. Similarly to DAO-rich pig kidney supplements, pea sprouts derived DAO supplements are complex extracts as well, containing a myriad of compounds not fully characterised [122].

3.1.3. Biotechnological sources

Recent advancements in biopharmaceuticals and protein-based nutraceuticals have shifted towards recombinant or microbial production systems, valued for their scalability, yield, and purity [127,128]. These systems provide a promising avenue for overcoming the limitations associated with natural DAO sources, such as variability in activity and availability, by enabling the production of tailored and consistent enzyme formulations [129]. In 2015, Gludovacz and colleagues produced recombinant human DAO in Chinese hamster ovarian (CHO) cells, achieving a stable cell line that produced active DAO with intact structure [17]. Subsequently, Razali et al. engineered a miniaturised version of DAO from *Arthrobacter globiformis*, obtaining enhanced stability and temperature resilience with reduced enzyme size [130].

With a focus on therapeutic potential, Gludovacz and colleagues introduced mutations to the heparin-binding motif of DAO, producing a variant with reduced clearance rates in rodents' blood, potentially allowing the development for intravenous DAO applications [131]. More recently, Kettner and colleagues over-expressed a *Yarrowia lipolytica* DAO with broad substrate specificity, demonstrating biochemical parameters similar to those of human and porcine DAO [116].

3.2. Current limitations in DAO supplementation

3.2.1. Absence of a cost-effective DAO activity assay for industrial applications

Numerous methods exist to measure DAO activity, including standard laboratory techniques like spectrophotometry [132], and HPLC-FL/HPLLC-MS [133]. Older approaches, such as radioactivity-based assays, are largely obsolete. Recent advances aim to overcome the drawbacks of current methods, with innovative approaches including nanoparticle-based assays [134] and zymography [135].

Historically, DAO activity was measured via radioactivity, using a radiolabeled substrate such as C14-cadaverine [136]. In this method, radioactivity released during DAO-mediated substrate degradation allows calculation of enzymatic activity. Additionally, another frequently employed technique in laboratories was the C14-putrescine assay, an isotope-based method reliant on the conversion of γ-aminobutyraldehyde, formed by DAO activity, into Δ-pyrroline. By extracting Δ-pyrroline from the aqueous phase into the organic phase and measuring its radioactivity, DAO activity can be assessed [136].

Spectrophotometry offers a simpler, cost-effective approach by monitoring substrate concentration decrease, or product increase, over time. A common method that involves a horseradish peroxidase-coupled reaction where DAO's oxidation of a substrate yields hydrogen peroxide, which then reacts with a chromophore [132]. The resulting change in absorbance, monitored spectrophotometrically, provides a measure of DAO activity. This method is favoured for its simplicity and safety, avoiding radioisotopes. The avoidance of reliance on radioisotopes makes it a safer and more cost-effective alternative to other techniques. However, it is often less precise for less purified enzymes, where noise and interactions can interfere [137]. Nonetheless, to date, spectrophotometric methods still present some drawbacks for it to be widely adopted.

On the contrary, HPLC-MS and HPLC-FL offer highly sensitive and specific alternatives for DAO activity measurement. These methods quantify histamine degradation by DAO over varied incubation times, followed by reaction termination via DAO inhibitors [133]. HPLC-based

methods are complex and costly but allow high-accuracy detection of low histamine concentrations even in complex matrices like plasma, without pre-purification [138].

Finally, more recent methods have been developed. Specifically, a colorimetric nanoparticle-based assay has been developed for the sensitive and rapid detection of DAO activity, employing gold nanoparticles functionalised with *p*-sulfonatocalix[6]arene. The assay is based on a host–guest interaction mechanism, whereby the amine groups of 1,6-hexanediamine induce the aggregation of gold nanoparticle, resulting in a visible color change due to interparticle plasmon coupling. In the presence of DAO, 1,6-hexanediamine is oxidized to its corresponding imine and hydrogen peroxide, thereby depleting the aggregation-inducing substrate and preventing nanoparticle clustering. This leads to a distinct color shift that correlates with DAO enzymatic activity. The method exhibits high sensitivity, with a detection limit of 0.062 mU/mL and a linear dynamic range spanning 0.15 to 4.5 mU/mL. Additionally, the assay is compatible with inhibitor screening applications, as demonstrated by quantifying the inhibitory effect of guanidine on DAO activity. This nanoparticle-based platform offers a promising tool for both biochemical studies and high-throughput screening of DAO modulators [134].

Additionally, another recent development has been zymography. It represents a powerful electrophoretic technique for the detection and characterisation of DAO activity directly within polyacrylamide gels. This method enables in situ visualization of enzymatic activity by incorporating peroxidase into the gel matrix, allowing the oxidative products of DAO-mediated substrate conversion to generate a colored or fluorescent signal post-electrophoresis. Following native polyacrylamide gel electrophoresis, the entrapped peroxidase facilitates signal development upon interaction with hydrogen peroxide produced during DAO-catalysed substrate oxidation. This assay permits the resolution and quantification of active DAO isoforms and has proven particularly useful for assessing enzyme stability under physiologically relevant stressors, such as gastrointestinal conditions and proteolytic degradation.

This technique offers several advantages for the biochemical evaluation of DAO, including direct detection of enzymatically active isoforms following electrophoretic separation, and its applicability to complex biological matrices without prior purification.

Overall, DAO zymography provides a robust, semi-quantitative tool for characterising enzyme activity and stability in diverse experimental contexts [135].

3.2.2. Need for standardised units in DAO activity measurement

The choice of units used to express DAO activity is crucial for accurately interpreting results and ensuring consistency across studies. The current use of varied units, such as milliunits (mU) and histamine degrading units (HDU), has led to discrepancies in the literature and underscores the need for standardisation.

In practice, both units have its advantages and disadvantages. Historically, HDU have been used to express DAO activity. One HDU corresponds to the DAO activity that degrades 1 pmol/mL (0.11 ng/mL) of histamine [139]. This unit is beneficial in reflecting the actual quantity of histamine degraded. However, due to a lack of uniformity in HDU measurement protocols, comparability between laboratories is challenging. HDU-based results can vary depending on the conditions used, such as pH, reaction temperature, and incubation time, which complicates standardised interpretation.

Contrariwise, Units (U), widely used to express enzymatic activity across various enzymes, are standardised in the international system of units [140]. This universal metric has become the preferred choice for many researchers due to its consistency and reproducibility across laboratories. One Unit of DAO activity is defined as the amount of enzyme that degrades one micromole of substrate (typically histamine) per minute under specified conditions of temperature and pH [140], accordingly, mU is a thousandth of a Unit.

Using mU for DAO activity enables accurate, reproducible, and standardised measurements, accounting for variables like time and other assay conditions. Unlike HDU, which only reflects histamine degradation without a time component, mU allows for better cross-study comparisons and consistency, as it can also be normalised to sample weight (e.g., mg), enhancing experimental replication and facilitating comparative analysis across laboratories.

3.2.3. Gaps in DAO-rich supplements characterisation

While the biochemical properties of purified DAO, especially from porcine kidneys, are relatively well-characterised and continue to be further studied, the characterisation of DAO-containing dietary supplements remains incomplete [23,141–144]. These supplements are often complex mixtures that include other proteins, fats, and bioactive small molecules, which may influence their functionality, stability, and interaction with the biological environment [145]. However, most studies to date focus solely on purified DAO enzymes, leaving a gap in understanding the properties and performance of commercially available supplements. This lack of comprehensive characterisation raises important unanswered questions. For instance, variability in enzyme activity among DAO supplement brands has been reported, likely due to differences in extraction methods, stabilisation processes, or formulations [113]. Such variability can impact the reliability of these products, necessitating standardised analytical protocols to assess their activity, purity, and overall efficacy.

3.2.4. Potential interactions of DAO supplements and drugs

Another area requiring further exploration is the potential interaction between DAO supplements and pharmacological drugs. Certain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), and antidepressants, have been shown to interact with DAO activity in preliminary studies [146–151]. While drug interactions are being continuously characterised, the impact of the majority of drugs on both endogenous DAO and supplemented DAO remains largely unexplored. Understanding how these drugs may alter the activity or stability of DAO enzyme is critical, as it could affect their therapeutic efficacy or lead to unexpected outcomes, a phenomenon found in other drug interactions cases [152–154], especially for the compounds that are most likely to be co-administered with DAO supplementation or being taken by DAO-deficient patients, like antihistaminic drugs or gut disorders treatments.

Addressing these gaps through detailed biochemical studies and clinical trials is crucial. Improved characterisation of DAO supplements, including their interaction profiles, would enhance their stability and efficacy, ultimately supporting better management of histamine-related disorders.

3.3. Regulatory frame and novel food specifications

The term “novel food” refers to any food not traditionally consumed by humans in a specific location before May 15, 1997. This classification was established under European Union Regulation (EC) No. 258/1997, which set guidelines for marketing novel foods or ingredients within the EU. The legislation was later revised by Regulation (EU) 2015/2283, which enhanced protections for human health and consumer safety [155].

DAO-rich porcine kidney extract falls under the novel food category. In 2012, the first product containing DAO derived from pig kidneys was introduced in the EU market following approval by the European Food Safety Authority (EFSA) [156]. Initially, it was approved as a food supplement and as a food supplement for special medical purposes, with an authorised maximum dose of three capsules per day. Each capsule contains 0.3 mg of DAO, resulting in a total daily dose of 12.6 mg of pig kidney extract and 0.9 mg of DAO [1].

In 2019, an extension to this authorisation permitted the inclusion of enteric-coated tablets, which maintained the same dosage per capsule/tablet for both pig kidney extract and DAO As discussed in the section on

units for expressing DAO activity, DAO activity in the novel food regulation was traditionally measured HDU, determined by radioactivity assays and expressed as HDU/g, though recently, mU have also been recognised as a valid unit for standardised measurement, this could facilitate the standardisation of the units in a better comparable manner [1].

In contrast, DAO-rich pea sprout supplements are classified as normal dietary supplements rather than novel foods. According to the EFSA, the processing methods used to produce DAO-rich pea sprout supplements are not considered to significantly alter the natural composition of the source material, and therefore, these supplements do not fall under the novel food classification. As a result, pea sprout-based DAO supplements are not subject to novel food regulation and its implications [157,158]. However, their classification as a dietary supplement still requires compliance with general food safety and labelling regulations [159]. This streamlined classification has likely contributed to their growing commercial availability and acceptance among consumers seeking plant-based alternatives.

Additionally, DAO-related products and technologies operate within a modestly regulated patent landscape. Over the past two decades, the patent landscape for DAO has evolved from broad, extract-based formulations towards highly engineered, recombinant and microbial-derived enzymes with tailored stability and activity profiles [160,161]. Early filings described general pharmaceutical and cosmetic compositions containing animal- or plant-sourced DAO for histamine-related disorders [160], whereas more recent applications focus on recombinant human and yeast-expressed enzymes optimized for oral bioavailability [119,162] or topical delivery [163]. Concurrently, the scope of therapeutic indications has broadened—from classical histamine-intolerance and dermatological uses to pain management (e.g., migraine and fibromyalgia) [164], gastrointestinal protection in neonates [165], and even neurological conditions such as attention deficit hyperactivity disorder (ADHD) [166]. Innovations in formulation technologies—enteric coatings [161], transdermal patches and topical gels [163], and infant-nutritional matrices [165]—reflect both consumer-product and prescription-drug strategies, underscoring a maturing field that increasingly emphasizes consistency of manufacturing, targeted delivery, and expanded clinical utility.

4. Conclusions and future outlook

DAO plays a critical role in the degradation of exogenous histamine, and its deficiency can disrupt histamine homeostasis, leading to histamine accumulation in various tissues. Elevated histamine levels in different systems can trigger a wide range of symptoms, including migraines, skin disorders, and GI complications. Clinical trials have shown the potential benefits of DAO supplementation in managing these conditions. Currently, DAO-rich supplements are predominantly derived from pig kidneys and pea sprouts, with ongoing research into new sources and enhancements.

Despite these advancements, significant challenges remain. DAO-rich supplements require more in-depth characterisation to understand their biochemical properties and interactions with other components in complex formulation. Such studies would help elucidate factors affecting their efficacy and stability, especially in real-world settings where supplements are consumed alongside various foods and medications. Furthermore, improving the enzymatic stability of DAO is crucial to ensure its activity is retained throughout manufacturing, storage, and distribution, thus maximising its therapeutic potential for patients.

Robust simple methods for enzymatic activity measurement would enhance screening and characterisation of novel DAO sources, as well as allow the development of new improved diagnostic tools. Standardising an activity unit, would also streamline the comparison of results across studies, supporting more consistent evaluations of DAO levels in related conditions and across different supplement sources. Addressing these limitations will not only enhance the reliability and effectiveness of DAO supplementation but also open avenues for innovative therapeutic applications targeting histamine-related disorders.

CRediT authorship contribution statement

Marc Alemany-Fornés: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Jaume Bori:** Writing – review & editing, Supervision, Conceptualization. **Begoña Muguerza:** Writing – review & editing, Supervision, Conceptualization. **Manuel Suárez:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Paperpal in order to improve readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.A.F and J.B are full time workers are DR Healthcare-AB biotek Health.

Data availability

No data was used for the research described in the article.

References

[1] O. Comas-Basté, S. Sánchez-Pérez, M.T. Veciana-Nogués, M. Latorre-Moratalla, M.D.C. Vidal-Carou, Histamine intolerance: the current state of the art, Biomolecules 10 (2020) 1–26, https://doi.org/10.3390/biom10081181.
[2] E. Kovacova-Hanuskova, T. Buday, S. Gavliakova, J. Plevkova, Histamine, histamine intoxication and intolerance, Allergol. Immunopathol. 43 (2015) 498–506, https://doi.org/10.1016/j.aller.2015.05.001.
[3] A. Mandola, A. Nozawa, T. Eiwegger, Histamine, histamine receptors, and antihistamines in the context of allergic responses, LymphoSign J. 6 (2019) 35–51, https://doi.org/10.14785/lymphosign-2018-0016.
[4] S. Kaur, A. Ali, Y. Siahbalaei, U. Ahmad, F. Nargis, A.K. Pandey, B. Singh, Association of diamine oxidase (DAO) variants with the risk for migraine from North Indian population, Meta Gene 24 (2020) 100619, https://doi.org/10.1016/j.mgene.2019.100619.
[5] E. García-Martín, C. Martínez, M. Serrador, H. Alonso-Navarro, P. Ayuso, F. Navacerrada, J.A.G. Agúndez, F.J. Jiménez-Jiménez, Diamine oxidase rs10156191 and rs2052129 variants are associated with the risk for migraine, Headache 55 (2015) 276–286, https://doi.org/10.1111/head.12493.
[6] L. Maintz, S. Benfadal, J.P. Allam, T. Hagemann, R. Fimmers, N. Novak, Evidence for a reduced histamine degradation capacity in a subgroup of patients with atopic eczema, J. Allergy Clin. Immunol. 117 (2006) 1106–1112, https://doi.org/10.1016/j.jaci.2005.11.041.
[7] G. Okutan, E. Ruiz Casares, T. Perucho Alcalde, G.M. Sánchez Niño, B.F. Penadés, A. Terrén Lora, L. Torrente Estríngana, S. López Oliva, I. San Mauro Martín, Prevalence of genetic diamine oxidase (DAO) deficiency in female patients with fibromyalgia in Spain, Biomedicines 11 (2023) 660, https://doi.org/10.3390/biomedicines11030660.
[8] W.J. Schnedl, M. Schenk, S. Lackner, D. Enko, H. Mangge, F. Forster, Diamine oxidase supplementation improves symptoms in patients with histamine intolerance, Food Sci. Biotechnol. 28 (2019) 1779–1784, https://doi.org/10.1007/s10068-019-00627-3.
[9] M.R. Yacoub, G.A. Ramirez, A. Berti, G. Mercurio, D. Breda, N. Saporiti, S. Burastero, L. Dagna, G. Colombo, Diamine oxidase supplementation in chronic spontaneous urticaria: a randomized, double-blind placebo-controlled study, Int. Arch. Allergy Immunol. 176 (2018) 268–271, https://doi.org/10.1159/000488142.

[10] J. Dyer, K. Warren, S. Merlin, D.D. Metcalfe, M. Kaliner, Measurement of plasma histamine: description of an improved method and normal values, J. Allergy Clin. Immunol. (1982) 82–87, https://doi.org/10.1016/0091-6749(82)90233-0.
[11] T. Yoshikawa, K. Yanai, Histamine clearance through polyspecific transporters in the brain, in: Handbook of Experimental Pharmacology, Springer New York LLC, 2017, pp. 173–187, https://doi.org/10.1007/164_2016_13.
[12] A. Rosell-Camps, S. Zlbetti, G. Pérez-Esteban, M. Vila-Vidal, L. Ferrés-Ramis, E. García-Teresa-García, Histamine intolerance as a cause of chronic digestive complaints in pediatric patients, Rev. Esp. Enferm. Dig. (2013) 201–207, https://doi.org/10.4321/S1130-01082013000400004.
[13] W.J. Schnedl, S. Lackner, D. Enko, M. Schenk, S.J. Holasek, H. Mangge, Evaluation of symptoms and symptom combinations in histamine intolerance, Intest. Res. 17 (2019) 427–433, https://doi.org/10.5217/ir.2018.00152.
[14] Y.O. Shulpekova, V.M. Nechaev, I.R. Popova, T.A. Deeva, A.T. Kopylov, K. A. Malsagova, A.L. Kaysheva, V.T. Ivashkin, Food intolerance: the role of histamine, Nutrients 13 (2021) 3207, https://doi.org/10.3390/nu13093207.
[15] B.O. Elmore, J.A. Bollinger, D.M. Dooley, Human kidney diamine oxidase: heterologous expression, purification, and characterization, J. Biol. Inorg. Chem. 7 (2002) 565–579, https://doi.org/10.1007/s00775-001-0331-1.
[16] C. Ekaterini Tiligada, E. Tiligada, M. Ennis, New uses for 21st century histamine pharmacology: from Sir Henry Dale to the 21st century, Br. J. Pharmacol. 177 (2020) 469, https://doi.org/10.1111/bph.v177.3/issuetoc.
[17] E. Gludovacz, D. Maresch, M. Bonta, H. Szöllösi, P.G. Furtmüller, R. Weik, F. Altmann, A. Limbeck, N. Borth, B. Jilma, T. Boehm, Characterization of recombinant human diamine oxidase (rhDAO) produced in Chinese Hamster Ovary (CHO) cells, J. Biotechnol. 227 (2016) 120–130, https://doi.org/10.1016/j.jbiotec.2016.04.002.
[18] E. Gludovacz, M. Resch, K. Schuetzenberger, K. Petroczi, D. Maresch, S. Hofbauer, B. Jilma, N. Borth, T. Boehm, Glycosylation site Asn168 is important for slow in vivo clearance of recombinant human diamine oxidase heparin-binding motif mutants, Glycobiology 32 (2022) 404–413, https://doi.org/10.1093/glycob/cwab122.
[19] K. Buczyłko, Usefulness of DAO biomarker in difficult allergy. Consideration based on own typical cases, Alergol. Pol. 9 (2022) 237–245, https://doi.org/10.5114/pja.2022.122003.
[20] L. Maintz, C.F. Yu, E. Rodríguez, H. Baurecht, T. Bieber, T. Illig, S. Weidinger, N. Novak, Association of single nucleotide polymorphisms in the diamine oxidase gene with diamine oxidase serum activities, Allergy: Eur. J. Allergy Clin. Immunol. 66 (2011) 893–902, https://doi.org/10.1111/j.1398-9995.2011.02548.x.
[21] E. Masini, D. Bani, C. Marzocca, M.A. Mateescu, P.F. Mannaioni, R. Federico, B. Mondovì, Pea seedling histaminase as a novel therapeutic approach to anaphylactic and inflammatory disorders: a plant histaminase in allergic asthma and ischemic shock, Sci. World J. 7 (2007) 888–902, https://doi.org/10.1100/tsw.2007.139.
[22] T.J. Williams, M.C. Falk, Spatial relationship between the copper and carbonyl cofactors in the active site of pig plasma amine oxidase, J. Biol. Chem. 261 (1986) 15949–15954, https://doi.org/10.1016/S0021-9258(18)66658-X.
[23] H.G. Schwelberger, E. Bodner, Purification and characterization of diamine oxidase from porcine kidney and intestine, Biochim. Biophys. Acta 1340 (1997) 152–164, https://doi.org/10.1016/S0167-4838(97)00039-3.
[24] E. Coudert, S. Gehant, E. de Castro, M. Pozzato, D. Baratin, T. Neto, C.J.A. Sigrist, N. Redaschi, A. Bridge, Annotation of biologically relevant ligands in UniProtKB using ChEBI, Bioinformatics 39 (2023), https://doi.org/10.1093/bioinformatics/btac793.
[25] L. Kettner, I. Seitl, L. Fischer, Recent advances in the application of microbial diamine oxidases and other histamine-oxidizing enzymes, World J. Microbiol. Biotechnol. 38 (2022), https://doi.org/10.1007/s11274-022-03421-2.
[26] R. Li, J.P. Klinman, S. Mathews, Copper amine oxidase from Hansenula polymorpha: the crystal structure determined at 2.4 Å resolution reveals the active conformation, Curr. Biol. 6 (1997) 293–307. http://biomednet.com/elecref/0969212600600293.
[27] H.N. Eisen, Diamine oxidase (histaminase) activity of kidney and other organs in the hypersensistive state, Am. Phys. Soc. J. 146 (1945) 56–60. www.physiology.org/journal/ajplegacy.
[28] G.N. Beall, P.P. Vanarsdel, Histamine metabolism in human disease, J. Clin. Invest. 39 (1960) 676–683, https://doi.org/10.1172/JCI104083.
[29] P. Velicky, K. Windsperger, K. Petroczi, S. Pils, B. Reiter, T. Weiss, S. Vondra, R. Ristl, S. Dekan, C. Fiala, D.E. Cantonwine, T.F. McElrath, B. Jilma, M. Knöfler, T. Boehm, J. Pollheimer, Pregnancy-associated diamine oxidase originates from extravillous trophoblasts and is decreased in early-onset preeclampsia, Sci. Rep. 8 (2018) 6342, https://doi.org/10.1038/s41598-018-24652-0.
[30] M. Knöfler, S. Haider, L. Saleh, J. Pollheimer, T.K.J.B. Gamage, J. James, Human placenta and trophoblast development: key molecular mechanisms and model systems, Cell. Mol. Life Sci. 76 (2019) 3479–3496, https://doi.org/10.1007/s00018-019-03104-6.
[31] T. Rokkasa, S. Vajaa, P. Tayiorb, G.M. Murphya, R.H. Dowlinga, Is the intestine the sole source of heparin-stimulated plasma diamine oxidase? Digestion 46 (1990) 439–446, https://doi.org/10.1159/000200419.
[32] M. Usami, S. Haji, K. Sakata, H. Kasahara, M. Yamamoto, I. Imamura, Y. Tabuchi, Plasma postheparin diamine oxidase activity after major abdominal surgery, Bulletin of Allied Medical Sciences Kobe: BAMS (Kobe) 13 (1997) 47–55. https://hdl.handle.net/20.500.14094/00188169 (accessed November 26, 2024).
[33] A. Robinson-White, S.B. Baylin, T. Olivecrona, M.A. Beaven, Binding of diamine oxidase activity to rat and guinea pig microvascular endothelial cells. Comparisons with lipoprotein lipase binding, J. Clin. Invest. 76 (1985) 93–100, https://doi.org/10.1172/JCI111983.
[34] J. Schiefer, J. Baron-Stefaniak, T. Boehm, P. Wadowski, G. Berlakovich, L. Kuessel, J. Mühlbacher, P. Jilma-Stohlawetz, M. Schwameis, B. Jilma, P. Faybik, Regulation of histamine and diamine oxidase in patients undergoing orthotopic liver transplantation, Sci. Rep. 10 (2020), https://doi.org/10.1038/s41598-020-57728-x.
[35] T.C. Pinzer, E. Tietz, E. Waldmann, M. Schink, M.F. Neurath, Y. Zopf, Circadian profiling reveals higher histamine plasma levels and lower diamine oxidase serum activities in 24% of patients with suspected histamine intolerance compared to food allergy and controls, Allergy: Eur. J. Allergy Clin. Immunol. 73 (2018) 949–957, https://doi.org/10.1111/all.13361.
[36] J. Klocker, R. Perkmann, P. Klein-Weigel, G. Mörsdorf, A. Drasche, A. Klingler, G. Fraedrich, H.G. Schwelberger, Continuous administration of heparin in patients with deep vein thrombosis can increase plasma levels of diamine oxidase, Vasc. Pharmacol. 40 (2004) 293–300, https://doi.org/10.1016/j.vph.2004.02.002.
[37] M. Guilarte, A. Sala-Cunill, O. Luengo, M. Labrador-Horrillo, V. Cardona, The mast cell, contact, and coagulation system connection in anaphylaxis, Front. Immunol. 8 (2017), https://doi.org/10.3389/fimmu.2017.00846.
[38] B. Ghebrehiwet, K. Joseph, A.P. Kaplan, The bradykinin-forming cascade in anaphylaxis and ACE-inhibitor induced angioedema/airway obstruction, Front. Allergy 5 (2024), https://doi.org/10.3389/falgy.2024.1302605.
[39] T. Boehm, B. Reiter, R. Ristl, K. Petroczi, W. Sperr, T. Stimpfl, P. Valent, B. Jilma, Massive release of the histamine-degrading enzyme diamine oxidase during severe anaphylaxis in mastocytosis patients, Allergy: Eur. J. Allergy Clin. Immunol. 74 (2019) 583–593, https://doi.org/10.1111/all.13663.
[40] E. Music, M. Silar, P. Korosec, M. Kosnik, M. Rijavec, Serum diamine oxidase (DAO) activity as a diagnostic test for histamine intolerance, Clin. Transl. Allergy 1 (2011) P115, https://doi.org/10.1186/2045-7022-1-s1-p115.
[41] K. Buczyłko, A. Bartnicka, J. Kruszewski, K. Plata-Nazar, K. Piwowarek, M. Kupczyk, R. Gawlik, D. Lebensztejn, Z. Bartuzi, J. Mazela, A. Szlagatys-Sidorkiewicz, Guidelines for the diagnosis and management of histamine intolerance, Alergol. Pol. 10 (2023) 141–151, https://doi.org/10.5114/pja.2023.131553.
[42] G. Rentzos, A. Weisheit, L. Ekerljung, J. van Odijk, Measurement of diamine oxidase (DAO) during low-histamine or ordinary diet in patients with histamine intolerance, Eur. J. Clin. Nutr. 78 (2024) 726–731, https://doi.org/10.1038/s41430-024-01448-2.
[43] J. van Odijk, A. Weisheit, M. Arvidsson, N. Miron, B. Nwaru, L. Ekerljung, The use of DAO as a marker for histamine intolerance: measurements and determinants in a large random population-based survey, Nutrients 15 (2023), https://doi.org/10.3390/nu15132887.
[44] W.J. Schnedl, D. Enko, Histamine intolerance originates in the gut, Nutrients 13 (2021), https://doi.org/10.3390/nu13041262.
[45] M. Mayo-Yáñez, A. Díaz-Díaz, C. Calvo-Henríquez, C. Chiesa-Estomba, A. Figueroa, C.S. Martín-Martín, Usefulness of the histamine intolerance assessment questionnaire for diagnosis, Rev. Fr. Allergol. 61 (2021) 87–91, https://doi.org/10.1016/j.reval.2020.10.002.
[46] O. Comas-Basté, M.L. Latorre-Moratalla, R. Bernacchia, M.T. Veciana-Nogués, M. C. Vidal-Carou, New approach for the diagnosis of histamine intolerance based on the determination of histamine and methylhistamine in urine, J. Pharm. Biomed. Anal. 145 (2017) 379–385, https://doi.org/10.1016/j.jpba.2017.06.029.
[47] H.G. Schwelberger, The origin of mammalian plasma amine oxidases, J. Neural Transm. (2007) 757–762, https://doi.org/10.1007/s00702-007-0684-x. Springer Wien.
[48] A.P. McGrath, K.M. Hilmer, C.A. Collyer, E.M. Shepard, B.O. Elmore, D.E. Brown, D.M. Dooley, J.M. Guss, Structure and inhibition of human diamine oxidase, Biochemistry 48 (2009) 9810–9822, https://doi.org/10.1021/bi9014192.
[49] A.N. Kucher, Association of polymorphic variants of key histamine metabolism genes and histamine receptor genes with multifactorial diseases, Russ. J. Genet. 55 (2019) 794–814, https://doi.org/10.1134/S102279541907010X.
[50] G. Okutan, T. Perucho Alcalde, E. Ruiz Casares, B.F. Penadés, G.M. Sánchez Niño, A. Terrén Lora, S. López Oliva, L. Torrente Estríngana, A. Duelo, I. San Mauro Martín, Cumulative effect of AOC1 gene variants on symptoms and pathological conditions in adult women with fibromyalgia: a pilot study, Front. Genet. 14 (2023), https://doi.org/10.3389/fgene.2023.1180777.
[51] J. Matysiak, Histamine intolerance (HIT), J. Med. Sci. (2022) e727, https://doi.org/10.20883/medical.e727.
[52] B.M. Dala-Paula, F.B. Custódio, M.B. Gloria, Health concerns associated with biogenic amines in food and interaction with amine oxidase drugs, Curr. Opin. Food Sci. 54 (2023), https://doi.org/10.1016/j.cofs.2023.101090.
[53] A. Duelo, O. Comas-Basté, S. Sánchez-Pérez, M.T. Veciana-Nogués, E. Ruiz-Casares, M.C. Vidal-Carou, M.L. Latorre-Moratalla, Pilot study on the prevalence of diamine oxidase gene variants in patients with symptoms of histamine intolerance, Nutrients 16 (2024), https://doi.org/10.3390/nu16081142.
[54] S. Lackner, V. Malcher, D. Enko, H. Mangge, S.J. Holasek, W.J. Schnedl, Histamine-reduced diet and increase of serum diamine oxidase correlating to diet compliance in histamine intolerance, Eur. J. Clin. Nutr. 73 (2019) 102–104, https://doi.org/10.1038/s41430-018-0260-5.
[55] S. Sánchez-Pérez, O. Comas-Basté, A. Duelo, M.T. Veciana-Nogués, M. Berlanga, M.L. Latorre-Moratalla, M.C. Vidal-Carou, Intestinal dysbiosis in patients with histamine intolerance, Nutrients 14 (2022), https://doi.org/10.3390/nu14091774.
[56] V. Cucca, G.A. Ramirez, P. Pignatti, C. Asperti, M. Russo, E. Della-Torre, D. Breda, S.E. Burastero, L. Dagna, M.R. Yacoub, Basal serum diamine oxidase levels as a

biomarker of histamine intolerance: a retrospective cohort study, Nutrients 14 (2022), https://doi.org/10.3390/nu14071513.
[57] M. Schink, P.C. Konturek, E. Tietz, W. Dieterich, T.C. Pinzer, S. Wirtz, M. F. Neurath, Y. Zopf, Microbial patterns in patients with histamine intolerance, J. Physiol. Pharmacol. 69 (2018) 579–593, https://doi.org/10.26402/jpp.2018.4.09.
[58] R. Catanzaro, M. Sciuto, F. Marotta, Lactose intolerance: an update on its pathogenesis, diagnosis, and treatment, Nutr. Res. 89 (2021) 23–34, https://doi.org/10.1016/j.nutres.2021.02.003.
[59] F. Siebenhaar, A. Melde, M. Magerl, T. Zuberbier, M.K. Church, M. Maurer, Histamine intolerance in patients with chronic spontaneous urticaria, J. Eur. Acad. Dermatol. Venereol. 30 (2016) 1774–1777, https://doi.org/10.1111/jdv.13778.
[60] D. Enko, G. Kriegshäuser, G. Halwachs-Baumann, H. Mangge, W.J. Schnedl, Serum diamine oxidase activity is associated with lactose malabsorption phenotypic variation, Clin. Biochem. 50 (2017) 50–53, https://doi.org/10.1016/j.clinbiochem.2016.08.019.
[61] J. Izquierdo-Casas, O. Comas-Basté, M.L. Latorre-Moratalla, M. Lorente Gascón, A. Duelo, L. Soler-Singla, M.C. Vidal-Carou, Diamine oxidase (DAO) supplement reduces headache in episodic migraine patients with DAO deficiency: a randomized double-blind trial, Clin. Nutr. 38 (2019) 152–158, https://doi.org/10.1016/j.clnu.2018.01.013.
[62] W.F. Stewart, J. Roy, R.B. Lipton, F. Sutter Health, Migraine Prevalence, Socioeconomic Status, and Social Causation, 2013. www.neurology.org. https://doi.org/10.1212/WNL.0b013e3182a43b32.
[63] J. Izquierdo-Casas, O. Comas-Basté, M.L. Latorre-Moratalla, M. Lorente-Gascón, A. Duelo, M.C. Vidal-Carou, L. Soler-Singla, Low serum diamine oxidase (DAO) activity levels in patients with migraine, J. Physiol. Biochem. 74 (2018) 93–99, https://doi.org/10.1007/s13105-017-0571-3.
[64] C. Vestergaard, M. Deleuran, Chronic spontaneous urticaria: latest developments in aetiology, diagnosis and therapy, Ther. Adv. Chronic Dis. 6 (2015) 304–313, https://doi.org/10.1177/2040622315603951.
[65] B. Guida, C. De Martino, S. De Martino, G. Tritto, V. Patella, R. Trio, C. D'Agostino, P. Pecoraro, L. D'Agostino, Histamine plasma levels and elimination diet in chronic idiopathic urticaria, Eur. J. Clin. Nutr. 54 (2000) 155–158, https://doi.org/10.1038/sj.ejcn.1600911.
[66] N. Wagner, D. Dirk, A. Peveling-Oberhag, I. Reese, U. Rady-Pizarro, H. Mitzel, P. Staubach, A popular myth – low-histamine diet improves chronic spontaneous urticaria – fact or fiction? J. Eur. Acad. Dermatol. Venereol. 31 (2017) 650–655, https://doi.org/10.1111/jdv.13966.
[67] J.H. Son, B.Y. Chung, H.O. Kim, C.W. Park, A histamine-free diet is helpful for treatment of adult patients with chronic spontaneous urticaria, Ann. Dermatol. 30 (2018) 164–172, https://doi.org/10.5021/ad.2018.30.2.164.
[68] M. Maurer, U. Raap, P. Staubach, G. Richter-Huhn, A. Bauer, E.M. Oppel, U. Hillen, D. Baeumer, M. Reinhardt, N. Chapman-Rothe, Antihistamine-resistant chronic spontaneous urticaria: 1-year data from the AWARE study, Clin. Exp. Allergy 49 (2019) 655–662, https://doi.org/10.1111/cea.13309.
[69] J.P. Thyssen, A.S. Halling, P. Schmid-Grendelmeier, E. Guttman-Yassky, J. I. Silverberg, Comorbidities of atopic dermatitis—what does the evidence say? J. Allergy Clin. Immunol. 151 (2023) 1155–1162, https://doi.org/10.1016/j.jaci.2022.12.002.
[70] R. Berke, Arshdeep Singh, M. Guralnick, Atopic dermatitis: an overview, Am. Fam. Phys. J. 86 (2012) (PMID:2962911).
[71] L.A. Beck, M. Deleuran, R. Bissonnette, M. de Bruin-Weller, R. Galus, T. Nakahara, S.J. Seo, F.A. Khokhar, J. Vakil, J. Xiao, A.R. Marco, N.A. Levit, J. T. O'Malley, A. Shabbir, Dupilumab provides acceptable safety and sustained efficacy for up to 4 years in an open-label study of adults with moderate-to-severe atopic dermatitis, Am. J. Clin. Dermatol. 23 (2022) 393–408, https://doi.org/10.1007/s40257-022-00685-0.
[72] E.L. Simpson, M. Gooderham, A. Wollenberg, S. Weidinger, A. Armstrong, J. Soung, S. Ferrucci, R.G. Lima, M.M. Witte, W. Xu, H. Elmaraghy, C.R. Natalie, E. Pierce, A. Blauvelt, Efficacy and safety of lebrikizumab in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis: a randomized clinical trial (ADhere), JAMA Dermatol. 159 (2023) 182–191, https://doi.org/10.1001/jamadermatol.2022.5534.
[73] A. Wagner, K. Buczyłko, H. Zielińska-Bliźniewska, W. Wagner, Impaired resolution of wheals in the skin prick test and low diamine oxidase blood level in allergic patients, Adv. Dermatol. Allergol. 36 (2019) 538–543, https://doi.org/10.5114/ada.2019.89504.
[74] M.E. Zapolskiy, M.O. Lebediuk, M.O. Dudchenko, N.B. Prokofyeva, K. V. Vasylyeva, A.V. Dobrovolska, Yu.V. Tepliuk, Role of trigger factors and effects of diamine oxidase deficiency on clinical manifestations of atopic dermatitis, Curr. Osteoporos. Rep. 16 (2022) 554–560, https://doi.org/10.26724/2079-8334-2022-1-79-68-73.
[75] M. Worm, E.M. Fiedler, S. Dölle, T. Schink, W. Hemmer, R. Jarisch, T. Zuberbier, Exogenous histamine aggravates eczema in a subgroup of patients with atopic dermatitis, Acta Derm. Venereol. 89 (2009) 52–56, https://doi.org/10.2340/00015555-0565.
[76] A. Heratizadeh, K. Wichmann, T. Werfel, Food allergy and atopic dermatitis: how are they connected? Curr Allergy Asthma Rep 11 (2011) 284–291, https://doi.org/10.1007/s11882-011-0202-y.
[77] R. Lama Tamang, A.F. Juritsch, R. Ahmad, J.D. Salomon, P. Dhawan, A.E. Ramer-Tait, A.B. Singh, The diet-microbiota axis: a key regulator of intestinal permeability in human health and disease, Tissue Barriers 11 (2023), https://doi.org/10.1080/21688370.2022.2077069.
[78] C. Mazziotta, M. Tognon, F. Martini, E. Torreggiani, J.C. Rotondo, Probiotics mechanism of action on immune cells and beneficial effects on human health, Cells 12 (2023), https://doi.org/10.3390/cells12010184.
[79] D. Lin, D.M. Medeiros, The microbiome as a major function of the gastrointestinal tract and its implication in micronutrient metabolism and chronic diseases, Nutr. Res. 112 (2023) 30–45, https://doi.org/10.1016/j.nutres.2023.02.007.
[80] K. Brown, D. DeCoffe, E. Molcan, D.L. Gibson, Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease, Nutrients 4 (2012) 1095–1119, https://doi.org/10.3390/nu4081095.
[81] S. Sánchez-Pérez, O. Comas-Basté, A. Duelo, M.T. Veciana-Nogués, M. Berlanga, M.C. Vidal-Carou, M.L. Latorre-Moratalla, The dietary treatment of histamine intolerance reduces the abundance of some histamine-secreting bacteria of the gut microbiota in histamine intolerant women. A pilot study, Front. Nutr. 9 (2022), https://doi.org/10.3389/fnut.2022.1018463.
[82] Y.J. Zhang, S. Li, R.Y. Gan, T. Zhou, D.P. Xu, H. Bin Li, Impacts of gut bacteria on human health and diseases, Int. J. Mol. Sci. 16 (2015) 7493–7519, https://doi.org/10.3390/ijms16047493.
[83] N.S. Lee, D. Fitzpatrick, E. Meier, H. Fisher, Influence of dietary histidine on tissue histamine concentration, histidine decarboxylase and histamine methyltransferase activity in the rat, Agents Actions 11 (1981) 307–311, https://doi.org/10.1007/BF01982463.
[84] M. Saaid, B. Saad, N.H. Hashim, A.S. Mohamed Ali, M.I. Saleh, Determination of biogenic amines in selected Malaysian food, Food Chem. 113 (2009) 1356–1362, https://doi.org/10.1016/j.foodchem.2008.08.070.
[85] J. Ma, Y. Nie, L. Zhang, Y. Xu, Ratio of histamine-producing/non-histamine-producing subgroups of tetragenococcus halophilus determines the histamine accumulation during spontaneous fermentation of soy sauce, Appl. Environ. Microbiol. 89 (2023), https://doi.org/10.1128/aem.01884-22.
[86] J.M. Landete, I. Pardo, S. Ferrer, Histamine, histidine, and growth-phase mediated regulation of the histidine decarboxylase gene in lactic acid bacteria isolated from wine, FEMS Microbiol. Lett. 260 (2006) 84–90, https://doi.org/10.1111/j.1574-6968.2006.00252.x.
[87] T. Zhang, X. Ma, W. Tian, J. Zhang, Y. Wei, B. Zhang, F. Wang, X. Tang, Global research trends in irritable bowel syndrome: a bibliometric and visualized study, Front. Med. (Lausanne) 9 (2022), https://doi.org/10.3389/fmed.2022.922063.
[88] R. Borghini, G. Donato, D. Alvaro, A. Picarelli, New insights in IBS-like disorders: Pandora's box has been opened; a review, Gastroenterol. Hepatol. Bed Bench. 10 (2017) 79–89, https://doi.org/10.22037/ghfbb.v0i0.1011.
[89] S. Smolinska, E. Winiarska, A. Globinska, M. Jutel, Histamine: a mediator of intestinal disorders—a review, Metabolites 12 (2022), https://doi.org/10.3390/metabo12100895.
[90] G. Barbara, B. Wang, V. Stanghellini, R. de Giorgio, C. Cremon, G. Di Nardo, M. Trevisani, B. Campi, P. Geppetti, M. Tonini, N.W. Bunnett, D. Grundy, R. Corinaldesi, Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome, Gastroenterology 132 (2007) 26–37, https://doi.org/10.1053/j.gastro.2006.11.039.
[91] T.K. Klooker, B. Braak, K.E. Koopman, O. Welting, M.M. Wouters, S. Van Der Heide, M. Schemann, S.C. Bischoff, R.M. Van Den Wijngaard, G.E. Boeckxstaens, The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome, Gut 59 (2010) 1213–1221, https://doi.org/10.1136/gut.2010.213108.
[92] D. Keszthelyi, Histamine-producing bacteria: the missing link in irritable bowel syndrome? Gastroenterology 164 (2023) 160–161, https://doi.org/10.1053/j.gastro.2022.08.053.
[93] G. Barbara, V. Stanghellini, R. De Giorgio, C. Cremon, G.S. Cottrell, D. Santini, G. Pasquinelli, A.M. Morselli-Labate, E.F. Grady, N.W. Bunnett, S.M. Collins, R. Corinaldesi, Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome, Gastroenterology 126 (2004) 693–702, https://doi.org/10.1053/j.gastro.2003.11.055.
[94] A. Fabisiak, J. Wlodarczyk, N. Fabisiak, M. Storr, J. Fichna, Targeting histamine receptors in irritable bowel syndrome: a critical appraisal, J. Neurogastroenterol. Motil. 23 (2017) 341–348, https://doi.org/10.5056/jnm16203.
[95] A. Shaukat, M.D. Levitt, B.C. Taylor, R. MacDonald, T.A. Shamliyan, R.L. Kane, T. J. Wilt, Systematic review: effective management strategies for lactose intolerance, Ann. Intern. Med. 152 (2010) 797–803, https://doi.org/10.7326/0003-4819-152-12-201006150-00241.
[96] P. Forget, C. Grandfils, J.L. Van Cutsem, G. Dandrifosse, Diamine oxidase and disaccharidase activities in small intestinal biopsies of children, Pediatr. Res. 18 (1984) 647–649, https://doi.org/10.1203/00006450-198407000-00016.
[97] D. Enko, A. Meinitzer, H. Mangge, G. Kriegshaüser, G. Halwachs-Baumann, E. Z. Reininghaus, S.A. Bengesser, W.J. Schnedl, Concomitant prevalence of low serum diamine oxidase activity and carbohydrate malabsorption, Can. J. Gastroenterol. (2016), https://doi.org/10.1155/2016/4893501.
[98] W.J. Schnedl, N. Meier-Allard, S. Lackner, D. Enko, H. Mangge, S.J. Holasek, Increasing expiratory hydrogen in lactose intolerance is associated with additional food intolerance/malabsorption, Nutrients 12 (2020) 1–8, https://doi.org/10.3390/nu12123690.
[99] Y. Hamada, Y. Shinohara, M. Yano, M. Yamamoto, M. Yoshio, K. Satake, A. Toda, M. Hirai, M. Usami, Effect of the menstrual cycle on serum diamine oxidase levels in healthy women, Clin. Biochem. 46 (2013) 99–102, https://doi.org/10.1016/j.clinbiochem.2012.10.013.
[100] L. Maintz, V. Schwarzer, T. Bieber, K. van der Ven, N. Novak, Effects of histamine and diamine oxidase activities on pregnancy: a critical review, Hum. Reprod. Update 14 (2008) 485–495, https://doi.org/10.1093/humupd/dmn014.

[101] O. Brew, L. Lakasing, M. Sullivan, Differential activity of histidine decarboxylase in normal and pre-eclamptic placentae, Placenta 28 (2007) 585–587, https://doi.org/10.1016/j.placenta.2006.05.003.
[102] G. Achari, K. Achari, K.K. Rao, Histaminase and histamine in normal and toxaemic pregnancy, Jpn. J. Pharmacol. 21 (1971) 33–40 (PMID: 5005072).
[103] M. Legge, G.B. Duff, Plasma diamine oxidase levels in pregnancy complicated by threatened abortion, J. Clin. Pathol. 34 (1981) 187–188, https://doi.org/10.1136/jcp.34.2.187.
[104] A.K. Sande, E.A. Torkildsen, R.K. Sande, I. Dalen, K.C. Danielsson, N.H. Morken, Use of antihistamines before or during pregnancy and risk of early-onset pre-eclampsia in allergic women: a population-based cohort study, BMJ Open 12 (2022), https://doi.org/10.1136/bmjopen-2022-061837.
[105] J.M. Gomez-Arguelles, O. Caceres, M. Blanco, C. Maestu, F. Martin, Improvement of digestive symptoms in fibromyalgia patients following a diet modification according to histamine release test - an observational study, Reumatologia 60 (2022) 209–212, https://doi.org/10.5114/reum.2022.117841.
[106] I.S.M. Martin, S. Brachero, E.G. Vilar, Histamine intolerance and dietary management: a complete review, Allergol Immunopathol (Madr) (2016), https://doi.org/10.1016/j.aller.2016.04.015.
[107] M. Bartuzi, M. Szamocka, N. Ukleja-Sokołowska, Social and economic difficulties of patients with food intolerances, Adv. Dermatol. Allergol. 40 (2023) 298–307, https://doi.org/10.5114/ada.2023.126412.
[108] K.B. Proctor, E. Rodrick, S. Belcher, W.G. Sharp, J.M. Kindler, Bone health in avoidant/restrictive food intake disorder: a narrative review, J. Eat. Disord. 11 (2023), https://doi.org/10.1186/s40337-023-00766-3.
[109] R.L. Bailey, J.J. Gahche, C.V. Lentino, J.T. Dwyer, J.S. Engel, P.R. Thomas, J. M. Betz, C.T. Sempos, M.F. Picciano, Dietary supplement use in the United States, 2003-2006, J. Nutr. 141 (2011) 261–266, https://doi.org/10.3945/jn.110.133025.
[110] K. Radimer, B. Bindewald, J. Hughes, B. Ervin, C. Swanson, M.F. Picciano, Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000, Am. J. Epidemiol. 160 (2004) 339–349, https://doi.org/10.1093/aje/kwh207.
[111] M. de la Fuente, L. Lombardero, A. Gómez-González, C. Solari, I. Angulo-barturen, A. Acera, E. Vecino, E. Astigarraga, G. Barreda-gómez, Enzyme therapy: current challenges and future perspectives, Int. J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms22179181.
[112] A. Missbichler, I. Mayer, C. Pongracz, F. Gabor, P. Komericki, 19 Supplementation of enteric coated diamine oxidase improves intestinal degradation of food-borne biogenic amines in case of histamine intolerance, Clin. Nutr. Suppl. 5 (2010) 11, https://doi.org/10.1016/s1744-1161(10)70019-3.
[113] M. Alemany-Fornes, J. Bori, M. Tintoré, J. Cuñé, C. de Lecea, How Reliable Are DAO Supplements?-A Comparison of Over-the-counter Diamine Oxidase Products, 2023, https://doi.org/10.1101/2023.04.13.536689.
[114] L. Kettner, I. Seitl, L. Fischer, Toward oral supplementation of diamine oxidase for the treatment of histamine intolerance, Nutrients 14 (2022), https://doi.org/10.3390/nu14132621.
[115] R. Federico, R. Angelini, A. Cesta, C. Pini, Determination of diamine oxidase in lentil seedlings by enzymic activity and immunoreactivity, Plant Physiol. 79 (1985) 62–64, https://doi.org/10.1104/pp.79.1.62.
[116] L. Kettner, C. Braun, I. Seitl, E. Pross, L. Fischer, Production and characterization of a new diamine oxidase from Yarrowia lipolytica, J. Biotechnol. 340 (2021) 39–46, https://doi.org/10.1016/j.jbiotec.2021.08.015.
[117] J. Costa-Catala, S. Pellicer-Roca, I. Iduriaga-Platero, S. Sánchez-Pérez, M. T. Veciana-Nogués, M.L. Latorre-Moratalla, M.C. Vidal-Carou, O. Comas-Basté, Impact of technological factors on diamine oxidase (DAO) activity in porcine kidney extracts as active ingredient for the dietary management of histamine intolerance, Appl. Food Res. 4 (2024), https://doi.org/10.1016/j.afres.2024.100592.
[118] J. Costa-Catala, I. Iduriaga-Platero, J. Bori, M.C. Vidal-Carou, M.L. Latorre-Moratalla, O. Comas-Basté, Optimization of agro-technological processing parameters to enhance diamine oxidase activity in edible legume sprouts, J. Agric. Food Res. 22 (2025), https://doi.org/10.1016/j.jafr.2025.102104.
[119] T. Bohm, B. Jilma, N. Borth, E. Gludovacz, New Recombinant Diamine Oxidase and its Use for the Treatment of Diseases Characterized by Excess Histamine. https://patents.google.com/patent/EP3927817A1/en, 2019. (Accessed 1 July 2025).
[120] P. Joseph, S.K. Srivastava, Photoregulation of diamine oxidase from pea seedlings, J. Plant Physiol. 146 (1995) 108–114, https://doi.org/10.1016/S0176-1617(11)81975-9.
[121] Y.A. Güvenilir, N. Deveci, The isolation and purification of diamine oxidase of pea seedlings and pig liver, Applied Biochemistry and Biotechnology 56 (1996) 235–241, https://doi.org/10.1007/BF02786955.
[122] O. Comas-Basté, M.L. Latorre-Moratalla, J. Rabell-González, M.T. Veciana-Nogués, M.C. Vidal-Carou, Lyophilised legume sprouts as a functional ingredient for diamine oxidase enzyme supplementation in histamine intolerance, LWT 125 (2020), https://doi.org/10.1016/j.lwt.2020.109201.
[123] P. Pietrangeli, E. Capuozzo, M.A. Mateescu, L. Marcocci, Copper-containing amine oxidase purified from Lathyrus sativus as a modulator of human neutrophil functions, Int. J. Mol. Med. 45 (2020) 1583–1590, https://doi.org/10.3892/ijmm.2020.4535.
[124] A.J. Tipping, M.J. McPherson, Cloning and molecular analysis of the pea seedling copper amine oxidase, J. Biol. Chem. 270 (1995) 16939–16946, https://doi.org/10.1074/jbc.270.28.16939.
[125] L. Blemur, T.C. Le, L. Marcocci, P. Pietrangeli, M.A. Mateescu, Carboxymethyl starch/alginate microspheres containing diamine oxidase for intestinal targeting, Biotechnol. Appl. Biochem. 63 (2016) 344–353, https://doi.org/10.1002/bab.1369.
[126] M. Megoura, P. Ispas-Szabo, M.A. Mateescu, Enhanced stability of vegetal diamine oxidase with trehalose and sucrose as cryoprotectants: mechanistic insights, Molecules 28 (2023), https://doi.org/10.3390/molecules28030992.
[127] B. Shanmugaraj, C.J.I. Bulaon, W. Phoolcharoen, Plant molecular farming: a viable platform for recombinant biopharmaceutical production, Plants 9 (2020) 1–19, https://doi.org/10.3390/plants9070842.
[128] B. Tihanyi, L. Nyitray, Recent advances in CHO cell line development for recombinant protein production, Drug Discov. Today Technol. 38 (2020) 25–34, https://doi.org/10.1016/j.ddtec.2021.02.003.
[129] Z.S. Olempska-Beer, R.I. Merker, M.D. Ditto, M.J. DiNovi, Food-processing enzymes from recombinant microorganisms-a review, Regul. Toxicol. Pharmacol. 45 (2006) 144–158, https://doi.org/10.1016/j.yrtph.2006.05.001.
[130] N.N. Razali, N.H. Hashim, A.T.C. Leow, A.B. Salleh, Conformational design and characterisation of a truncated diamine oxidase from Arthrobacter globiformis, High Throughput 7 (2018), https://doi.org/10.3390/HT7030021.
[131] E. Gludovacz, K. Schuetzenberger, M. Resch, K. Tillmann, K. Petroczi, M. Schosserer, S. Vondra, S. Vakal, G. Klanert, J. Pollheimer, T.A. Salminen, B. Jilma, N. Borth, T. Boehm, Heparin-binding motif mutations of human diamine oxidase allow the development of a first-in-class histamine-degrading biopharmaceutical, Elife 10 (2021) 1–21, https://doi.org/10.7554/eLife.68542.
[132] A. P. N, K. A., Rapid Spectrophotometric Micromethod for Determination of Histaminase Activity, Academic Press, 1964, https://doi.org/10.1038/2041195a0.
[133] O. Comas-Basté, M.L. Latorre-Moratalla, S. Sánchez-Pérez, M.T. Veciana-Nogués, M.C. Vidal-Carou, In vitro determination of diamine oxidase activity in food matrices by an enzymatic assay coupled to UHPLC-FL, Anal. Bioanal. Chem. 411 (2019) 7595–7602, https://doi.org/10.1007/s00216-019-02178-2.
[134] B. Wu, F. Zou, X. Wang, K. Koh, K. Wang, H. Chen, The colorimetric assay of diamine oxidase activity with high sensitivity based on calixarene derivative-capped gold nanoparticles, Anal. Methods 9 (2017) 2153–2158, https://doi.org/10.1039/c7ay00227k.
[135] S. Ahmadifar, T.C. Le, L. Marcocci, P. Pietrangeli, M.A. Mateescu, Zymographic approach to determine the intrinsic enzyme specific activity of diamine oxidase in presence of interfering enzymes, Anal. Chim. Acta 975 (2017) 78–85, https://doi.org/10.1016/j.aca.2017.04.006.
[136] S.H. Snyder, E.D. Hendley, Sensitive fluorometric and radiometric assays for monoamine oxidase and diamine oxidase, Methods in Enzymology 17B (1971) 741–746, https://doi.org/10.1016/0076-6879(71)17129-7.
[137] L. Kettner, I. Seitl, L. Fischer, Evaluation of porcine diamine oxidase for the conversion of histamine in food-relevant amounts, J. Food Sci. 85 (2020) 843–852, https://doi.org/10.1111/1750-3841.15069.
[138] X. Hu, X. Bian, W.Y. Gu, B. Sun, X. Gao, J.L. Wu, N. Li, Stand out from matrix: ultra-sensitive LC−MS/MS method for determination of histamine in complex biological samples using derivatization and solid phase extraction, Talanta 225 (2021), https://doi.org/10.1016/j.talanta.2020.122056.
[139] G. Manzotti, D. Breda, M. Di Gioacchino, S.E. Burastero, Serum diamine oxidase activity in patients with histamine intolerance, Int. J. Immunopathol. Pharmacol. 29 (2016) 105–111, https://doi.org/10.1177/0394632015617170.
[140] Committee of the international union of biochemistry, Units of enzyme activity: recommendations 1978, Eur. J. Biochem. 97 (1979) 319–320, https://doi.org/10.1111/j.1432-1033.1979.tb13116.x.
[141] T.K. Lim, Pisum sativum, in: Edible Medicinal and Non-medicinal Plants, Springer Netherlands, 2012, pp. 849–866, https://doi.org/10.1007/978-94-007-1764-0_93.
[142] A. Karim, A.W. Wahab, I. Raya, H. Natsir, A.R. Arif, Utilization of diamine oxidase enzyme from mung bean sprouts (Vigna radiata L) for histamine biosensors, in: Journal of Physics: Conference Series, Institute of Physics Publishing, 2018, https://doi.org/10.1088/1742-6596/979/1/012014.
[143] B. Mondov, G. Rotilio, M.T. Costa, A. Finazzi-Agr, E. Chiancone, R.E. Hansen, H. Beinert, Diamine oxidase from pig kidney improved purification and properties, J. Biol. Chem. 242 (1967) 1116–1167 (PMID: 4290315).
[144] A. Rinaldi, G. Floris, P. Vecchini, Diamine oxidase from pig kidney: new purification method and amino acid composition, Prep. Biochem. Biotechnol. 12 (1982) 11–28, https://doi.org/10.1080/00327488208065547.
[145] T. Boehm, M. Karer, E. Gludovacz, K. Petroczi, M. Resch, K. Schuetzenberger, K. Klavins, N. Borth, B. Jilma, Simple, sensitive and specific quantification of diamine oxidase activity in complex matrices using newly discovered fluorophores derived from natural substrates, Inflamm. Res. 69 (2020) 937–950, https://doi.org/10.1007/s00011-020-01359-5.
[146] Y. Tobajas, M. Alemany-Fornés, I. Samarra, J. Romero-Giménez, M. Tintoré, A. del Pino, N. Canela, J.M. del Bas, N. Ortega-Olivé, C. de Lecea, X. Escoté, Interaction of diamine oxidase with psychostimulant drugs for ADHD management, J. Clin. Med. 12 (2023), https://doi.org/10.3390/jcm12144666.
[147] Y. Tobajas, M. Alemany-Fornés, I. Samarra, J. Romero-Giménez, M. Tintoré, A. del Pino, N. Canela, J.M. del Bas, N. Ortega-Olivé, C. de Lecea, X. Escoté, Diamine oxidase interactions with anti-inflammatory and anti-migraine medicines in the treatment of migraine, J. Clin. Med. 12 (2023), https://doi.org/10.3390/jcm12237502.
[148] Y. Tobajas, M. Alemany-Fornés, I. Samarra, J. Romero-Giménez, J. Cuñé-Castellana, M. Tintoré, A. del Pino, N. Canela, J.M. del Bas, N. Ortega-Olivé, C. de Lecea, X. Escoté, Exploring the relationship between diamine oxidase and psychotropic medications in fibromyalgia treatment, finding no reduction in diamine oxidase levels and activity except with citalopram, J. Clin. Med. 13 (2024), https://doi.org/10.3390/jcm13030792.

[149] W.F. Novotny, O. Chassande, M. Baker, M. Lazdunski, P. Barbry, Diamine oxidase is the amiloride-binding protein and is inhibited by amiloride analogues, J. Biol. Chem. 269 (1994) 9921–9925, https://doi.org/10.1016/s0021-9258(17)36970-3.
[150] R. Leitner, E. Zoernpfenning, A. Missbichler, Evaluation of the inhibitory effect of various drugs / active ingredients on the activity of human diamine oxidase in vitro, Clin. Transl. Allergy 4 (2014), https://doi.org/10.1186/2045-7022-4-s3-p23.
[151] J. Sattler, R. Hesterberg, W. Lorenz, U. Schmidt, M. Crombach, C.D. Stahlknecht, Inhibition of human and canine diamine oxidase by drugs used in an intensive care unit: relevance for clinical side effects? Agents Actions 16 (1985) 91–94, https://doi.org/10.1007/BF01983109.
[152] A.G. Roberts, M.E. Gibbs, Mechanisms and the clinical relevance of complex drug–drug interactions, Clin. Pharm. 10 (2018) 123–134, https://doi.org/10.2147/CPAA.S146115.
[153] C.L. Rodríguez, B.S. Kaas-Hansen, R. Eriksson, J.H. Biel, K.G. Belling, S. E. Andersen, S. Brunak, Drug interactions in hospital prescriptions in Denmark: prevalence and associations with adverse outcomes, Pharmacoepidemiol. Drug Saf. 31 (2022) 632–642, https://doi.org/10.1002/pds.5415.
[154] D. Gnjidic, K. Johnell, Clinical implications from drug-drug and drug-disease interactions in older people, Clin. Exp. Pharmacol. Physiol. 40 (2013) 320–325, https://doi.org/10.1111/1440-1681.12081.
[155] C. Zarbà, G. Chinnici, M. D'Amico, Novel food: the impact of innovation on the paths of the traditional food chain, Sustainability (Switzerland) 12 (2020), https://doi.org/10.3390/su12020555.
[156] R. López-Rodríguez, L. Domínguez, V. Fernández-Ruiz, M. Cámara, Extracts rich in nutrients as novel food ingredients to be used in food supplements: a proposal classification, Nutrients 14 (2022), https://doi.org/10.3390/nu14153194.
[157] European Commission, Commission Implementing Regulation (EU) 2017/2469. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R2469, 2017.
[158] European Commission, Commission Implementing Regulation (EU) 2017/2470. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R2470, 2017.
[159] European Parliament, Council, Regulation (EU) 2015/2283 of the European Parliament and of the Council. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32015R2283, 2015.
[160] F. Gabor, H. Reichl, Diaminooxidase-Containing Pharmaceutical Compositions. https://patents.google.com/patent/WO2006003213A1/en, 2005. (Accessed 1 July 2025).
[161] S. Sipka, Z. Gyory, J. Borberly, T. Keresztes, T. Biro, Perorally Applicable Preparation Containing Histaminase of Vegetable Origin, Resistant to Pepsin and Trypsin and a Process for Producing It. https://patents.google.com/patent/EP2611454A1/en, 2010. (Accessed 1 July 2025).
[162] Lutz Fischer, New Microbial Diamine Oxidase Derived From Yarrowia Lipolytica for the Degradation of Biogenic Amines. https://data.epo.org/publication-server/rest/v1.0/publication-dates/20221221/patents/EP4105323NWA1/document.pdf, 2021. (Accessed 1 July 2025).
[163] C. Duelo Riu, J. Duelo Riu, Topical Compositions Comprimising Diamineoxidase for the Treatment or Prevention of Diseases Associated with High Histamine Levels which Involve an Increase in Pain. https://portal.unifiedpatents.com/patents/patent/WO-2012127381-A1, 2012. (Accessed 1 July 2025).
[164] C. Duelo Riu, J. Duelo Riu, Alimentos funcionales que contienen diamino oxidasa y sus usos. https://patents.google.com/patent/ES2388166A1/es, 2011. (Accessed 2 July 2025).
[165] A. Hanna, Compositions and Methods for the Prevention and Treatment of Colitis in Infants. https://patents.google.com/patent/WO2018067923A1/en, 2016. (Accessed 1 July 2025).
[166] C. Duelo Riu, J. Duelo Riu, Diamine Oxidase for Use in the Treatment or Prevention of Attention Deficit Hyperactivity Disorder (ADHD). https://patents.google.com/patent/US9795654B2/en, 2013. (Accessed 1 July 2025).
[167] H. Blasco-Fontecilla, M. Bella-Fernández, P. Wang, M. Martin-Moratinos, C. Li, Prevalence and clinical picture of diamine oxidase gene variants in children and adolescents with attention deficit hyperactivity disorder: a pilot study, J. Clin. Med. 13 (2024), https://doi.org/10.3390/jcm13061659.
[168] K.M. Hoffmann, E. Gruber, A. Deutschmann, J. Jahnel, A.C. Hauer, Histamine intolerance in children with chronic abdominal pain, Arch. Dis. Child. 98 (2013) 832–833, https://doi.org/10.1136/archdischild-2013-305024.
[169] P. Komericki, G. Klein, N. Reider, T. Hawranek, T. Strimitzer, R. Lang, B. Kranzelbinder, W. Aberer, Histamine intolerance: lack of reproducibility of single symptoms by oral provocation with histamine: a randomised, double-blind, placebo-controlled cross-over study, Wien. Klin. Wochenschr. 123 (2011) 15–20, https://doi.org/10.1007/s00508-010-1506-y.