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RESEARCH PAPER

In vitro determination of diamine oxidase activity in food matrices by an enzymatic assay coupled to UHPLC-FL

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Abstract

Intestinal diamine oxidase (DAO) acts as a protective barrier against exogenous histamine. A deficit of DAO activity can lead to the appearance of histamine intolerance, a clinical condition that may be treated by a low-histamine diet and oral DAO supplementation to enhance intestinal histamine degradation. As sources of DAO, porcine kidneys and certain legume seedlings are suitable components for the formulation of a DAO supplement. The aim of this work was to develop a rapid and reliable methodology for the in vitro determination of DAO activity in food matrices based on an enzymatic assay coupled to UHPLC-FL. The proposed method showed a satisfactory linearity and sensitivity and provided a relative standard deviation lower than 3%, guaranteeing method precision, and a mean recovery greater than 99% both for lyophilized pea sprouts and porcine kidney protein extracts. A high specificity is a key attribute of this method due to the use of histamine as the reaction substrate and the direct quantification of its degradation. Moreover, the lack of interference of catalase and hydrogen peroxide is another advantage in comparison with previously published methods. Lyophilized pea sprouts showed the greatest histamine-degrading activity (0.40 ± 0.01 mU/mg), followed by porcine kidney protein extracts (0.23 ± 0.01 mU/mg) and commercial DAO supplements (0.09 ± 0.06 mU/mg). This technique could be used as a tool to validate the DAO activity of food matrices of potential interest for the treatment of histamine intolerance.

Keywords UHPLC-FL · Enzymatic assay · Histamine · Diamine oxidase (DAO) enzyme · Porcine kidney · Pea sprouts

Introduction

The enzyme with histamine-degrading capacity, discovered in 1929 by Charles H. Best in autolyzing lung tissues, was first known as histaminase [1]. After subsequent studies revealed its ability to deaminate other diamines, such as putrescine and cadaverine, the enzyme was renamed diamine oxidase (DAO) [2, 3]. DAO (EC 1.4.3.22), which belongs to the category of copper-containing amine oxidases, is a homodimeric and ubiquitous enzyme found in microorganisms, plants, and animals, generally in the range of 140 to 200 kDa [4–8]. In particular, DAO catalyzes the oxidative deamination of the primary amino group of histamine to imidazole acetaldehyde, consuming dioxygen with the concomitant release of stoichiometric amounts of ammonia and hydrogen peroxide (Fig. 1) [9, 10].

In humans, DAO is mainly located in the intestines, placenta, and kidneys [6, 11]. Intestinal DAO acts as a protective barrier against exogenous histamine, especially of food origin [12–14]. A deficiency of DAO enzyme may thus lead to exceed the normal plasmatic levels of histamine (0.3–1.0 ng/mL) and the subsequent appearance of histamine intolerance symptoms [15, 16]. Due to the diverse effects and functions of histamine in multiple organs and systems of the body, histamine intolerance is characterized by a variety of complaints, including gastrointestinal (abdominal pain, diarrhea, or vomiting), dermatological (urticaria, dermatitis, or pruritus), respiratory (rhinitis, nasal congestion, or asthma),

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Fig. 1 Oxidative deamination of histamine by DAO

cardiovascular (hypotonia or arrhythmias), or neurological (headaches) [14–17]. The most frequently used treatment for histamine intolerance consists of following a low-histamine diet [15, 18]. Only foods with histamine levels below detectable limits can be considered safe for histamine-intolerant patients, and unfortunately for this population, histamine is widespread among all food categories in highly variable concentrations [19, 20]. In this context, considering that DAO is the key enzyme in the breakdown of dietary histamine at the intestinal level, orally administered DAO supplements have been proposed as a strategy to enhance histamine degradation and improve the quality of life of intolerant individuals undergoing those dietary restrictions [21, 22]. As sources of DAO, porcine kidneys and certain legume seedlings are suitable components of such an enzymatic supplement [21, 23].

A wide range of methods to detect in vitro DAO activity are described in the literature. With the aim of measuring the rate of substrate degradation or the generation of by-products of this enzymatic reaction, most methods are based on the detection of hydrogen peroxide, aldehyde, or dioxygen by spectrophotometric [13, 21, 24, 25], fluorometric [26], polarographic [27, 28], or amperometric [29, 30] techniques. Radioimmunoassay techniques have also been extensively described, consisting of the radioactive labeling of the substrate and the scintillation counting of its consumption [3, 11, 31]. Although chromatographic analytical procedures are widely used, this approach has only been applied to measure histamine or other biogenic amine degradation capacity in microbial starter cultures involved in food-fermenting processes [10, 32, 33]. Despite some of these methods may be advantageous in terms of rapidity or automation, they generally have a limited sensitivity, require a laborious experimental setup, or entail a high cost in the correct storage and handling of radioactive waste. Moreover, in those methods in which the DAO activity is estimated through the determination of hydrogen peroxide or dioxygen, the action of other enzymes, such as catalase, may interfere by H_2O_2 consuming or O_2 releasing [34, 35]. Additionally, the most extensively used reaction substrates in the methods reported so far are putrescine and cadaverine, which have different affinity or kinetic parameters to histamine [36, 37].

Therefore, the aim of this work was to develop a reliable, rapid, and highly sensitive methodology for the determination of in vitro DAO activity of several matrices using histamine as the substrate and based on the direct quantification of its degradation during the reaction process. Specifically, an enzymatic assay coupled to an ultra-high performance liquid chromatography and fluorimetric (UHPLC-FL) detection method was proposed, validated, and tested for applicability in porcine kidney protein extracts, legume sprouts, and commercialized DAO supplements.

Material and methods

Reagents and chemicals

Histamine dihydrochloride, purified DAO from porcine kidney, and catalase from bovine liver were purchased from Sigma-Aldrich (St. Louis, MO, USA). UHPLC-grade methanol and acetonitrile, hydrochloric acid 0.1M, perchloric acid 70%, sodium di-hydrogen phosphate anhydrous, and disodium hydrogen phosphate anhydrous were obtained from PanReac Química (Castellar del Vallès, Spain). Acetic acid, boric acid, 1-octanesulfonic acid sodium salt, ammonium formate, phthaldialdehyde (OPA), and brij® L23 solution were acquired from Sigma-Aldrich (St. Louis, MO, USA); and formic acid, sodium acetate anhydrous, potassium hydroxide, and 2-mercaptoethanol from Merck (Darmstadt, Germany). A LaboStar System from Evoqua Water Technologies (Warrendale, PA, USA) was used to produce ultrapure water (18.2 MΩcm).

Samples

For the analytical method development and validation, porcine kidney protein extracts and lyophilized pea sprouts (*Pisum sativum*) were used. Porcine kidney extracts were provided by a biotechnology company specialized in the extraction of biomolecules from animal tissues. These extracts consisted of a homogenate powder obtained by an acetonic extraction followed by a drying process. Porcine kidney extracts consisted of 84% of protein, estimated by applying the nitrogen-to-protein conversion factor (6.25) to the total nitrogen determined following the Kjeldahl method (2200 Kjeltec® Auto Distillation Unit, Foss Iberia S.A.U., Barcelona, Spain). Etiolated pea sprouts were obtained in our laboratory through the germination of peas at 27 °C and 70% HR. After the sprouts were freeze-dried (Cryodos-50, Telstar, Terrassa, Spain), a lyophilized extract consisting of 39% of protein was obtained. Samples were kept under refrigeration (4–8 °C) until analysis.

The applicability of the method was assayed with 13 different production batches of porcine kidney protein extract, 7 batches of lyophilized pea sprouts and 6 commercialized DAO supplements available in the market. These dietary supplements were in the form of gastro-resistant-coated capsules or tablets, all of them containing 4.2 mg of porcine kidney protein extract.

In vitro determination of DAO activity

The capacity of the DAO enzyme to degrade histamine in a working solution with a defined initial concentration of histamine was tested under controlled optimal conditions (37 °C, pH 7.2). The subsequent analysis of degraded histamine during the reaction time was performed by UHPLC-FL. Specific DAO activity is expressed in mU/mg, referring to the amount of histamine that is degraded by a milligram of sample per minute (nmol of degraded histamine per minute/mg of sample).

Enzymatic assay

Figure 2 illustrates in a schematic manner the experimental procedure of the enzymatic assay for the in vitro determination of DAO activity. In detail, 1 to 20 mg of porcine kidney protein extract, lyophilized pea sprouts, or the content of one tablet or capsule of dietary supplement were thoroughly homogenized in 20 mL of 0.05M phosphate buffer solution (pH 7.2) and placed in a shaker incubator (Ivymen® 100-D, JP SELECTA S.A., Abrera, Spain) for at least 30 min (37 °C, 200 rpm). The addition of a histamine standard solution to reach an initial concentration of 45 µM in the homogenized sample marked the start of the enzymatic reaction. The enzyme in contact with its substrate was kept in constant incubation and 500 µL aliquots were progressively extracted at different sampling times (*t* = 0, 1, 2, 4, and 6 h). To stop the enzymatic reaction, 15 µL of 2N perchloric acid solution was added to the extracted aliquot, vigorously mixed with a vortex mixer, and centrifuged (4 °C, 5 min, 15000 rpm). The supernatant was filtered through a 0.22-µm GHP filter and stored at 4 °C until UHPLC analysis. Each sample was analyzed in duplicate and a positive control was performed with 1 mg of purified DAO.

To assay the potential interference effect of catalase on the DAO activity determination, porcine kidney protein extract was assayed with the addition of catalase enzyme at two different concentrations (100 and 500 U/mL) using the same experimental procedure.

UHPLC-FL analysis

Chromatographic separation was performed using a UHPLC-FL system consisting of a Waters Acquity™ Ultra Performance Liquid Chromatography apparatus, which comprised a quaternary pump, an auto-sampler and a fluorescence detector, and a post-column reagent manager connected to a zero dead volume union between the column outlet and the detector. Data acquisition was performed using the Empower^{TM} 3 software (Waters Corp., Milford, MA, USA).

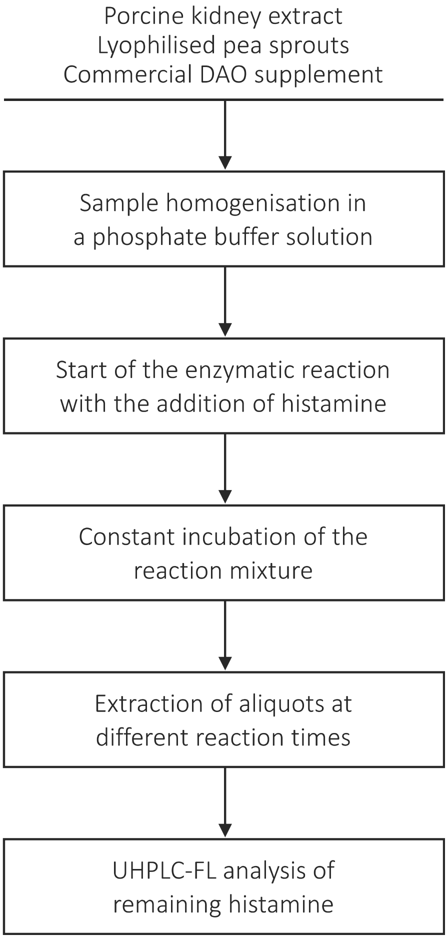

Fig. 2 Schematic experimental procedure of the enzymatic assay for the in vitro determination of DAO activity

The chromatographic determination of histamine was performed by ion-pair reverse-phase UHPLC coupled with post-column online derivatization with OPA and fluorescence detection. Elution time was 7 min. Chromatographic conditions were as previously described by Latorre-Moratalla et al. [38], briefly summarized in Table 1.

Statistical analysis

The software package IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA) for Windows (version 22) was used for the statistical analysis of data. The reliability of the method was tested by means of analysis of variance for linear regression and the data sets were compared using the Student's *t* test. Cochran's *C* test was used to assess the homogeneity of variances.

Table 1 Chromatographic conditions for the UHPLC-FL determination of histamine

Stationary phase	
Column	Acquity UPLC™ BEH C18 column (1.7 µm, 2.1 mm × 50 mm)
Column temperature	42 °C
Mobile phase	
Eluent A	H_2O solution with 0.1 M sodium acetate and 10 mM sodium octanesulfonate (adjusted to pH 4.8 with acetic acid)
Eluent B	H_2O solution with 0.2 M sodium acetate and 10 mM sodium octanesulfonate (adjusted to pH 4.5 with acetic acid): Acetonitrile (6.6:3.4)
Linear gradient	0 min, 80% A; 2 min, 80% A; 3 min, 60% A; 4 min 50% A; 5 min, 40% A; 6 min, 20% A; 6.40 min, 80% A; 7 min, 80% A
Flow rate	0.8 mL/min
Injection volume	1 µL
Fluorescence detection	
Derivatization reagent	OPA (0.2 mg/mL), brij®, 2-mercaptoethanol, methanol, potassium hydroxide and boric acid
Excitation and emission wavelengths	340 nm and 445 nm
Flow rate	0.4 mL/min

Results and discussion

The method developed in this work is based on the direct addition of a defined amount of histamine to a food matrix homogenized in an aqueous solution. During the incubation period of the mixture, the DAO enzyme potentially present in the sample progressively degrades the substrate. DAO activity was determined by comparing the absolute amount of histamine degraded during the reaction time with the initial substrate concentration. The absence of histamine degradation when assaying the same amount of substrate but lacking the DAO enzyme or samples as a negative control proved that the degradation of histamine in the proposed method is exclusively mediated by the enzyme.

The UHPLC-FL method allowed us to unequivocally determine the remaining histamine in the samples with a chromatographic elution time of 7 min and without the need for tedious pre-column derivatization procedures. The selected substrate concentration was 45 µM of histamine, in accordance with published kinetic data for DAO activity on this specific amine, to ensure optimal performance of the enzymatic reaction [9, 39, 40]. The degradation of histamine was monitored for 48 h to study the enzymatic reaction. A linear histamine degradation rate was observed in the first 6 h of the assay ($r > 0.9990$) for both porcine and legume matrices.

Method reliability

The linearity of the method was assessed by performing in triplicate seven determinations of different enzymatic activities using purified DAO and verified by analysis of the variance of the regression. A correlation coefficient of $r = 0.9998$ and a coefficient of determination (r^2) higher than 99% were obtained ($p < 0.001$), demonstrating the satisfactory performance of the method within the DAO activity range of 0.7 to 4.5 mU. Regarding method sensitivity, the limit of detection (LOD) and the limit of quantification (LOQ) were estimated using a regression curve with low DAO activity values and considering the mean response of a blank plus three or ten times the standard deviation of the blank, respectively [41]. Specifically, the value obtained for LOD was 0.025 mU, and for the LOQ, it was 0.038 mU.

The precision and recovery of the proposed method for routine analysis of DAO activity were assessed with different batches of porcine kidney protein extract and lyophilized pea sprouts. The precision was evaluated by performing 7 independent determinations of DAO activity for each food matrix (Table 2). The relative standard deviation was in both cases lower than 3%, showing a satisfactory level of precision. The Horwitz equation for intra-laboratory studies confirmed the acceptability of this precision data [42]. Recovery was evaluated by performing 7 independent determinations of porcine kidney extract and lyophilized pea sprouts, considering 3 addition levels with purified DAO (Table 2). The recovery values obtained for the three levels of addition were satisfactory and no statistical differences from the theoretical value 100% were found ($p > 0.05$) [42]. The variance of the recovery values was not dependent on the content of the analyte according to Cochran's *C* test ($p > 0.05$).

Among the range of methodologies described in the literature that challenge the determination of DAO activity, the majority are based on the measurement of the liberation of hydrogen peroxide or the consumption of oxygen occurring along the oxidative deamination reaction [13, 21, 24–30]. Those largely used approaches face an important drawback, as the presence of hydrogen peroxide and dioxygen may be

Table 2 Precision and recovery results for porcine kidney extracts and lyophilized pea sprouts

	Precision		Recovery[c]			
	RSD (%)[a]	RSDH (%)[b]	Addition level I	Addition level II	Addition level III	Cochran's test C_{exp}[d]
Porcine kidney extract	2.76	3.45-4.60	100.54 (4.98)	102.69 (5.44)	99.14 (2.52)	0.41
Lyophilized pea sprouts	2.80	3.27-4.36	101.28 (0.90)	100.00 (0.76)	100.51 (2.61)	0.05

[a] Relative standard deviation (RSD) for seven determinations

[b] Acceptable range for relative standard deviations according to the Horwitz equation for intra-laboratory studies (1/2–2/3 of the interlaboratory study calculate by the formula)

[c] Mean recovery percentages and standard deviation in parentheses for three addition levels corresponding to enzymatic activities of 0.5, 1.0, and 2.0 mU for porcine kidney extract and 1.0, 2.0, and 4.0 mU for lyophilized pea sprouts

[d] Cochran's C variance outlier test, C_{tab} (6, 2, 0.05) = 0.8534.

markedly influenced by the concomitant presence of other enzymatic capacities in certain complex biological matrices [34, 35]. This is the case of catalase, an enzyme commonly found in plant and animal tissues, which can lead to the underestimation of DAO activity by consuming H_2O_2 and releasing O_2 [34, 35]. Therefore, the frequent occurrence of catalase in DAO-positive matrices makes those techniques unadvisable due to major interference effect. In this sense, Ahmadifar et al. [35] have recently proposed a zymographic approach consisting in an electrophoretic separation of DAO enzyme followed by its densiometric image analysis capable to evaluate the DAO activity of a sample in the presence of interfering catalase. Concurrently, all those methods consisting in the monitoring of hydrogen peroxide release through a coupled reaction with peroxidase entail further complexities, such as a potential partial substrate inhibition produced by excess of hydrogen peroxide [43]. In general, coupled peroxidase assays may be targeted as unreliable when working with purified DAO enzyme and totally unadvisable when studying non-purified complex samples due to the presence of peroxidase inhibitors or other enzymatic activities [34, 44]. In fact, Calinescu et al. [34] evaluated the DAO capacity of formulation containing a vegetal extract with the presence of catalase, using both a peroxidase-coupled assay and an alternative assay non-related to peroxidase enzyme. In this context, the authors described the unsuitability of the peroxidase-coupled assay due to the diminution of released H_2O_2 by catalase enzyme, emphasizing the need to seek for enzymatic tests not affected by the presence of catalase [34]. In this sense, methods based in the direct measurement of the degradation of the amine substrate, hitherto scarcely described in the literature, may overcome this limitation. In the proposed method, DAO activity of the porcine kidney extract did not significantly differ ($p > 0.05$) when it was determined with or without the addition of catalase, and independently of the concentration of this enzyme added to the sample. Therefore, the proposed method herein is not influenced by the presence of catalase present in the analyzed food matrices, since it is based in the direct determination of histamine.

Although the largely used spectrophotometric techniques seem to be sensitive enough for the analysis of samples with an elevated degree of purification, there is a lack of a reliable and sensitive methods that allow to determine DAO activity in complex biological or food matrices, which will not only contain several potential interferences but will also show relatively low enzymatic rate. In this case, radiochemical detection techniques based on the use of C^{14}-labeled putrescine becomes the preferred approach [44]. However, while a high sensitivity may be attributed to the latter, serious concerns related to the hazardous potential in the handling of radioactive material and the high cost and unsuitability of its storage need to be considered. The proposed method shows the advantages of sensitivity, reproducibility, and automatization of an UHPLC approach while avoiding user-related hazardous potential and becomes a suitable approach to analyze DAO activity in complex non-purified matrices.

Suitability of the method for the determination of DAO activity in porcine kidney protein extracts, lyophilized pea sprouts, and DAO supplements

The applicability of the developed method was tested by analyzing several production batches of porcine kidney protein extract and lyophilized pea sprouts. Additionally, the enzymatic capacity of porcine kidney extract in DAO supplements available in the market was studied. All analyzed products showed in vitro histamine-degrading capacity (Fig. 3). Lyophilized pea sprouts were the most effective, with a mean enzymatic activity of 0.40 (± 0.01) mU/mg, compared with 0.23 (± 0.01) mU/mg for porcine kidney protein extracts. It is worth highlighting that the DAO activity of both products showed minimal variation among different production batches. These results are in good agreement with previously published data indicating a higher catalytic turnover rate for plant- than animal-derived DAO [5, 23, 37]. The amine-degrading capacity described in the literature for these food matrices is highly variable, with values ranging from 0.1 to 500 mU/mg. Different behavior toward the same amino

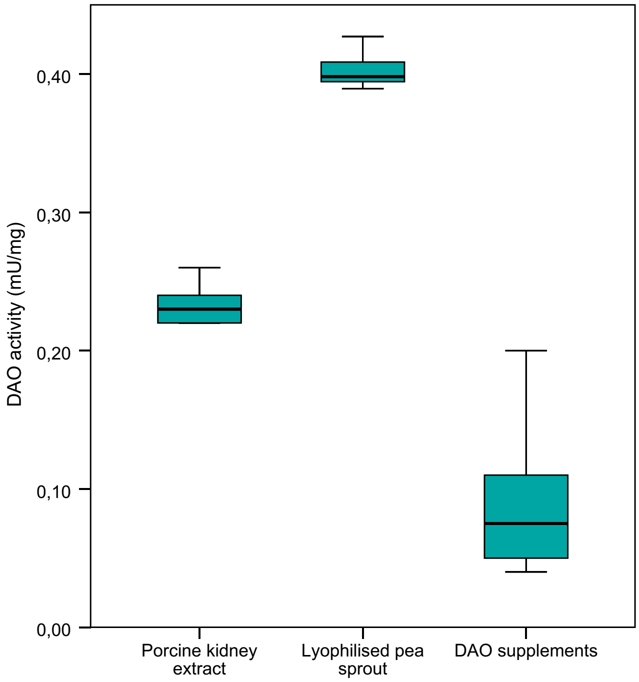

Fig. 3 In vitro DAO activity of several production batches of porcine kidney protein extract, lyophilized pea sprouts, and different commercial DAO supplements

substrates has been reported for DAO enzymes depending on whether they are of animal or plant origin [37]. This heterogeneity could also be explained by differences in methodology between studies, as a range of detection techniques and substrates have been used. Thus, Kivirand et al. [7] suggested that the substrate specificity data available for DAO varied according to the experimental method and recognized an important difficulty to find comparable data due to the evidenced dispersion of methodological procedures. Concretely, the wide range of used substrates (i.e., putrescine, cadaverine, agmatine, histamine, spermidine, and spermine) may easily lead to differences in the reported enzymatic activities, as the affinity of DAO for each substrate varies [36, 37]. Due to the evidenced differences in kinetic parameters depending on the amino substrates, histamine is the optimal substrate in order to have an available methodology to determine the enzymatic activity of potential new sources of DAO, considering the degradation of this target substrate and no other amines.

Porcine kidneys and pea seedlings are the main sources of DAO according to the literature [21, 23], but it can also be found in other food products, such as certain legumes (*Cicer arietinum*, *Lathyrus sativus*, *Lens esculenta*), barley (*Hordeum vulgare*), maize (*Zea mays*), and tea (*Thea sinensis*) [21, 23, 36]. The method proposed here could be applied to validate the in vitro enzymatic capacity of these food matrices and to screen for new potential sources of DAO.

The DAO activity of the six commercial DAO supplements ranged widely from 0.04 to 0.20 mU/mg, despite all being formulated with the same amount of porcine kidney extract (4.2 mg) (Fig. 3). In comparison with the raw porcine extract (0.23 ± 0.01 mU/mg), a markedly lower DAO activity was generally observed in these supplements. The application of different galenic formulation processes may influence the enzymatic capacity of the kidney extract, which would explain both the variability and loss of activity of the DAO supplements. Further studies are required to understand how different technological parameters linked to the manufacturing process of these supplements influence the enzymatic activity. The variable activity of commercial DAO supplements could help explain the different efficacy rates reported by clinical studies evaluating the use of exogenous DAO to treat symptoms associated with histamine intolerance [22, 45–47].

Few studies have estimated the intestinal DAO activity in a healthy population. An enzymatic activity of 0.001–0.03 mU/mg has been reported in the intestinal mucosa, with higher values given for intestinal protein (0.2–0.33 mU/mg) [31, 48–50]. As indicated by the manufacturers, the usual posology of DAO supplements is 1 capsule before each meal, which provides an enzymatic activity in the range of 0.17 to 0.84 mU, depending on the product. In view of these results, more accurate studies are needed in order to establish the effective dosage of DAO that can provide a complementary intestinal protective barrier for histamine-intolerant individuals.

Conclusion

The proposed method, consisting of an enzymatic assay coupled to a UHPLC-FL technique, allowed the in vitro determination of DAO activity in food matrices using histamine as the reaction substrate. This method provided satisfactory experimental performance in terms of linearity, sensitivity, precision, and recovery, and its suitability was tested on different food matrices reported as sources of DAO. The DAO activity of lyophilized pea seedlings was nearly two-fold higher than that of porcine kidney protein extracts. The histamine-degrading capacity of the six DAO supplements available in the market was variable and lower compared with the other analyzed matrices. Due to the growing awareness of histamine intolerance, it is important to have effective methods for validating the DAO activity of supplements and foods of potential interest for the treatment of this disorder.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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