

Pea Seedling Amine Oxidase Application: an Emerging Antihistamine Strategy in Tuna Fish

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Abstract

Despite the known antihistaminic effects of PSAO, this enzyme remains unrecognized as an antihistamine additive in the food industry. The objective of this study was to ascertain the plausible histamine-degrading effects of a new food-grade additive (pea seedling extract) in tuna fish. PSAO was purified from cultured pea seedlings via ion-exchange and size-exclusion chromatography. SDS-PAGE results indicated that the PSAO subunit has an apparent molecular weight of about 95 kDa. To evaluate the optimized conditions for antihistaminic activity of the enzyme, the reaction of PSAO and histamine was carried out in KPi buffer under conditions relevant to the fish processing industry. 1 unit mL⁻¹ of PSAO significantly reduced the histamine content at pH 7.0 but not at pH 5.0. Accordingly, its antihistaminic activity was assessed in homogenized skipjack tuna fish (*Katsuwonus pelamis*) using an ion-paired HPLC method. The results showed that PSAO can reduce 87.14% of the histamine content of the tuna fish at pH 7.0, 37°C. This study indicates that PSAO - purified or even filtrate of pea seedling homogenate - can degrade histamine, which suggests practical application of this enzyme in fish processing industry.

Keywords: Pea seedling Amine oxidase (PSAO); Antihistamine activity; Tuna fish

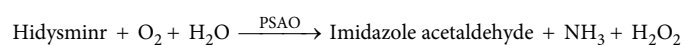
Introduction

Histamine can only be synthesized by the decarboxylation of L-histidine via L-histidine decarboxylase (HDC) (E.C. 4.1.1.22). In addition, histamine seems to be the toxic component of scombrototoxin, which causes scombroid poisoning. This allergy-like foodborne disease is mostly associated with the consumption of fish, particularly of the *Scombridae* and *Scomberesocidae* families [1].

Preventative measures, such as the proper onboard handling of fish and an unbroken cold chain, will reduce the risk of scombroid poisoning. Histamine is a thermostable compound: once the synthesis occurs via improper onboard handling or a broken cold chain, it cannot be degraded by industrial thermal processes [2]. Despite the reported levels of histamine in (processed) fish, outbreaks of scombroid poisoning - often underreported - continue to occur [3-5]. Since there is no industrial process of histamine degradation, these measures remain the only method of reducing histamine level in fish and preventing outbreaks of scombroid poisoning.

Diamine oxidases (DAOs), a group of amine oxidases, prefer to metabolize the biogenic amines such as putrescine, cadaverine and histamine. In the body, DAO is the main enzyme for the metabolism of ingested histamine; Moreover, DAO of plant origin was proposed for the general treatment of histamine-related pathologic conditions [6-8].

Intriguingly, pea seedling amine oxidase (PSAO), a copper-containing diamine oxidase, catalyzes the oxidative deamination of histamine to the corresponding aldehyde *i.e.* imidazole acetaldehyde-concomitant with the reduction of dioxygen to hydrogen peroxide [9,10]:



Provided that the histamine-reducing effect of PSAO also applies to seafood and histamine-rich fermented foods, PSAO could offer a natural additive to the corresponding food industries. The objective of the present work was to evaluate the potential impact of PSAO on the oxidative degradation of histamine generated in tuna fish.

Materials and Methods

Preparation of plant materials

Pea seeds (*Pisum sativum* L) were purchased from *Nunhems Zaden BV, Haelen*, Netherlands. The seeds, disinfected with a solution of sodium hypochlorite, were cultured in plastic plug-trays with a soilless media of cocopeat and perlite (1:1 v/v). The etiolated (dark-grown) seedlings were harvested above the roots after 12-days germination at room temperature. After harvesting, immediate purification of PSAO was carried out at 4°C.

PSAO purification

PSAO was purified by modifying a published procedure [11]. The slick slurry of pea seedling homogenate was made with 2 volume of potassium phosphate buffer (KPi buffer) (0.1 M, pH 7.0) in an Ultra-Turrax® (T50 basic, Germany) blender (10,000 rpm) for 10 minutes. The homogenate was filtered through four layers of cheese cloth, and the resulting filtrate was centrifuged at 27,000 g (F-28/50 rotor of RC-5 Superspeed Refrigerated Centrifuge, Sorvall) for 30 min at 4°C. The supernatant was brought to 30% saturation in ammonium sulphate solution. After a second centrifugation at 27,000 g for 20 min, the supernatant was further fractionated with ammonium sulphate in 70% saturation. The precipitate was then separated by centrifugation at 27,000 g for 20 min, resuspended in 20 mL of KPi buffer (0.1 M, pH 7.0), and dialyzed against the same buffer overnight (D6066, Sigma-Aldrich). The dialyzed solution was stored at -18°C and used as a crude extract. This dialyzed solution was then applied onto a

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diethylaminoethyl (DEAE) cellulose column ($\varnothing=2.5$ cm, $l=20$ cm) (D3764, Sigma-Aldrich) and washed with KPi buffer (0.02 M, pH 7.0) at a flow rate of 15 mL/h. The elution was performed by KPi buffer (0.1 M, pH 7.0) containing 0.1 M KCl at a flow rate of 15 mL/h. Fractions showing enzymatic activity-tubes 9-21-were pooled and lyophilized to 3 mL volume and then loaded onto a column of Sephadex G-200 superfine ($\varnothing=1.5$ cm, $l=53$ cm) (84961, Sigma-Aldrich). The sample was washed with KPi buffer (0.02 M, pH 7.0) at a flow rate of 15 mL/h. Once again active fractions were pooled and lyophilized.

Enzyme assay: An established spectrophotometric assay-as described by Kluetz et al. [12] was used to evaluate the activity of PSAO. The enzyme was applied to benzylamine substrate, and the increase in absorbance, due to the benzaldehyde formation, was monitored on a Gilford Model 252 UV-vis spectrophotometer for at least 10 min. One unit of enzymatic activity is defined as the amount that catalyzes the conversion of 1 μ mole of substrate to product per minute at 37°C.

Total protein assay: The total protein amount was determined spectrophotometrically using both the Lowry and Bradford methods.

SDS-PAGE analysis: SDS-PAGE was performed on a discontinuous gel system with two sequential gels (10% T, 2.5% C). The samples (2 mg.mL⁻¹) dissolved in a sample buffer and boiled at 100°C for 10 min before the application on gel. The gels were stained with Coomassie Brilliant Blue G-250 while PageRuler™ Plus Prestained Protein Ladder (SM1811, Fermentas) was used as a protein molecular weight marker.

HPLC evaluation of histamine

Histamine detection by high performance liquid chromatography (HPLC) was performed as described previously [13], in which procedure had no laborious pre-treatment, clean up and derivatization. All of the HPLC evaluations were done in triplicate.

HPLC chemicals: HPLC-grade methanol (34869) and acetonitrile (34998), histamine dihydrochloride (H7250), 1,1-dimethylbiguanide hydrochloride (D150959) and 1-decanesulfonic acid sodium salt (30633) were supplied by Sigma-Aldrich (Munich, Germany). Analytical grade reagents (KH₂PO₄, K₂HPO₄·3H₂O and HClO₄) were supplied by Merck (Darmstadt, Germany). The water used was obtained using the Milli-Q purification system of Millipore.

HPLC solutions and eluents: The 1000 ppm stock solutions of 1,1-dimethylbiguanide hydrochloride and histamine dihydrochloride prepared by dissolving them in HCl (0.1 M). The histamine working solutions at a concentration of 2-5-8-10-15-30-50 mg/l in HCl (0.1 M) were prepared fresh every day. The final concentration of 1,1-dimethylbiguanide hydrochloride (chromatographic reference standard) which added to all the solutions was about 5 mg L⁻¹. Solution of HClO₄ (1 M) was used as an extraction solvent of histamine from fish. A mobile phase of buffer solution: methanol: acetonitrile (75:10:15, v/v/v) was delivered at a flow rate of 1.0 mLmin⁻¹ to the column. The buffer solution, 1.72 g of KH₂PO₄, 2.7 g of K₂HPO₄·3H₂O and 0.49 g of C₁₀H₂₁O₃Na (sodium 1-decanesulfonate) in 1 L water with a final pH of 6.7, was filtrated through a 0.45- μ m Millipore membrane filter, and degassed before use in an ultrasonic bath (Sonorex Super[®] RK 100/H). The buffer solution was prepared at the time of use.

HPLC equipment and conditions: The HPLC analyses were carried out using an Agilent HPLC system (Agilent 1100 series, Waldbronn, Germany) equipped with a quat pump G1311A, autosampler G1313A, variable wavelength detector (VWD) G1314A and degasser G1379A. The separations were performed under isocratic conditions using a 5

μ m C18 column of 250 mm×4.6 mm i.d. (Spherical, Optimal[®] ODS-H, Capital HPLC, UK) fitted with a 5 μ m C18 guard column of 20 mm×4.6 mm (Spherical, Optimal[®] ODS-H, Capital HPLC, UK). The flow rate was 1.0 mLmin⁻¹, the injection volume 30 μ L and the VWD was positioned at a wavelength of 214 nm.

In vitro optimization of antihistamine activity of PSAO

The antihistamine activity of 1 unit mL⁻¹ SEC-PSAO (Size-exclusion chromatography pool of PSAO) has been evaluated upon the substrate of histamine dihydrochloride with KPi buffers (0.02 M; pH 5.0 and pH 7.0) at two temperatures (25°C and 37°C) within three time periods (0, 30 and 60 minutes). Application of KPi buffer instead of the enzyme was used as control and the HPLC without any histamine-extraction procedure was performed for the evaluation of antihistamine activity of PSAO.

Evaluation of antihistamine effect of PSAO in tuna fish

Histamine production of an onboard-frozen skipjack tuna fish - with negligible amount of histamine - was enhanced by incubation at the optimum temperature of histamine formation in skipjack tuna fish (37°C, 24h) [14]. The initial histamine level was spotted after the incubation (F1). Thereafter, to obtain at least 50% histamine degradation; tuna fish experimental groups encompass: control plain fish (F2), and the rest comprise tuna fish associated with 4 μ molg⁻¹ pyridoxal 5'-phosphate (P9255, Sigma-Aldrich, Munich, Germany) (F3), 4 unit mL⁻¹ SEC-PSAO (F4), 4 unitmL⁻¹ filtrate of pea seedling homogenate (F5), 4 unitmL⁻¹ filtrate of pea seedling homogenate plus 4 μ mol g⁻¹ pyridoxal 5'-phosphate (F6) were hygienically provided from the homogenized (Ultra-Turrax[®] T25D, Germany; 1000 rpm, 3 min) anterio-dorsal fish meat. The treatments (F2 - F6) were incubated (37°C, 30 min) providing optimum enzymatic situation, while thenceforth PSAO was inactivated through high temperature (100°C, 10 min). Afterwards, histamine extraction of previously homogenized tuna fish was performed by weighing out 5 grams of each experiment into a centrifuge test tube and 250 μ L of the chromatographic reference standard (1,1-dimethylbiguanide hydrochloride) added so as to obtain a concentration of about 5 mg L⁻¹ and allowed to stand at room temperature for 30 minutes. 20 mL of HClO₄ (1 M) was then added to the test tube; the mixture was homogenized at 1000 rpm for 3 min and then centrifuged at +4°C (4200 rpm, 15 min), the supernatant was filtered through a Whatman filter into a 50 mL flask. This procedure was repeated twice. The combined extracts brought up to volume with distilled water, filtered through a PTFE (0.45 μ m) and injected into the HPLC-VWD system.

Statistical analysis

Values in all experiments are represented as mean \pm SD of experiments done in triplicate. The decrease in histamine content - due to the PSAO activity - was considered significant at p<0.05 using One-Way ANOVA, followed by the Duncan's post-hoc test. (Statistical package SPSS version 16.0)

Results and Discussions

PSAO purification

It has been hypothesized that the PSAO activity - per gram of pea seedling tissue - is proportional to the growth rate and conditions. In general, etiolated seedlings have higher DAO levels as compared to those detected in light-grown seedlings. The 12-day-old etiolated seedlings had the highest PSAO-specific activity [12,15]. Purification

scheme of PSAO is demonstrated in Table 1. The measured quantities listed were obtained following the stated step in the procedure.

Figure 1 shows the results of purification of PSAO from 12-day-old etiolated pea seedlings. Several peaks were obtained from the DEAE-cellulose column; however, the fractions showing enzymatic activity were pooled. In this purification procedure, almost no contamination with other proteins was detectable after performing chromatography upon Coo-massive Brilliant Blue staining of the electrophoresis gel.

Electrophoresis of partially purified PSAO on SDS-PAGE showed a single band. Upon comparing the band's mobility of DAO to those of known molecular weight standard proteins on 10% gels, we determined the subunit molecular weight of DAO to be about 95 kDa (Figure 2). Kluetz et al. [12] found similar properties for the PSAO and also illustrated that, when these two subunits were cross-linked with dimethylsuberimidate, a new band could appear with a molecular weight of approximately 178 kDa, which suggests that the native enzyme consists of two apparently-identical subunits.

HPLC analysis and quantification of histamine

Histamine is not stable in water; but well-stable in acidic conditions. Based on this rationale, acidic histamine extraction of fish samples in HClO₄ provides a good chromatographic peak resolution [13].

The ion-pairing HPLC with sodium 1-decanesulfonate as an ion

pairing reagent was performed while the anionic sulfonate counterion, which permits the separation and resolution of positively charged analytes such as histamine [16]. In this specific method of histamine quantification in fish, the differences between the retention/migration times has been reduced to ± 1% by applying the chromatographic reference standard of 1,1-dimethylbiguanide, a basic compound with characteristics similar to histamine [13]. Before histamine measurement, seven histamine standards generate the calibration curves while the correlation coefficient exceeded 0.999. Histamine peak in samples was recognized and quantified by comparing its retention time to the chromatographic reference peak and also to histamine standards. Under the HPLC conditions adopted, the analytes were fully separated in 10 min (Figure 3).

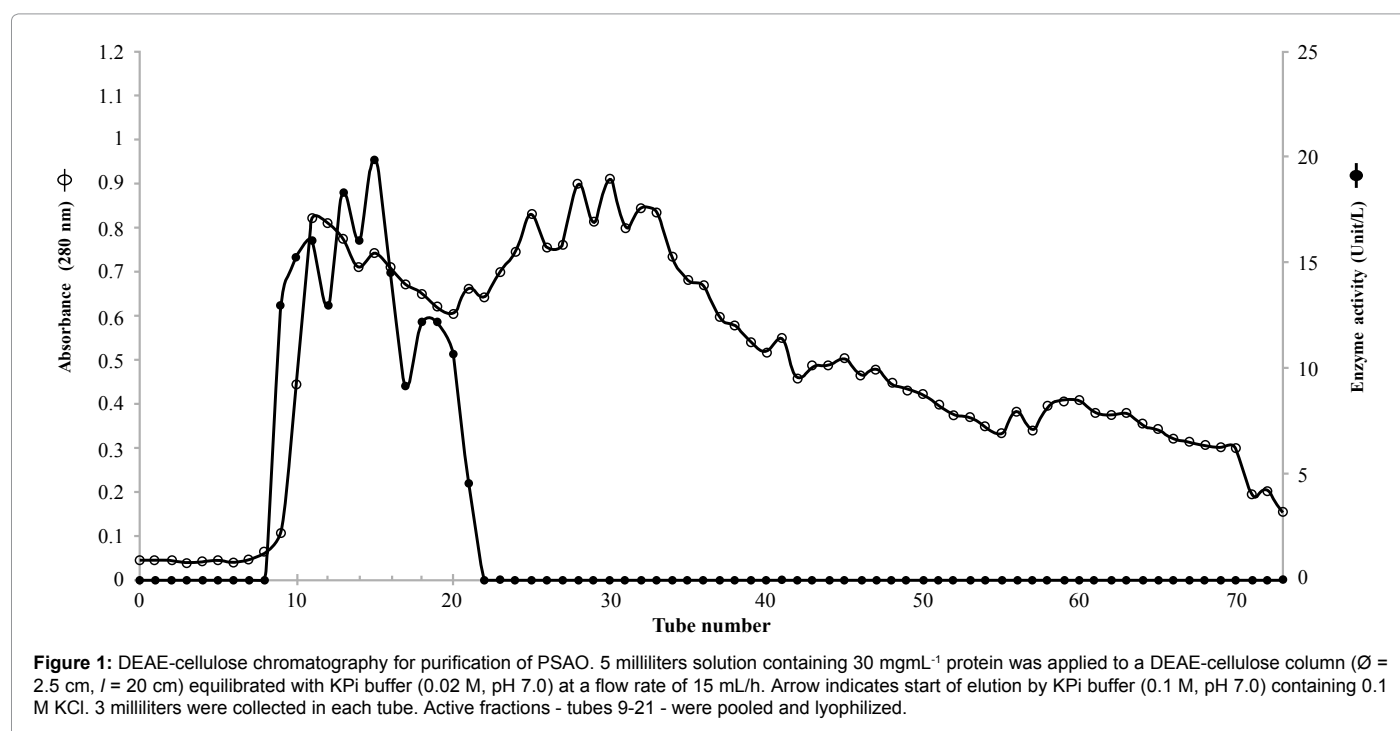
Optimization of antihistamine activity of PSAO

To obtain a deeper insight into PSAO potential for histamine degradation in tuna fish, its antihistaminic effect was investigated in a buffered system, prior to application in fish, through an HPLC experiment. According to Huss et al. [17], pH value in most of the processed fish (e.g: lightly preserved, fermented, semi-preserved and heat-processed) is between acidic and neutral; hence, the antihistamine activity of PSAO was evaluated at pH=5 and pH=7 of KPi buffer system. Two temperatures were tested for the antihistamine activity of the enzyme: 37°C, the optimum temperature of porcine diamine

Step	Total Activity	Specific Activity	Yield
	units	units/mg	%
filtrate of pea seedling homogenate	28204.22	1.08	100
30% A.S. ¹ fractionation	25941.98	1.23	92
70% A.S. fractionation	23173.61	3.62	82.3
DEAE-cellulose chromatography	14638.97	4.07	52
Sephadex G-200 chromatography	13143.66	8.85	46.6

1: ammonium sulfate

Table 1: Purification steps of PSAO. The data have been normalized to a starting value of 1 kg of plant tissue.



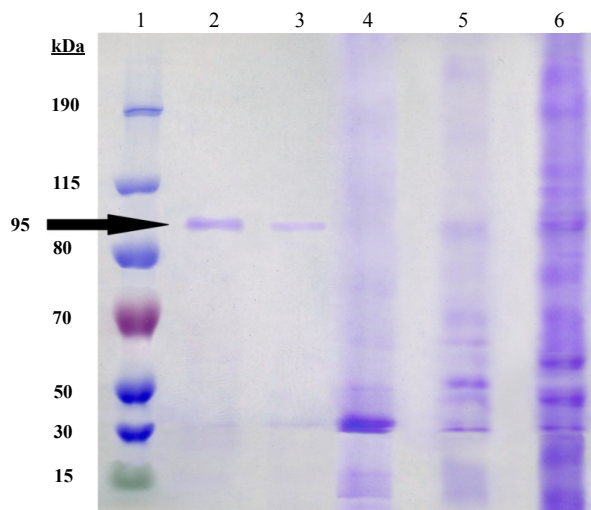


Figure 2: Electrophoretic analysis of PSAO on different stages of its purification. Proteins (2 mg mL^{-1}) at each purification step were resolved by SDS-PAGE and stained with Coomassie Brilliant Blue. Line 1: molecular mass markers, line 2: Sephadex G-200 chromatography, line 3: DEAE-cellulose chromatography, line 4: 70% ammonium sulfate fractionation, line 5: 30% ammonium sulfate fractionation and line 6: filtrate of pea seedling homogenate.

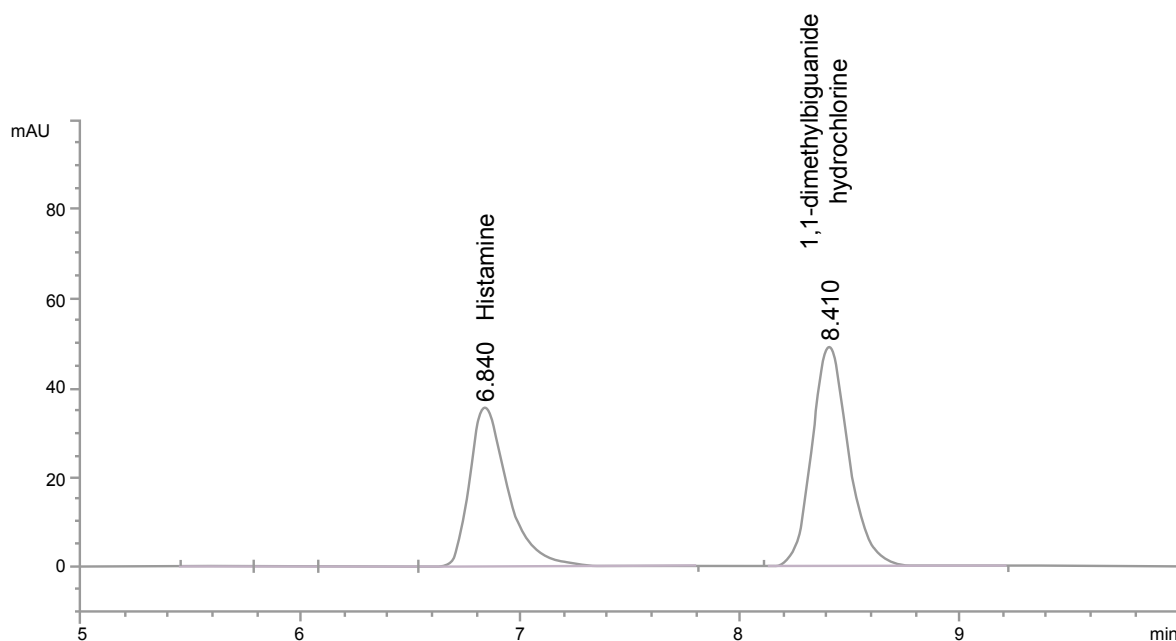


Figure 3: HPLC chromatogram of histamine (200 ppm) and 1,1-dimethylbiguanide standard in KPi buffer (pH 7.0, 37°C); conditions: column Optimal ODS-H C18 (250 mm×4.6 mm i.d.) at +35°C, buffer solution: methanol: acetonitrile (75:10:15, v/v/v) at a flow-rate of 1.0 mL min⁻¹, injection loop 30 μL and monitored at 214 nm.

oxidase according to Dapkevicius et al. [18]; and 25°C, since the probable application of the enzyme in fish processing industry might occur at room temperature. Antihistamine activity was determined by measuring the decrease in histamine concentration of KPi buffer (Figure 4).

In contrast to the control group, PSAO could not reduce histamine content of KPi buffer system in pH 5.0 (in neither 25°C nor 37°C) (One-Way ANOVA; $p < 0.05$). Possible causes include the histamine charge alteration in pH 5.0 [19] resulting in improper attachment of histamine

into the enzyme active site, the withdrawal of the enzyme from its optimum pH range, and even the feasibility of PSAO denaturation [20].

However, PSAO represented a significant reduction in histamine content of KPi buffer of pH 7.0 after 30 minutes (in either 25°C or 37°C) in comparison to control group (One-Way ANOVA; $p < 0.05$). This is consistent with previous studies [18,21] and suggests that this pH is suitable for PSAO antihistaminic activity.

No significant difference was observed in antihistaminic activity of PSAO between 25°C and 37°C (One-Way ANOVA, Duncan; $p < 0.05$).

Interestingly, whereas no decline of enzyme activity at 25°C was observed, it is plausible to apply PSAO in ambient temperature (such as a fish processing environment).

Evaluation of antihistamine effect of PSAO in tuna fish

The initial histamine level of the onboard-frozen skipjack tuna fish was 3.27 ± 1.73 ppm. Histamine content of the fish was elevated to 16.06 ± 1.74 ppm after 24h at 37°C.

In spite of the report that porcine diamine oxidase fitted into an exponential decline model of histamine degradation [22], PSAO did not show a significance difference in reduction of histamine in KPi buffer system after 30 or 60 minutes. Regarding food industry condition (and to decrease the risk of food bacterial overload), it is important that the food undergo a minimal holding time before the main thermal process (such as sterilization). Hence, the antihistaminic activity of PSAO-which can be used before the thermal process in a fish factory - was evaluated after 30 minutes in tuna fish.

The histamine content of the thoroughly homogenized fish increased to 35.72 ± 7.83 ppm after 30 minutes incubation at 37°C

(control group). The application of PSAO in homogenized tuna fish (37°C, 30 min) not only prevented the histamine raise - more frequent in the homogenized texture of meat through bacterial action-but also reduced the already existent histamine to the initial level of the skipjack tuna fish frozen onboard (One-Way ANOVA, Duncan; $p < 0.05$), (Figure 5).

Notably, antihistaminic activity of two steps of enzyme purification (filtrate of pea seedling homogenate and SEC-PSAO steps) was not significantly different (One-Way ANOVA, Duncan; $p < 0.05$). Accordingly, it is suggested that the filtrate of pea seedling homogenate has the feasibility of histamine reduction in foods.

Although it was concluded that pyridoxal phosphate is a coenzyme for diamine oxidase [23], presently, topaquinone (TPQ) - derived from the modification of a protected tyrosyl residue - has been introduced as the enzyme cofactor [24]. Nonetheless, it has been confirmed that pyridoxal phosphate works as a substrate for peroxidase in pea seedling extracts. Therefore, pyridoxal phosphate does not activate DAO, but prevents the inactivation of the enzyme which might occur by peroxidases [10,25].

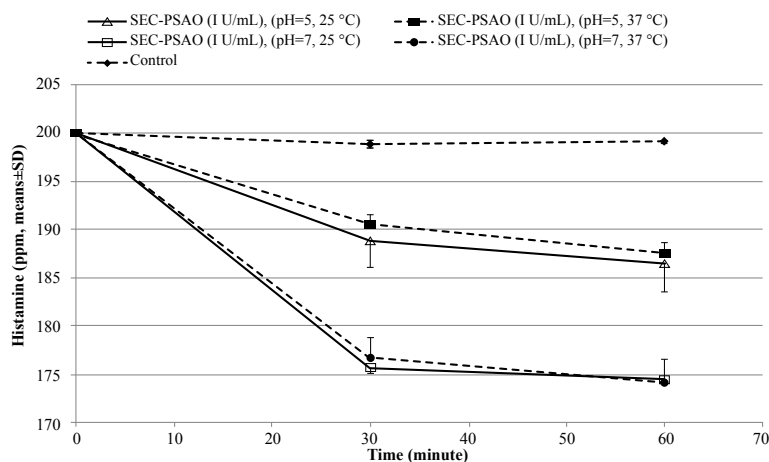


Figure 4: The influence of pH and temperature of phosphate buffer (0.02 M) on the antihistamine activity of PSAO; the data have been normalized to a starting value of 200 ppm.

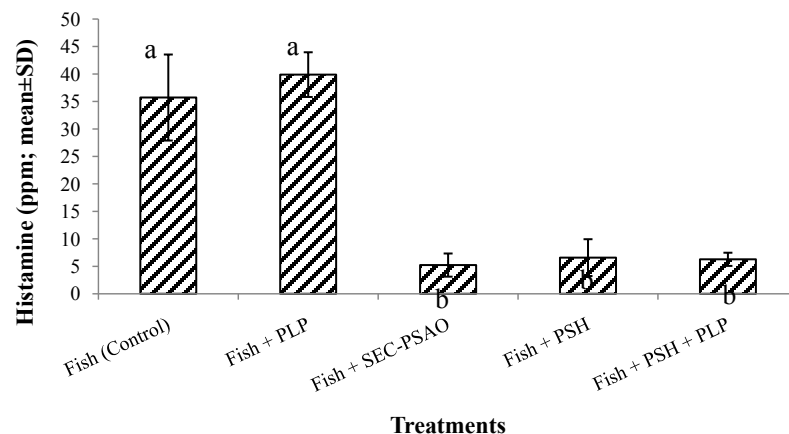


Figure 5: Antihistamine activity of PSAO in skipjack tuna fish after 30 minutes at 37 °C (PLP: pyridoxal 5-phosphate (4 μmol mL⁻¹); SEC-PSAO (4 unit mL⁻¹); PSH: filtrate of pea seedling homogenate (4 unit mL⁻¹). Different letters indicate a significant difference (Duncan; $p < 0.05$).

In this study, application of pyridoxal phosphate beside the enzyme at 37°C did not enhance PSAO activity after 30 minutes, which is consistent with previous studies (One-Way ANOVA, Duncan; $p < 0.05$); however, pyridoxal phosphate usage resulted in higher histamine content (even if it was not statistically significant) of the tuna fish, which is likely due to its being the cofactor of HDC [26].

Conclusions

The antihistamine properties assigned to PSAO and the feasibility of efficient enzyme extraction by chromatographic methods, elicits a novel enzymatic strategy for histamine degradation in tuna fish. Accordingly, in this study, 4 unit mL⁻¹ of PSAO reduced 87.14% of the histamine content of the skipjack tuna fish (*Katsuwonus pelamis*) at pH 7.0, 37°C. Since the filtrate of pea seedling homogenate exerted the same antihistamine results of purified PSAO, its application in fish is more practical because the preparation process is less time and energy consuming. Despite the fruitful results of the study, it seems that the enzyme efficacy can vary due to the diversity and distribution of the enzyme inhibitors regarding the variety of fish species, their environment, and fishing styles [27,28].

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