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(54) Benævnelse: **HYDROLYSATER AF ANIMALSKE PROTEINER AF MARIN OPRINDELSE MED NEUROBESKYTTENDE EGENSKABER**

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Hydrolysates of animal proteins of marine origin with neuroprotective properties

The invention relates to treatments intended to reduce the risk factors associated with the development of ageing-related neurodegenerative disorders, to prevent the appearance of these disorders and/or slow down their development. The invention relates more particularly to active compositions intended to be administered orally, to preserve the health of the nervous tissue of an individual/patient. These compositions, of the dietary supplement, neutraceutical and medicament type, comprise a hydrolysate of animal proteins of marine origin having proven neuroprotective properties.

The invention also extends to food or pharmaceutical ingredients intended to enter into the composition of these dietary supplements, neutraceuticals or medicaments; these ingredients contain a hydrolysate of animal proteins of marine origin with proven neuroprotective properties.

Ageing is a complex, slow and progressive process, with multiple effects, which causes a set of anatomical, biological and physiological modifications. It leads to a progressive reduction and/or dysfunction of the physical and/or intellectual functions of an individual.

In the nervous system, ageing is symptomised by progressive deterioration of the functioning of the neuronal cells, extending as far as cell death. Depending on the regions damaged, the disorders will affect locomotion, language, memory, behaviour, concentration, humour… These disorders, called neurodegenerative disorders (which, in certain cases, can correspond to senile dementias, to disorders symptomatic of Alzheimer's disease, of Parkinson's disease…) demonstrate the seriousness of damage to the nervous tissue.

Among the factors identified as responsible for ageing of the nervous system, reference is often made to oxidative stress. More than any other organ, the brain is particularly sensitive to the accumulation of free radicals, the primary cause of oxidative stress.

Indeed, the brain has a high aerobic metabolism. And although it only represents 2% of the weight of the human body, it uses more than 20% of the respiration oxygen. It is thus the centre for high production of free radicals. Even in a normal physiological state, it achieves efficient regulation of their level, with age, this ability is reduced, accentuating the risk of neurodegenerative mishaps.

The invention is intended to propose active antioxidant agents having effectiveness in terms of neuroprotection and able to be prescribed in order to prevent the development of ageing-

related neurodegenerative disorders and/or to reduce the risk factors associated with the development of these disorders. In particular, the invention has the aim of proposing antioxidant agents able to preserve the health of the nervous tissue, in particular with regard to oxidative stress.

Another aim of the invention is to propose antioxidant agents with neuroprotective effects, which are 100% natural and effective when they are administered orally, for example, in the form of a *per os* medicament, a dietary supplement, a neutraceutical. In this same context, the invention is also intended to propose ingredients integrating such antioxidant agents, which will be intended to be used in the preparation of medicaments, of dietary supplements and/or of neutraceuticals (i.e. a ready-to-use food having health advantages).

Patent applications WO 2006/084383 and WO 2009/101146 describe hydrolysates of proteins originating from salmon, from mackerel, from bib, from cod or from pollock.

The article by VANDANJON et al., *J. Food Engineer.*, vol. 95, No. 1, 1 November 2009, pages 36 - 44, teaches a hydrolysate of proteins originating from blue whiting.

The article by SAMARANAYAKA et al., *Food Chemistry*, vol. 107, No. 2, 19 November 2007, pages 768 - 776, discloses the antioxidant effect of a hydrolysate of proteins originating from European hake.

The article by SORENSEN et al., Nahrung, vol. 48, No. 1, February 2004, pages 53-56, observes that a hydrolysate of proteins originating from salmon is capable of inhibiting prolyl endopeptidase.

The invention thus relates to hydrolysates of animal proteins of marine origin having neuroprotective properties. These hydrolysates originate from at least one source of proteins selected from mackerel, salmon, green crab and white fish (in particular cod, ling, pollock, bib, blue ling, whiting and European hake).

The invention thus and firstly results from the demonstration performed by the inventors that peptides originating from marine animals - in this case, mackerel, salmon, green crab and white fish - have an antioxidant effect capable of improving the survival of neuronal cells when they are subjected to oxidative stress.

Other hydrolysates of animal proteins of marine origin, originating from other sources, have also been prepared and tested by the inventors for their neuroprotective potential. However,

due to relatively high cytotoxicity, none of them has been retained.

The invention also results from the demonstration performed by the inventors that particular hydrolysates according to the invention not only have remarkable neuroprotective antioxidant activity, but also activity inhibiting prolyl endopeptidase (PEP). This enzyme, expressed in the cortical zones of the human brain and to a lesser extent in the cerebellum, takes part in the catabolism of a number of neurotransmitters involved in the memory and learning processes. Moreover studies conducted in elderly patients afflicted with neurodegenerative disorders have revealed a correlation between memory loss and an anormal increase in PEP activity. More recently, works which led to an improvement in the cognitive functions of rats rendered amnesic have thus confirmed the growing interest in PEP inhibitors for the preventative and/or curative treatment of ageing-related neurodegenerative disorders, in particular those for which memory loss and cognitive disorders are symptomatic. In this context, certain hydrolysates according to the invention, particularly the hydrolysates of proteins of mackerel and ling, are positioned as serious contenders.

The hydrolysates of animal proteins of marine origin with neuroprotective effects, according to the invention, can be prepared in many ways, from mackerel, salmon, green crab and/or white fish (in particular, cod, ling, pollock, bib, blue ling, whiting and European hake). In particular, they can be prepared by enzymatic digestion, by means of endopeptidases and/or exopeptidases, for example papain, subtilisin, aminopeptidase, trypsin, chymotrypsin… Optionally, enzymatic digestion is preceded by a step of mechanical grinding of the protein source to be worked.

More particularly, the invention relates to hydrolysates of animal proteins of marine origin prepared from mackerel, salmon, green crab and/or white fish and of which the peptides together have a distribution by molecular weight of the following profile:

- more than 20% of the total mass of the peptides correspond to peptides of molecular weight lower than 300 Da,
- 20 to 35% of the total mass of the peptides correspond to peptides of molecular weight between 300 and 500 Da,
- 15 to 35% of the total mass of the peptides correspond to peptides of molecular weight of between 500 and 1000 Da,
- less than 15% of the total mass of the peptides correspond to peptides of molecular weight greater than 1000 Da.

The invention also extends to compositions intended to be administered orally, comprising a hydrolysate of animal proteins of marine origin as described above. Said compositions are

advantageously used/prescribed in order to reduce the risk factors associated with the development of ageing-related neurodegenerative disorders, to prevent the appearance of these disorders and/or to slow their development. According to the invention, these compositions can consist of medicaments, food supplements or neutraceuticals.

The invention extends to food and/or pharmaceutical ingredients comprising a hydrolysate of animal proteins of marine origin according to the invention and intended to be used for the preparation of these medicaments, these food supplements and/or these neutraceuticals.

In whatever form they are (medicament, food supplement, neutraceutical, food ingredient), in addition to said hydrolysate of animal proteins of marine origin as described above, present in neuroprotective quantity, the compositions according to the invention can also comprise at least one additive and/or at least one excipient acceptable from the pharmaceutical and/or food point of view, added in order to obtain a galenic form for oral administration. These additives and/or excipients are for example binders, lubricants, sweeteners, dilutants, excipients, effervescent agents, coating agents…

In particular, the compositions according to the invention can be made in galenic forms and various formulations, particularly:

- in the form of a mixture of solid and divided particles, for example an effervescent or non-effervescent powder, the taking of which requires it to be mixed with water,
- in the form of an effervescent or non-effervescent tablet, to be swallowed with a little water, to be sucked or to be crushed,
- in the form of a solution, for example a suspension, a syrup, a liquid composition which can be coated in a hard or soft capsule.

The present invention also relates to the use of hydrolysates of animal proteins of marine origin such as described above, for the manufacture of a medicament intended to reduce the risk factors associated with the development of ageing-related neurodegenerative disorders, to prevent the appearance of these disorders and/or to slow down their development.

The invention also relates to hydrolysates of animal proteins of marine origin prepared from mackerel, salmon, green crab and/or white fish, as well as compositions - of the food supplement, neutraceutical, medicament or ingredient type - comprising a neuroprotective quantity of said hydrolysates of animal proteins of marine origin, characterised in combination by all or part of the characteristics mentioned above or below.

Other aims, characteristics and advantages of the invention will become apparent on reading

the following detailed description which presents, on the one hand, particular methods of preparation of different hydrolysates according to the invention and, on the other, tests revealing their neuroprotective effect. This detailed description is illustrative and non-limiting.

The experimental results obtained are in particular presented in the form of attached graphical representations, in which:

- Figure 1 is a representation in the form of histograms, showing the non-toxicity of hydrolysates according to the invention, tested on Neuro2A cells;
- Figure 2 is a representation in the form of histograms, showing the neuroprotective antioxidant effect of hydrolysates according to the invention, tested on Neuro2A cells subjected to oxidative stress induced by H_2O_2;
- Figure 3 is a representation in the form of histograms of the inhibiting power exercised by hydrolysates according to the invention on prolyl endopeptidase (PEP).

Example 1: Preparation of hydrolysates according to the invention

1. Preparation of a hydrolysate of mackerel

Fresh and whole mackerel are directly subjected to enzymatic hydrolysis, by papain. For this purpose, the mackerel are mixed with water, in a [fish]/[water] proportion of the order of 2:1. The papain is added to the mixture, in a proportion of the order of 0.12% relative to the weight of fish to be treated. The pH of the mixture is adjusted to 5.8 ± 0.1 by means of acetic acid (80%), and its temperature is maintained at 52°C. The hydrolysis reaction is conducted for 4 hours under agitation, and then 4 hours without agitation.

The digestive action of the papain is stopped by raising the temperature of the mixture to approximately 85°C. The mixture is left in this state, for a minimum of 4 hours, without agitation.

The hydrolysate of proteins of mackerel obtained is then filtered so as to remove the insolubles. Filtration is firstly performed on a rotary sieve (1 mm mesh) and then by means of a filter press. The clarified fraction is recovered and pasteurised at 95°C for 1 hour, and then concentrated under vacuum.

2. Preparation of a hydrolysate of salmon pulp

Once the fillets have been removed, the backbone pulp is recovered (mechanically), refined and frozen, for preservation purposes, until the step of enzymatic hydrolysis, performed by

the action of papain.

After grinding, the pulp is mixed with water, in a [fish]/[water] proportion of the order of 1:1. The mixture is brought to 55°C. The papain is added to it, in a proportion of the order of 0.05% relative to the weight of pulp to be treated.

The digestive action of the papain is stopped after 3 hours, by raising the temperature to approximately 85°C. The mixture is left in this state for approximately 120 minutes.

The hydrolysate of proteins of salmon obtained is then filtered so as to remove the insolubles and backbone residues. Filtration is performed on a rotary sieve (1 mm mesh). Centrifugation completes the removal of the insoluble materials as well as the removal of the fatty material (centrifugal force equivalent to a minimum of 1000 g).

The aqueous phase recovered is pasteurised at 90°C, for 120 to 180 minutes maximum, then the temperature is lowered to 80°C. The hydrolysate is then concentrated under vacuum.

3. Preparation of a hydrolysate of green crab

The frozen whole green crabs are ground mechanically before being subjected to enzymatic hydrolysis by papain. For this purpose, the ground crab is mixed with water, in a [ground matter]/[water] proportion of 1:1. The papain is added to the mixture, in a proportion of the order of 0.05% relative to the weight of crab to be treated. The mixture is brought to 58°C and is maintained at this temperature for 3 hours.

The digestive action of the papain is then stopped by raising the temperature of the mixture to approximately 85°C. The mixture is left in this state for 90 minutes, under agitation.

The insolubles of the mixture are removed by screening on a rotary sieve (1 mm mesh) and then the recovered juice is centrifuged in order to remove soluble materials (centrifugal force equivalent to a minimum of 1000 g).

The recovered supernatant is pasteurised at 95°C, for 2 to 3 hours, and then concentrated under vacuum.

4. Preparation of a hydrolysate of ling fillets

The fresh or frozen fish filleting byproducts are subjected to enzymatic hydrolysis, performed

by combined action of papain and alcalase. For this purpose, the selecting filleting byproducts, ground or otherwise, are mixed with water, in a [fish]/[water] proportion of the order of 10:3. The mixture is brought to 55°C. The papain is added to it, in a proportion of the order of 0.06% relative to the weight of fish to be treated. During the hydrolysis reaction, the pH of the mixture is adjusted to 5.9 ± 0.1 by means of food-grade phosphoric acid (30%).

After 90 minutes of papain hydrolysis, the alcalase is added to the mixture in a proportion of the order of 0.2% relative to the weight of fish. The total enzymatic hydrolysis reaction will last 8 hours.

The digestive action of the papain and of the alcalase is stopped by raising the temperature to approximately 85°C. The mixture is left in this state for 90 minutes.

The hydrolysate of proteins of ling obtained is then filtered so as to remove the insolubles. The filtration is firstly performed on a rotary sieve (1 mm mesh) and then through a pocket filter (1 mm cloth). Centrifugation completes the removal of the insolubles (centrifugal force equivalent to a minimum of 1000 g).

The soluble fraction is recovered and pasteurised at 90°C, for 90 minutes, the pH value is adjusted to approximately 4.8 by means of food-grade phosphoric acid (30%). On completion of pasteurisation, the product is concentrated under vacuum.

5. Physico-chemical characterisation of the hydrolysates according to the Invention

The hydrolysates of animal proteins of marine origin, prepared above, were subjected to physico-chemical analysis. The results obtained are displayed in Table 1 below.

	Hydrolysate of mackerel	Hydrolysate of salmon	Hydrolysate of green crab	Hydrolysate of ling
pH at 10%	5.9	6.5	7.1	4.9
Dry extract (%)	59.7	63.0	57.2	66.2
Proteins/Dry extract (%)	91.6	70.0	78.1	80.8
Degree of hydrolysis(%)	39.8	-	42.7	38.6
NaCl/Dry extract (%)	3.6	19.3	17.7	
Minerals/Dry extract (%)	<1	25.0	22.3	9.5
Lipids/Dry extract (%)	<1	<5		10.0

Peptide profile (Da)				
MW > 7000	0.21%	5.54%	0.35%	0.15%
7000 > MW > 5000	0.07%	0.32%	0.15%	0.07%
5000 > MW > 3000	0.25%	0.53%	0.68%	0.27%
3000 >MW > 1000	5.39%	8.85%	4.32%	7.55%
1000 > MW > 500	25.28%	30.19%	16.02%	31.09%
500 > MW > 300	28.54%	29.66%	23.81%	31.72%
300 > MW	40.26%	24.94%	54.67%	29.15%
Most represented MW (Da)	321	384	263	349

Table 1

Example 2: Assessment of the neuroprotective potential of the hydrolysates according to the invention

Each of the four hydrolysates described above were tested for their neuroprotective potential.

1. Measurement of the antioxidant effect of the hydrolysates according to the invention, on Neuro2A cells

The neuroprotective antioxidant effect of the hydrolysates according to the invention was assessed by means of Neuro2A cells subjected to oxidative stress induced by H_2O_2 (300 µM).

1.1. Materials and methods

- Preparation and treatment of the Neuro2A cells

The Neuro2A cells are seeded on 96-well culture trays, then cultivated at 37°C, 5% CO_2 in the medium with 10% of serum. After one night of culture, the cells are rinsed with 1X PBS buffer, and then pretreated for 2 hours with the trial products or the positive control (Trolox, 10 µM), in a culture medium not containing serum. Oxidative stress is then induced by the addition of H_2O_2 to a final concentration of 300 µM. The cells are thus incubated for 24 hours.

The survival of the Neuro2A cells is then assessed via measurement of their metabolic activity. For this purpose, the cells, with the treatment medium previously removed, are incubated for 2 hours at 37°C and 5% CO_2 with MTT bromide. This composition is transformed into MTT formazan by the metabolically active cells. The MTT formazan produced is then dissolved in DMSO, and then quantified by reading absorbance at 570 nm.

- Preparation of the hydrolysates and products to be tested

From the raw hydrolysates to be tested and preserved at -18°C, aliquots are prepared and preserved at +4°C. From the aliquot preserved at +4°C, each trial product is diluted in the culture medium of the Neuro2A cells in order to obtain a concentration of 100 mg/ml.

For the tests, intermediate dilutions are formed.

1.2. Assessment of the non-toxicity of the hydrolysates according to the invention to Neuro2A cells

Prior to the measurement of their antioxidant potential to Neuro2A cells, the hydrolysates according to the invention were tested for their cellular non-toxicity. Figure 1 presents the results obtained.

60 µM Digitonin, used as positive toxicity control, causes a significant reduction ($p<0.001$) in the cellular viability relative to the control. This result validates the cytotoxicity test.

10 µM Trolox (positive protection control) as well as the hydrolysates according to the invention do not exhibit toxicity; the cellular viability is close to that of the control and is greater than 80%.

1.3. Assessment of the antioxidant effect of the hydrolysates according to the invention on Neuro2A cells

The neuroprotective effect of the trial hydrolysates was tested on Neuro2A cells subjected to oxidative stress induced by H_2O_2. Figure 2 presents the results obtained diagrammatically, in the form of histograms. More detailed results are entered in Table 2 below.

The viability of the control induced by H_2O_2 (300 µM) is significantly reduced by approximately 35% relative to the non-induced control, which validates the induction of oxidative stress to all of the Neuro2A cells. 10 µM Trolox permits a significant increase ($p<0.001$) in the viability of the Neuro2A cells which had been subjected to oxidative stress, which validates the test (approximately 20% protection).

In view of the results obtained, it is found that the protection of the cells from oxidative stress varies little from one tested hydrolysate to the other:

- the neuroprotective antioxidant effect of the hydrolysate of mackerel and of green crab appears from the 0.3 µg/ml concentration;
- the neuroprotective antioxidant effect of the hydrolysate of ling is of note at the 3 µg/ml

concentration;

- the neuroprotective antioxidant effect of the hydrolysate of salmon is of note from the 3 µg/ml concentration and is remarkable at 30 µM.

Trial products	**Dose µg/ml**	**Cytotoxicity** % viability (v. control)	**p-value** (t-test v. control)	**Neuroprotect.** % Viability (v. H_2O_2 control)	**p-value** (t-test v. H_2O_2 control)
Control		100% ± 7%	-	100% ± 6%	-
Control + H_2O_2		-	-	66% ± 14%	-
Digitonin	60 µM	18% ± 3%	0.000	-	-
Trolox	10 µM	93% ± 12%	0.003	86% ± 9%	0.000
Hydrolysate of mackerel	0.03	96% ± 5%	0.072	70% ± 9%	0.530
	0.3	95% ± 6%	0.053	76% ± 10%	0.067
Hydrolysate of green crab	0.03	92% ± 6%	0.000	76% ± 8%	0.040
	0.3	90% ± 7%	0.000	80% ± 8%	0.008
Hydrolysate of ling	3	89% ± 10%	0.000	78% ± 10%	0.025
	30	92% ± 9%	0.003	77% ± 7%	0.032
Hydrolysate of salmon	3	95% ± 5%	0.023	75% ± 7%	0.056
	30	94% ± 6%	0.005	80% ± 10%	0.007

Table 2

Example 3: Inhibition of propyl endopeptidase (PEP)

1. Materials and methods:

The enzymatic test on PEP is performed *in tubo*, in a 96-well tray. The PEP and the trial products (hydrolysates, controls: Bacitracin and Z-Pro-Prolinal) are diluted in the reaction buffer to the required concentrations. After 5 minutes of incubation at ambient temperature, the substrate (Z-Gly-Pro-pNA) is added to a final concentration of 160 µM. The enzymatic reaction is then initiated by placing the tray at 37°C.

The absorbance of each point is measured at 410 nm kinetically at 37°C, every 5 minutes for 45 minutes. A control condition without inhibitor (substrate + enzyme), as well as a control condition without enzyme are created. In order to determine the absorbance of the trial products alone, and to remove possible interferences, a condition without enzyme is created for each concentration.

2. Analysis of the data

PEP inhibition is measured at the end of 45 minutes. The absorbance values at this time are used to calculate the inhibition percentages of the PEP. The data obtained for the trial products are normalised relative to the enzymeless (blank) points, then the percentages are calculated according to the formula:

$$\frac{A\ trial\ product\ -\ A\ control}{A\ control} \times 100\ = PEP\ inhibition\ percentage$$

A trial product: normalised absorbance of each point

A control: mean absorbance of the control points (with enzyme)

The hydrolysates of mackerel and ling, as described above, were analysed for their aptitude to be able to inhibit PEP.

Figure 3 presents the results obtained, in the form of histograms. These data indicate that the hydrolysates tested inhibit PEP in significant and dose-dependent manner. In the doses tested, the inhibition can attain 60%.

PATENTKRAV

1. Hydrolysat af animalske proteiner af marin oprindelse, som stammer fra mindst én kilde til proteiner valgt blandt makrel, laks, strandkrabbe og hvidfisk, kendetegnet ved, at samlingen af peptider i hydrolysatet har en molekylvægtsfordeling med følgende profil:
   - mere end 20% af den samlede vægt af peptiderne svarer til peptider med en molekylvægt på mindre end 300 Da,
   - 20 til 35% af den samlede vægt af peptiderne svarer til peptider med en molekylvægt på mellem 300 og 500 Da,
   - 15 til 35% af den samlede vægt af peptiderne svarer til peptider med en molekylvægt på mellem 500 og 1000 Da,
   - mindre end 15% af den samlede vægt af peptiderne svarer til peptider med en molekylvægt på mere end 1000 Da.

2. Hydrolysat ifølge krav 1, hvilket hydrolysat stammer fra en hvidfisk valgt blandt: kabliau, lange, mørksej, skægtorsk, middelhavslange, hvilling og kulmule.

3. Kosttilskud, som omfatter et hydrolysat af animalske proteiner af marin oprindelse ifølge krav 1 eller 2.

4. Funktionel fødevare, som omfatter et hydrolysat af animalske proteiner af marin oprindelse ifølge krav 1 eller 2.

5. Farmaceutisk sammensætning, som er beregnet til oral administration, og som omfatter et hydrolysat af animalske proteiner af marin oprindelse ifølge krav 1 eller 2.

6. Ingrediens, som omfatter et hydrolysat af animalske proteiner af marin oprindelse ifølge krav 1 eller 2.

7. Hydrolysat af animalske proteiner af marin oprindelse ifølge krav 1 eller 2 til anvendelse som lægemiddel.

8. Anvendelse af et hydrolysat af animalske proteiner af marin oprindelse ifølge krav 1 eller 2 til fremstilling af et lægemiddel, som er beregnet til at reducere de risikofaktorer, der er associeret med udvikling af aldringsrelaterede neurodegenerative lidelser.

9. Anvendelse af et hydrolysat af animalske proteiner af marin oprindelse ifølge krav 1 eller 2 til fremstilling af et lægemiddel, som er beregnet til at forebygge og/eller forsinke

udviklingen af en aldringsrelateret neurodegenerativ lidelse.

10. Anvendelse af et hydrolysat af animalske proteiner af marin oprindelse ifølge krav 9, hvilket hydrolysat stammer fra mindst én kilde til proteiner valgt blandt makrel og lange.

Figure 1

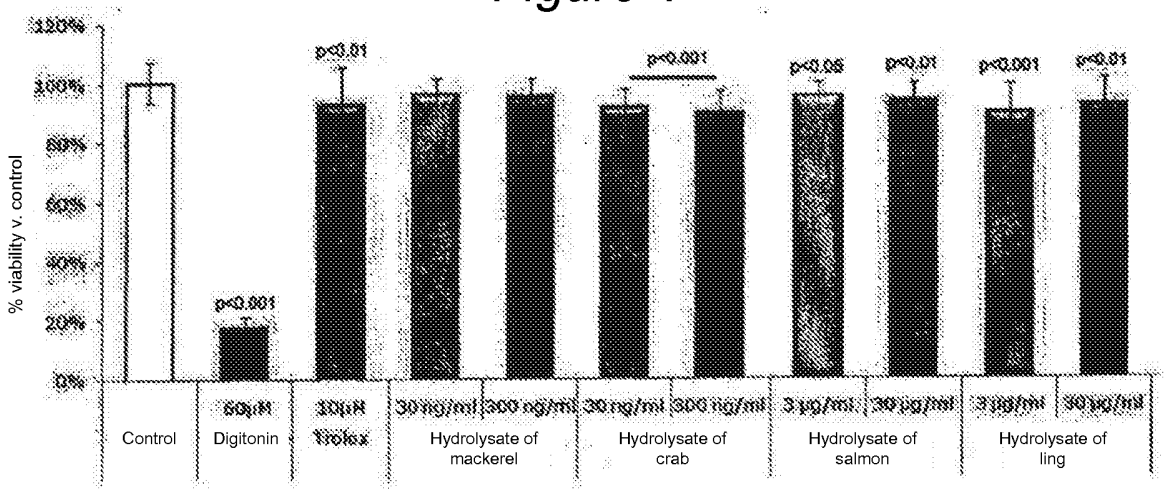


Figure 2

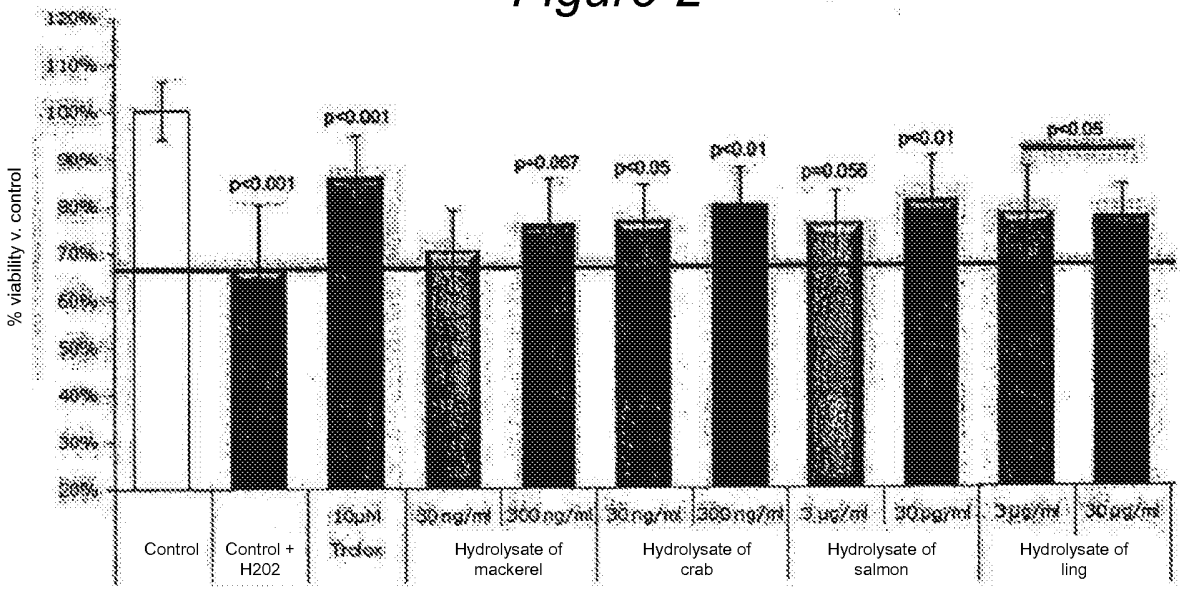
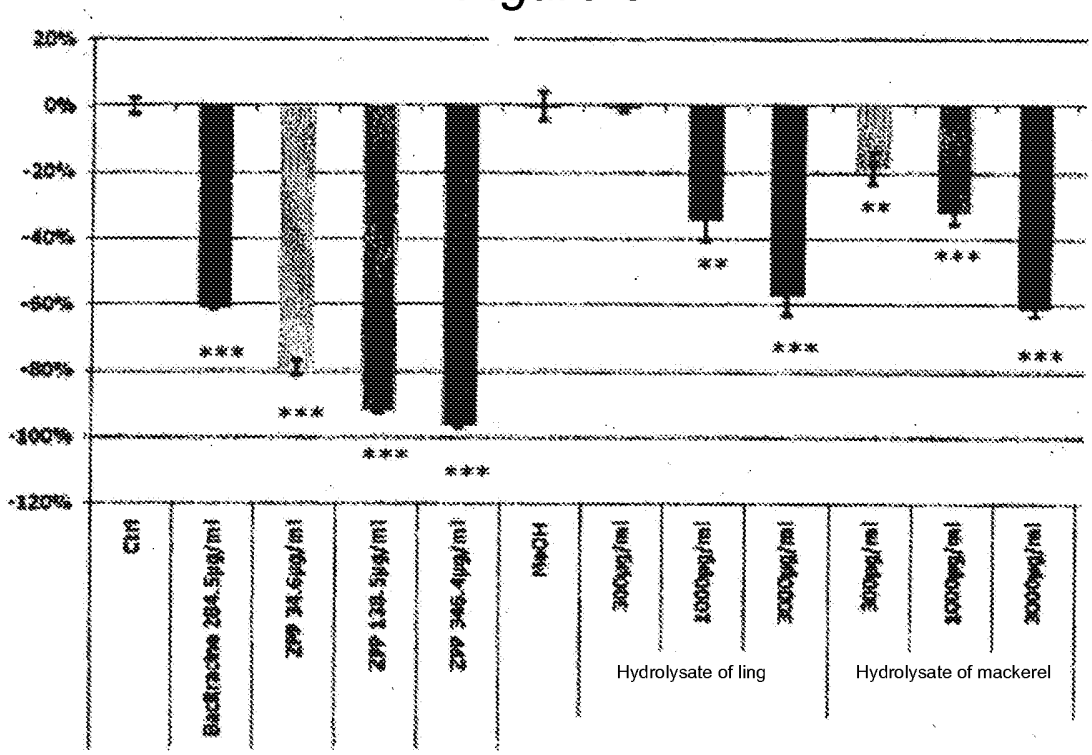


Figure 3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Hydrolysate of ling
Hydrolysate of mackerel