

## Comparison of glutathione peroxidase-1 in free divers with their counterparts: A model study for sports informatics

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**Abstract:** Free diving is a popular sport because there are many features of free diving such as sustainability, eco-friendly and challenges to nature. Due to increased interest on this sport in recent years, the number of competitions is also increasing gradually. On the other hand, the scientific reports on the understanding of breath-holding mechanisms and metabolism are still unclear. To provide contributions on this phenomenon, glutathione peroxidase (GPX) was selected as a model enzyme because of its critical importance in breath-holding. The GPX enzymes from human and free diving animals were compared by using bioinformatics tools such as ProtParam, Swiss-Model, Clustal Omega and the results are discussed in the present paper. In conclusion, the specific amino acid sequences can be considered in the selection of elite free divers for international competitions to get the best results. However, it should be noted that special training methods should also be applied to have better breath-holding capacities.

**Keywords:** apnea, free diving, glutathione peroxidase, GPX-1

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### 1. Introduction

Free diving is a physical exercise based on breath-holding under the water without a SCUBA apparatus. Free diving for air-breathing vertebrates requires important adaptations such as overcoming increasing pressure under the water, decreased visibility, and temperature of the water. Mankind has long been interested in free diving due to many purposes such as hunting, military purposes or sports. There are many different sports disciplines nowadays such as spearfishing, underwater hockey, underwater rugby, synchronized swimming and apnea which require strong breath-holding capacity. The athletes under these disciplines always search for alternative techniques to develop their breath-holding capacities. Unfortunately, very limited information exists in the scientific literature for the techniques to develop breath-holding time. There are only seven papers when the keyword “free diver” is searched in Pubmed on 15.02.2023 (Wilkinson, 2009; Ioannidis et al., 2015; Cormack et al., 2017; Rich et al., 2019; Bart and Lau, 2021; Annen et al., 2021; Scott et al., 2021). Since there is a great need for scientific studies on increasing the breath-holding capacity, we wanted to propose sample and basic bioinformatics based selection for suitable athletes for international competitions organized by international federations such as

Confédération Mondiale des Activités Subaquatiques (CMAS).

*In silico* techniques in biology provide important contributions for life sciences such as medicine, biochemistry, molecular biology, and genetics. The tools developed under bioinformatics are now a necessary part of analyzing bio-based data such as protein and DNA sequences. After the completion of human genome project, many different tools have so far been developed to evaluate the big data in the life sciences. The data banks on protein and DNA sequences provide big contributions for understanding of biological phenomena in various dimensions. From this perspective, important metabolism-based features from well-adapted animals can be extracted to be used in the selection of best athletes. Glutathione peroxidase-1 (hereafter GPX-1) was selected as a model enzyme due to its vital importance for the protection of hemoglobin in free diving (Rousseau et al., 2002). GPX-1 has a special role in the decomposition of hydrogen peroxide and lipid hydroperoxide in the metabolism. Since GPX-1 is an important enzyme oxygen metabolism, we wanted to compare the structure of GPX-1 in human and breath-holding animals. Moreover, GPX-1 sequences can also be available for well-adapted breath-holding animals in ocean ecosystems to compare with human GPX-1. These

species are *Delphinapterus leucas*, *Physeter macrocephalus*, *Balaenoptera acutorostrata scammoni*, *Callorhinus ursinus*, *Neomonachus schauinslandi*, *Leptonychotes weddellii*, *Zalophus californianus*, *Neophocaena asiaeorientalis asiaeorientalis*, *Lipotes vexillifer* and, *Tursiops truncatus*. These animals have significantly higher breath-holding times compared to *Homo sapiens*. Therefore, in this study, it is aimed to compare GPX enzymes from human and breath-holding animals by using bioinformatics tools.

## 2. Materials and Method

### 2.1 Retrieval of GPX-1 Enzyme sequences

Total of 11 GPX-1 enzyme sequences belonging to different species were retrieved from UniProt which is publicly available at (<http://www.uniprot.org>) (Uniprot Consortium, 2021). Accession IDs of the related enzymes are listed in Table 1.

### 2.2 Multiple sequence alignment

The GPX-1 enzyme sequences in Table 1 are aligned by using Clustal Omega (Sievers et al., 2011). Multiple sequence alignment of the GPX-1 enzymes is shown in Figure 1.

### 2.3 Construction of phylogenetic tree

Phylogenetic tree is constructed by using the using Clustal omega (Sievers et al., 2011).

### 2.4 Amino acid composition and protein parameters of GPX-1 enzymes

ProtParam tool (Gasteiger et al., 2005) is used for analysis of amino acid compositions and chemical properties such as pI, net charge, instability index of the related enzymes.

## 2.5 3-Dimensional modeling of GPX-1

3-D models of the GPX-1 enzyme belonging to different species are constructed by using Swiss-Model protein structure homology-modelling server (Waterhouse et al., 2018; Studer et al., 2020).

## 3. Results

### 3.1 GPX-1 protein retrieval

Sports informatics may provide important contributions to sports science. In this study, we compared amino acid sequences of the GPX-1 enzymes from free diving animals including human. The accession IDs of GPX-1 enzyme, length, and the name of the organisms are given in Table 1.

### 3.2 Multiple sequence alignment of the selected proteins

Multiple sequence analysis of the studied enzymes is compared in Figure 1. The sequence belonging to *Physeter macrocephalus* is removed because of the incompleteness of the sequence. Regardless of this species, the amino acid sequence of the all studied enzymes starts with Met-Cys-Ala-Ala except for *Balaenoptera acutorostrata scammoni*. It could be said that this tetrapeptide must be conserved. After that there is a gap with 6 amino acid residues. These residues differ from species to species. The gap in *Homo sapiens* is longer than other studied animals. After this gap, polyalanine residues are generally observed. It is interesting to note that leucine is one of the amino acids within these polyalanine residues. Since alanine is a hydrophobic amino acid, it could be said that these polyalanine residues can be in the inner region of the GPX-1 enzymes in the study.

**Table 1.** Accession IDs and length of the retrieved GPX-1 proteins from different species.

Entry name	Organism	Length
P07203	<i>Homo sapiens</i> (Human)	203
A0A455ATU6	<i>Physeter macrocephalus</i> (Sperm whale)	139
A0A2Y9GTM2	<i>Neomonachus schauinslandi</i> (Hawaiian monk seal)	209
A0A2U3Z8Z4	<i>Leptonychotes weddellii</i> (Weddell seal)	209
A0A341AVW4	<i>Neophocaena asiaeorientalis asiaeorientalis</i> (Yangtze finless porpoise)	206
A0A2Y9N3R9	<i>Delphinapterus leucas</i> (Beluga whale)	206
A0A384BFI6	<i>Balaenoptera acutorostrata scammoni</i> (North Pacific minke whale)	238
A0A3Q7RKY4	<i>Callorhinus ursinus</i> (Northern fur seal)	208
A0A340YI12	<i>Lipotes vexillifer</i> (Yangtze river dolphin)	206
A0A6J2CIH9	<i>Zalophus californianus</i> (California sea lion)	208
A0A2U3VAH2	<i>Tursiops truncatus</i> (Atlantic bottle-nosed dolphin)	206

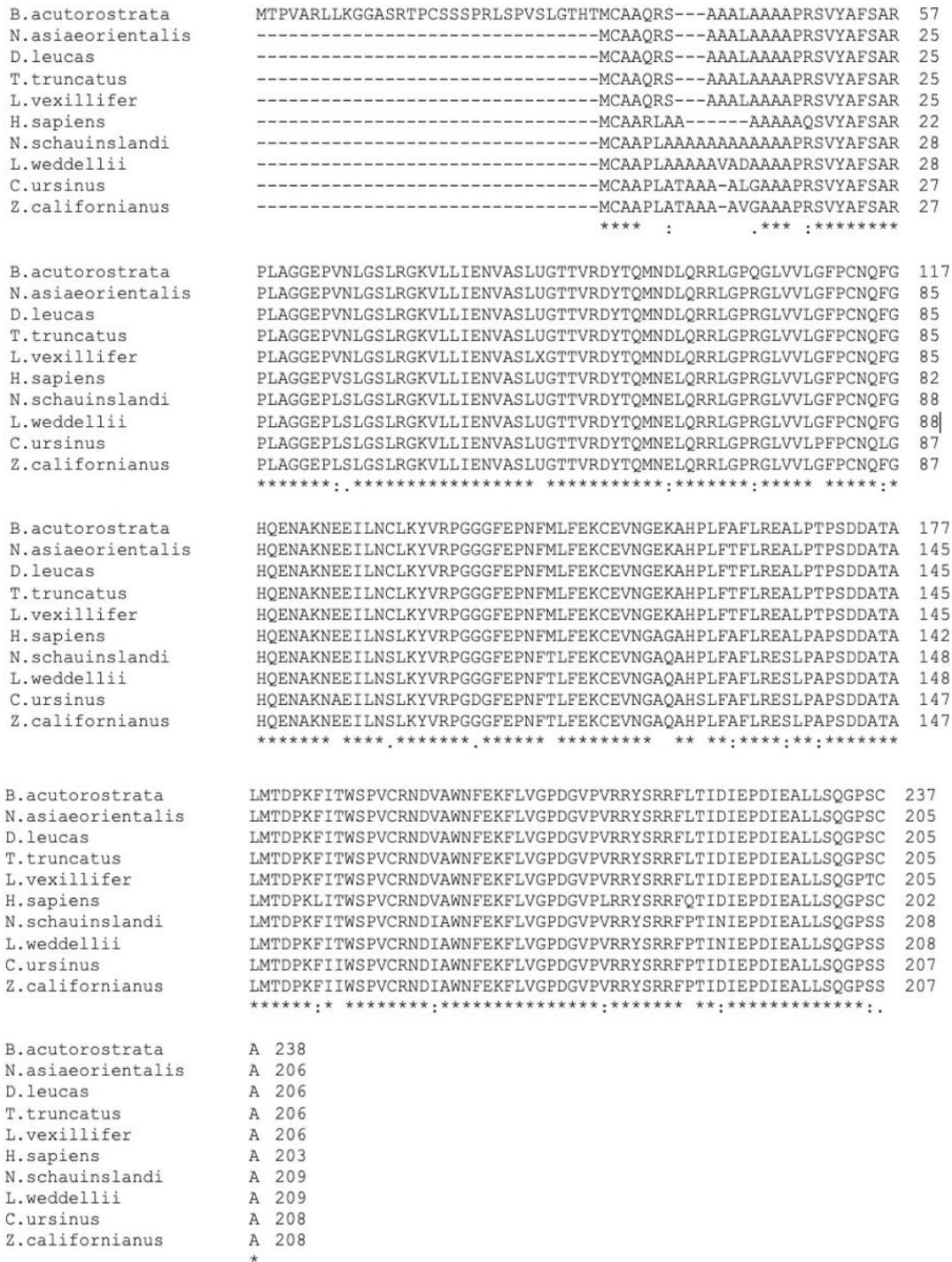


Fig 1. Multiple sequence alignment results for the GPX-1 enzymes of selected breath-holding animals.

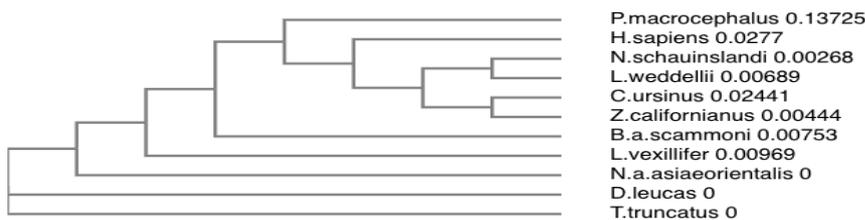


Fig 2. Phylogenetic tree based on GPX-1 enzymes of the selected aquatic organisms.

### 3.3 Phylogenetic tree construction

Phylogenetic relationship was also studied in this paper. Clustal omega based phylogenetic tree was shown in Figure 2. *Tursiops truncatus*, *Delphinapterus leucas*, *Neophocaena asiaeorientalis asiaeorientalis*, and *Lipotes vexillifer* are located different clades (Figure 2).

### 3.4 ProtParam protein composition analysis

Protein parameters of the analyzed enzymes were studied by using the ProtParam tool (Gasteiger et al., 2005). The amino acid lengths of the enzymes are revealed in Table 1. According to the results, the maximum number of amino acids observed in *Balaenoptera acutorostrata scammoni* is 238. The minimum length was found to be 139 and it is in *Physeter macrocephalus*. The amino acid percentages and numbers are given in Table 2. The results show that the

enzymes can be clustered based on maximum amino acid percentages. The amino acid with maximum percentage is found for alanin in *Homo sapiens*, *Physeter macrocephalus*, *Neomonachus schauinslandi*, *Leptonychotes weddellii*, *Callorhinus ursinus* and *Zalophus californianus*. On the other hand, leucine is maximum in *Neophocaena asiaeorientalis asiaeorientalis*, *Delphinapterus leucas*, *Balaenoptera acutorostrata scammoni* and *Lipotes vexillifer*. ProtParam tool also gives important characteristics of the proteins such as theoretical pI, total number of negatively and positively charged residues, net charges and instability index. The results of these parameters are tabulated in Table 3. The diving depth and breath holding capacities of the mammals with apnea ability are given in Table 4 for comparison. According to Table 4, *Physeter macrocephalus* dives the deepest following with *Delphinapterus leucas*.

**Table 2.** Amino acid numbers and percentages in the GPX-1 enzymes in the study.

	<i>Homo sapiens</i>		<i>Neomonachus schauinslandi</i>		<i>Leptonychotes weddellii</i>		<i>Neophocaena asiaeorientalis asiaeorientalis</i>		<i>Delphinapterus leucas</i>		<i>Balaenoptera acutorostrata scammoni</i>		<i>Callorhinus ursinus</i>		<i>Lipotes vexillifer</i>		<i>Zalophus californianus</i>		<i>Tursiops truncatus</i>	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Ala(A)	24	11.8	28	13.4	26	12.4	21	10.2	21	10.2	24	10.1	25	12.0	21	10.2	24	11.5	21	10.2
Arg(R)	14	6.9	14	6.7	14	6.7	15	7.3	15	7.3	17	7.1	14	6.7	15	7.3	14	6.7	15	7.3
Asn(N)	10	4.9	11	5.3	11	5.3	11	5.3	11	5.3	11	4.6	10	4.8	11	5.3	10	4.8	11	5.3
Asp(D)	8	3.9	7	3.3	8	3.8	9	4.4	9	4.4	9	3.8	9	4.3	9	4.4	8	3.8	9	4.4
Cys(C)	5	2.5	4	1.9	4	1.9	6	2.9	6	2.9	7	2.9	4	1.9	6	2.9	4	1.9	6	2.9
Gln(Q)	7	3.4	6	2.9	6	2.9	6	2.9	6	2.9	7	2.9	6	2.9	6	2.9	6	2.9	6	2.9
Glu(E)	13	6.4	13	6.2	13	6.2	13	6.3	13	6.3	13	5.5	12	5.8	13	6.3	13	6.2	13	6.3
Gly(G)	17	8.4	16	7.7	16	7.7	16	7.8	16	7.8	19	8.0	15	7.2	16	7.8	17	8.2	16	7.8
His(H)	2	1.0	2	1.0	2	1.0	2	1.0	2	1.0	3	1.3	2	1.0	2	1.0	2	1.0	2	1.0
Ile(I)	6	3.0	7	3.3	7	3.3	6	2.9	6	2.9	6	2.5	8	3.8	6	2.9	8	3.8	6	2.9
Leu(L)	23	11.3	22	10.5	22	10.5	22	10.7	22	10.7	26	10.9	24	11.5	22	10.7	22	10.6	22	10.7
Lys(K)	6	3.0	6	2.9	6	2.9	7	3.4	7	3.4	8	3.4	6	2.9	7	3.4	6	2.9	7	3.4
Met(M)	4	2.0	3	1.4	3	1.4	4	1.9	4	1.9	5	2.1	3	1.4	4	1.9	3	1.4	4	1.9
Phe(F)	11	5.4	12	5.7	12	5.7	12	5.8	12	5.8	12	5.0	11	5.3	12	5.8	12	5.8	12	5.8
Pro(P)	15	7.4	18	8.6	18	8.6	16	7.8	16	7.8	20	8.4	18	8.7	16	7.8	18	8.7	16	7.8
Ser(S)	11	5.4	13	6.2	13	6.2	10	4.9	10	4.9	16	6.7	14	6.7	9	4.4	13	6.2	10	4.9
Thr(T)	7	3.4	8	3.8	8	3.8	9	4.4	9	4.4	12	5.0	8	3.8	10	4.9	8	3.8	9	4.4
Trp(W)	2	1.0	2	1.0	2	1.0	2	1.0	2	1.0	2	0.8	2	1.0	2	1.0	2	1.0	2	1.0
Tyr(Y)	4	2.0	4	1.9	4	1.9	4	1.9	4	1.9	4	1.7	4	1.9	4	1.9	4	1.9	4	1.9
Val(V)	13	6.4	12	5.7	13	6.2	14	6.8	14	6.8	16	6.7	12	5.8	14	6.8	13	6.2	14	6.8
Pyl(O)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sec(U)	1	0.5	1	0.5	0	0.0	1	0.5	1	0.5	1	0.4	1	0.5	0	0.0	1	0.5	1	0.5

**Table 3.** Protein parameters in the GPX-1 enzymes of selected breath-holding animals.

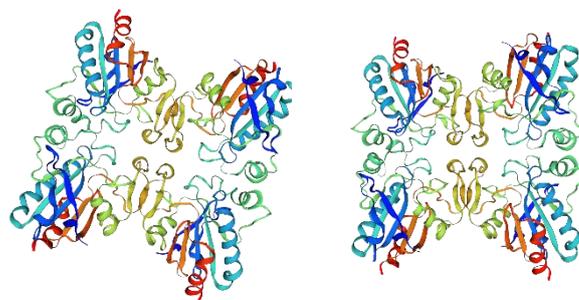
Species	#aa	Mw (Kda)	Theoretical pI	Negatively Charged Residues (Asp+Glu)	Positively Charged Residues (Arg+Lys)	Net Charge	Instability Index
<i>Homo sapiens</i>	203	22088.17	6.15	21	20	-1	47.96
<i>Neomonachus schauinslandi</i>	209	22566.64	6.74	20	20	0	51.55
<i>Leptonychotes weddellii</i>	209	22600.00	6.15	21	20	-1	50.27
<i>Neophocaena asiaeorientalis asiaeorientalis</i>	206	22651.85	6.73	22	22	0	50.50
<i>Delphinapterus leucas</i>	206	22651.85	6.73	22	22	0	50.50
<i>Balaenoptera acutorostrata scammoni</i>	238	25841.54	8.50	22	25	+3	51.78
<i>Callorhinus ursinus</i>	208	22562.69	6.14	21	20	-1	49.55
<i>Lipotes vexillifer</i>	206	22627.16	6.73	22	22	0	47.10
<i>Zalophus californianus</i>	208	22552.66	6.15	21	20	-1	49.54
<i>Tursiops truncatus</i>	206	22651.85	6.73	22	22	0	50.50

**Table 4.** Reported maximum breath-holding times of the animals in the study.

Organism	Breath holding time (min)	Deep diving depth (m)	References
<i>Homo sapiens</i> (Human)	10.45	100	www.cmas.org
<i>Physeter macrocephalus</i> (Sperm whale)	<138	<2000	Watkins et al., 1993
<i>Neomonachus schauinslandi</i> (Hawaiian monk seal)	20	<550	NOAA fisheries, 2018
<i>Leptonychotes weddellii</i> (Weddell seal)	<70	<600	Kooyman, 1966; Zaopol et al., 1979
<i>Neophocaena asiaeorientalis</i> (Yangtze finless porpoise)	2	20	Bi et al., 2015
<i>Delphinapterus leucas</i> (Beluga whale)	<20	20- 900	Heide-Jørgensen et al., 1998
<i>Balaenoptera acutorostrata scammoni</i> (North Pacific minke whale)	9.6	106	Gales et al., 2013
<i>Callorhinus ursinus</i> (Northern fur seal)	5	175	Zeppelin et al., 2019
<i>Lipotes vexillifer</i> (Yangtze river dolphin)	5	20	Zhou et al., 1979
<i>Zalophus californianus</i> (California sea lion)	12	536	Steven et al., 1989
<i>Tursiops truncatus</i> (Atlantic bottle-nosed dolphin)	5	450	Leigh et al., 2007

### 3.5 3-Dimensional modelling of the protein structures

Three-dimensional model of human GPX was modeled by using the Swiss Model (Figure 3) (Waterhouse et al., 2018; Studer et al., 2020). Swiss Model created the model by using the template coded 1gp1.1.A. The sequence identity was found to be 90.16%. The resolution of the model was given as 0.2 nm. GMQE and QMEANDisCo Global values were found as 0.89 and  $0.90 \pm 0.05$ , respectively. In this study, we also wanted to see 3-D structural differences between the GPX-1 of *Homo sapiens* and *Tursiops truncatus* (Atlantic bottle-nosed dolphin). We wanted to select *T.truncatus* since it can dive greater than 450 m. *T.truncatus* was selected in this study since it is one of the common animals. The complete enzyme sequence for *Physeter macrocephalus* does not exist in Uniprot database. The 3-dimensional structure of *T.truncatus* was also shown in Figure 3b. From the Swiss model parameters, it could be said that the GPX-1 enzymes found in these organisms are quite similar. Due to the high similarities, GPX-1 enzymes are house-keeping enzymes and therefore, highly conserved sequences among the species. Possible mutations observed within these sequences may affect the diving times.

a) *Homo sapiens*b) *Tursiops truncatus***Fig 3.** Swiss-Models of GPX-1 enzymes from *Homo sapiens* (a) and *Tursiops truncatus* (b) (template: 1gp1.1.A).

In protein data bank (rcsb.org), 3-D structures of different GPX-1 enzymes can also be accessible. For example, crystal structure of the selenocysteine to glycine mutant of human glutathione peroxidase 1 is also accessible through the code of 2F8A.

#### 4. Discussion

GPX-1 is of great importance in detoxification of hydrogen peroxide which is formed as a product of many metabolic processes in human metabolism. Effects of physical exercise on GPX is complicated. According to a very recent meta-analysis, physical exercise has no effect on GPX in human (Wang et al., 2023). In this paper, GPX-1 from breath-holding animals were compared and it is found that the sequence of this enzyme is mostly conserved in all animals due to its critical function in the metabolism.

According to Uniprot.org, the human GPX-1 enzyme reveals important amino acid modifications. The modifications such as phosphoserine, N6-acetyllysine, N6-succinyllysine are observed at the residues 34, 88, 114, 148, 197 and 201. From this research, it could be said that whatever the breath holding species is in the paper, the amino acid sequence of GPX-1 is highly conserved.

In this report, we also compared the diving times and also depth of some of the breath holding animals (Table 5). The diving time and depth for *Homo sapiens* (human) is reported as 10.45 min and 100 meters, respectively (www.cmas.org). Maximum diving time and depth were found as 138 min and deeper than 2000 m, respectively, from *Physeter macrocephalus* (Sperm whale) (Watkins et al., 1993). Other samples of the animals are also given in Table 4. Based on the mutations in the amino acid sequence sports informatics methods can be developed for the selection of athletes for apnea competitions. This is a sample basic research of GPX-1 enzyme among different species. The anatomical structures of the species analyzed are not investigated which also play a role in dive depth and breath holding e.g. lung size presence of tail and special traits for swimming and diving. Further studies based on different enzymes should be conducted especially on human breath-holding times. Since bioinformatics tools may reveal interesting outputs. After the availability of GPX-1 sequence data among humans, the selection of the athletes would be possible based on differences in amino acid sequences.

#### 5. Conclusion

Sports informatics is a new field in sports science. The biological data in bioinformatics databases such as DNA and protein sequences related to performances can effectively be used in sport sciences for many purposes such as talent selection, prevention of sport injuries and development of special trainings. This paper shows that amino acid sequences of GPX-1 from different breath holding animals are highly conserved. Therefore, GPX-1 enzyme activities, mRNA levels and its sequence can be checked in athletes who are interested in breath holding sports such as apnea, spear fishing, underwater hockey and underwater rugby.

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#### Authors' contributions:

L.C. conceived of the presented idea. L.C., E.C. and O.A. developed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. All authors agreed to submit the paper to the Eurasian Journal of Biological and Chemical Sciences.

#### Conflict of interest disclosure:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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