PASS and ADMET Analyses For Eight Compounds From Nile tilapia (Oreochromis niloticus) Viscera Waste Hydrolysate as Anti-Inflamatory Nutraceutical

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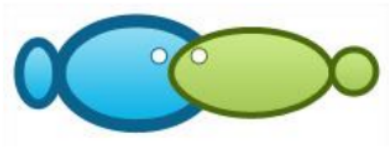

PASS and ADMET analyses for eight compounds from Nile tilapia (*Oreochromis niloticus*) viscera waste hydrolysate as anti-inflammatory nutraceutical

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Abstract. Increased Nile tilapia (*Oreochromis niloticus*) production results in increased fish waste. Waste from fish include viscera, skin, bones, and scales. Waste affects environmental, health, social, and economic issues when not properly managed. One prospective is to develop food products from the waste from the fisheries industry into a nutraceutical product. This article aims to obtain a potential profile of Nile tilapia viscera hydrolysate as an anti-inflammatory nutraceutical with PASS (prediction of activity spectra for biologically active substances) and ADMET (absorption, distribution, metabolism, excretion, toxicity) analyses. The predominant 8 compounds in Nile tilapia viscera hydrolysate are choline, eicosapentaenoic acid, 4-piperidone, ethyl palmitoleate, L-phenylalanine, anacardic acid, 9-oxo-10(E), 12(E)-octadecadienoic acid, and 1-linoleoyl glycerol. The PASS analysis indicates 5 compounds with a probability activity (Pa) value of more than 0.5, meaning that the compounds tend to exhibit activity as anti-inflammatories. ADME analysis suggests that 8 compounds can be moderately good medicinal ingredients based on Lipinski's rules analysis and pharmacokinetic properties. The study of toxicity based on Pro Tox predictions indicates that there is no potential for hepatotoxicity, carcinogenicity, immunotoxiticity, mutagenicity, cytotoxicity.
Key Words: 4-piperidone, choline, eicosapentaenoic acid, pharmacokinetics, probability activity.

Introduction. Increased Nile tilapia production will result in increased waste. The waste includes head, skin, fins, bones, viscera, and scales. Solid waste is the most significant contributor to the fisheries waste industry (Arvanitoyannis & Kassaveti 2008). The fish waste in the form of fish viscera can be utilized as raw materials for protein hydrolysate (Ishak & Sarbon 2017). It can minimize environmental and health problems and can reduce the economic impact (Harnedy & FitzGerald 2012).

One prospective is to develop nutraceutical products from fish waste (Mine et al 2010). Nutraceuticals are substances with physiological benefits like protection against chronic diseases (Nasri et al 2014). They are included in therapies for hypertension (Riyadi 2018), cancer (Nurdiani et al 2017), or cardiovascular disease (Bhat et al 2015). Grand View Research (2020) reported that the global nutraceutical market size was valued at 382.51 billion USD in 2019 and it is expected to expand at a compound annual growth rate of 8.3% over the forecast period. Developing Nile tilapia viscera into nutraceutical products is an opportunity for the fisheries business.

Research with the approach of bioinformatics in the health field is always related to efforts to overcome human diseases. The use of in-house offline applications such as MOE, GROMACS, and AUTODOCK for the throttling and dynamics of molecules is a common method (Parikesit et al 2016). However, if the computing resources to perform

those applications are unavailable, other steps using the cloud-based tool can taken. Some of the tools available online are DOCK BLASTER for predicting molecular-molecules (Irwin et al 2009), MDWEB, and MDMOBY for the analysis of molecular dynamics (Hospital et al 2012), ADMET and DRUGBANK for the development of drug databases (Knox et al 2011), as well as PreADME for ADMET tools (Lee et al 2003). Since 2000, the PASS has served as a free accessible web resource to predict spectral biological activity (Lagunin et al 2000). This study aimed to obtain a potential profile of the nile tilapia viscera hydrolysate as an anti-inflammatory nutraceutical with PASS and ADMET analyses.

Material and Method

Materials. The materials used in this study are Nile tilapia viscera waste, alcalase enzyme, Aquades, NaOH (Merck), pH paper, formaldehyde 35% (Merck), selenium, H_2SO_4 (Merck), NaOH, HCl (Merck), H_3BO_3 (Sigma), and hexane (Merck), HCl 0.1 N (Merck), NaOH 0.5 N, solvent buffer phosphate 0.2 M pH 8, HCl 6 N and 0.01 N. Hydrolyzed waste of nile tilapia viscera was obtained with alcalase enzyme 1.5% (w/V), pH 7.9, at 55.8°C, for 1.5 h, the hydrolysis degree being 41.51% (Riyadi et al 2019a, 2019b). The tools used in this research are a hand blender (Philips HR 1364), oven (Memmert), lube (Himac CR 21 g), Waterbath Shaker (Wisebath), beaker glass 50 mL, burette, pH meter, liquid chromatography - high-resolution accurate mass spectrometry (LC-HRMS), and a set of computers.

Compounds analysis using LC-HRMS. The screening of compounds is conducted with a LC-HRMS Shimadzu (Shimadzu Corp, Kyoto, Japan). 1 µL of sample was injected into the capillary column. Chromatography separation was done using Hyperil column Gold (1.9 µm x 1 mm x 50 mm). The mobile phase consisted of a combination of A (0.1% formic acid in water, v/v) and B (0.1% formic acid in acetonitrile, v/v). The linier gradient was from 4 to 20% B (v/v) at 40 min, to 35% B at 60 min, to 100% B at 61 min and head at 100% B to 65 min. The LC-HRMS used is the ThermoFisher Scientific Q Exactive with 70000 resolution for MS1 plus 17500 resolution for MS2. The polarity used was positive. The software used to read the results was mzCloud MS/MS Library with the latest updates (May 2019).

PASS (Prediction of activity spectra for biologically active substances) analysis. The analysis was done in 2 stages, namely: the first phase of accessing the server PubChem (https://pubchem.ncbi.nlm.nih.gov/) to get canonical SMILE information; the next step is to predict biological activity with PASS analysis, using the website http://www.way2drug.com/PASSOnline/index.php by entering the canonical SMILE structure (Jamkhande et al 2016).

ADMET (Absorption, distribution, metabolism, excretion, toxicity) analysis. Compounds were analyzed for the properties of absorption, distribution, metabolism, and excretion using swissADME (http://www.swissadme.ch/) (Riyadi et al 2020). LD_{50} toxicity prediction was conducted using Pro Tox online predictions (http://tox.charite.de/protox_II/ index.php) (Banerjee et al 2018).

Results and Discussion. LC-HRMS results indicated that there are 8 compounds with high levels in nile tilapia viscera waste hydrolysate. The compounds are choline, docosapentaenoic acid, 4-piperidone, ethyl palmitoleate, L-phenylalanine, anacardic acid, 9-oxo-10(E), 12(E)-octadecadienoic acid, and 1-linoleoyl glycerol. The 8 compounds ammount to 60.01% of the Nile tilapia viscera waste hydrolysate.

The estimated probability activity (Pa) value of biological activity from the PASS online application is presented in Table 1. The potential prediction of medicinal ingredients was recently developed by the method *in silico* (Wang et al 2015). Table 1 shows 4 of the 8 compounds with a Pa value of more than 0.7 for anti-inflammatory properties. A value higher than 0.7 Pa means that the compounds are very likely to exhibit anti-inflammatory activity in the experiment. The experiments in question are *in*

vitro and *in vivo*. Such compounds are eicosapentaenoic acid, anacardic acid, 9-Oxo-10 (E) 12 (E)-octadecadienoic acid 1-Linoleoyl glycerol. Eicosapentaenoic acid exhibits anti-inflammatory effects through the GPR120 in the 3T3-L1 adipocytes and weakens the inflammation of adipose tissues in diet-induced obesity mice (Yamada et al 2017), Anacardic acid has an anti-inflammatory impact on TNF-α-induced human saphenous vein endothelial cell culture model (Burak et al 2020). 9-oxo-10 (E) 12 (E)-octadecadienoic acid and daphnetin inhibited the secretion of inflammatory drug cytokine via the suppression of the NF-κB and MAPKs pathways (Mohri et al 2018). In addition, ethyl palmitoleate has a Pa value between 0.5 and 0.7, tending to exhibit anti-inflammatory activity (Lagunin et al 2000).

Table 1

PASS analysis of the 8 compounds of Nile tilapia viscera waste hydrolysate (number of sequences based on the relative composition)

No	*Compound*	*RA (%)*	*Canonical SMILE*	*Pa*	*Pi*
1	Choline	24.76	C[N+](C)(C)CCO	-	-
2	Eicosapentaenoic acid	14.57	CCC=CCC=CCC=CCC=CCC=CCCCC(=O)O	0.804	0.006
3	4-Piperidone	4.86	C1CNCCC1=O	0.367	0.019
4	Ethyl palmitoleate	3.95	CCCCCCC=CCCCCCCCC(=O)OCC	0.672	0.019
5	L-Phenylalanine	3.24	C1=CC=C(C=C1)CC(C(=O)O)N	0.429	0.016
6	Anacardic acid	3.00	CCCCCCCCCCCCCCCC1=C(C(=CC=C1)O)C(=O)O	0.706	0.003
7	9-Oxo-10(E),12(E)-octadecadienoic acid	2.72	CCCCCC=CC=CC(=O)CCCCCCCC(=O)O	0.770	0.009
8	1-Linoleoyl glycerol	2.71	CCCCCC=CCC=CCCCCCCCC(=O)OCC(CO)O	0.746	0.011

Note: RA - relative amount; Pa - probability of activity; Pa - probability of inactivity.

In comparison, 4-Piperidone and L-Phenylalanine have a Pa value of less than 0.5. Pa values less than 0.5 suggest that the substance tends to exhibit less anti-inflammatory activity. Choline has no data related to PASS analysis. However, there is research that suggests choline as an anti-inflammatory agent. Choline has anti-inflammatory and antinociceptive activities in mouse models for postoperative pain (Rowley et al 2010).

The analysis of the pharmacokinetics properties of Nile tilapia viscera waste hydrolysate was performed to see if such compounds can reach the target location, and if they can persist for the time needed to produce intended effects. The results are presented in Figures 1 to 8.

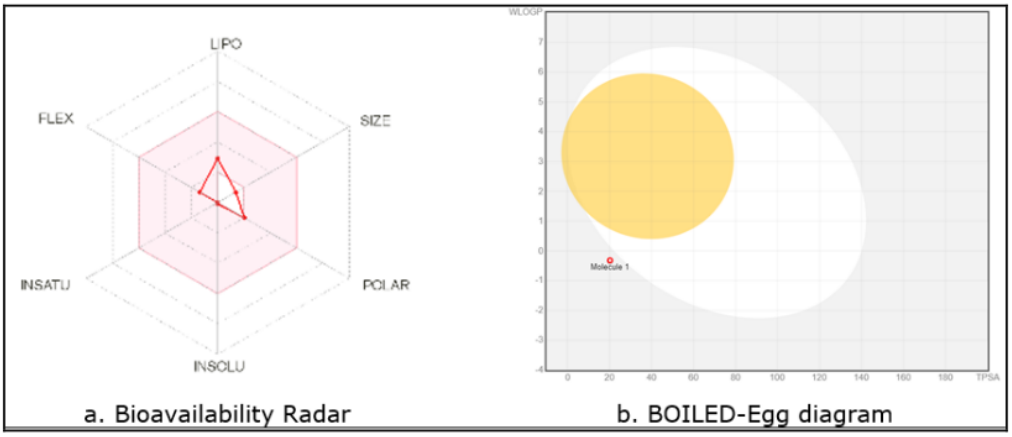

Figure 1. Pharmacokinetics properties of choline.

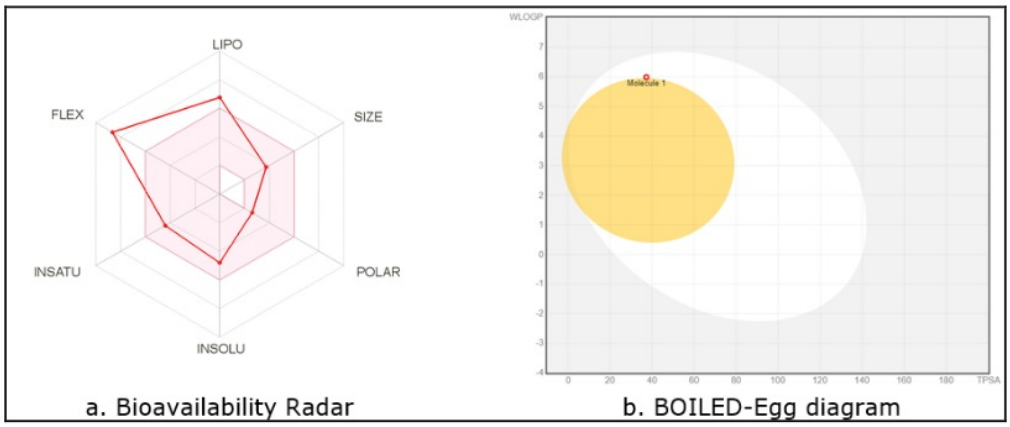

Figure 2. Pharmacokinetics properties of eicosapentaenoic acid.

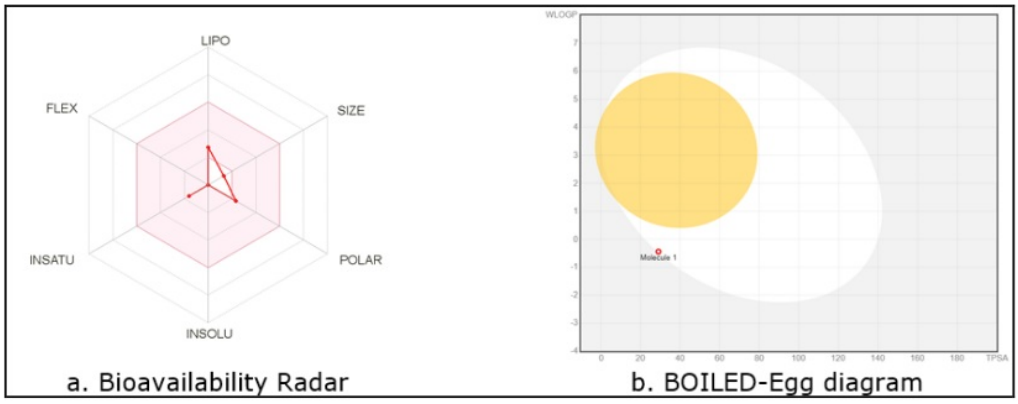

Figure 3. Pharmacokinetics properties of 4-Piperidone.

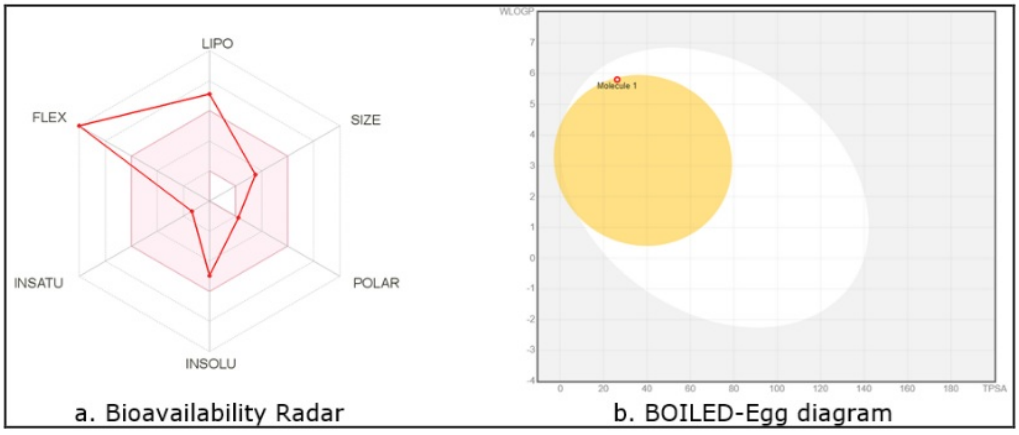

Figure 4. Pharmacokinetics properties of ethyl palmitoleate.

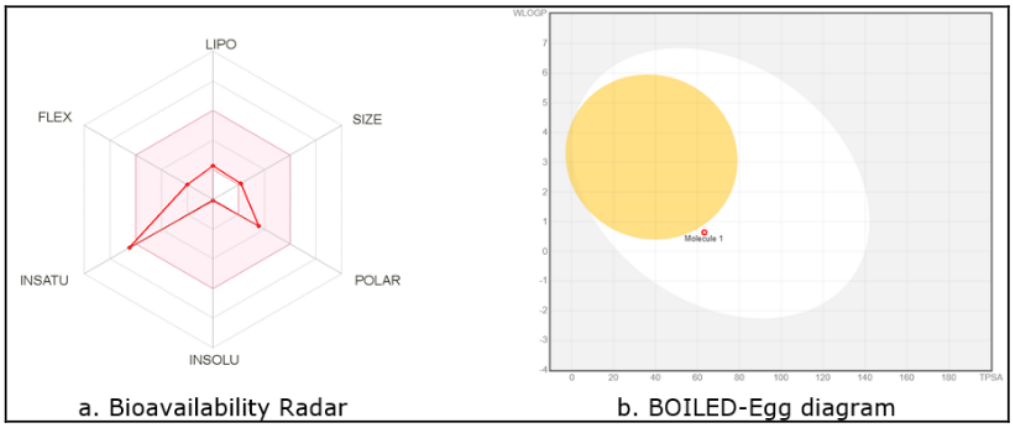

Figure 5. Pharmacokinetics properties of L-Phenylalanine.

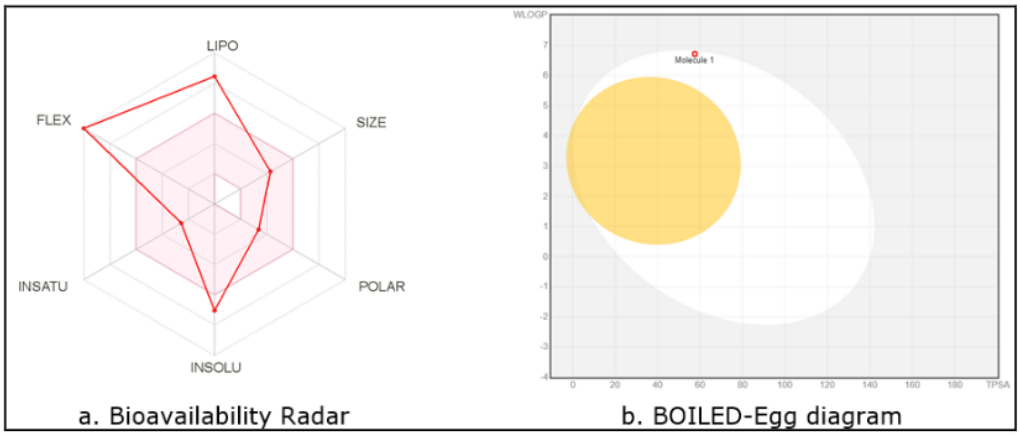

Figure 6. Pharmacokinetics properties of anacardic acid.

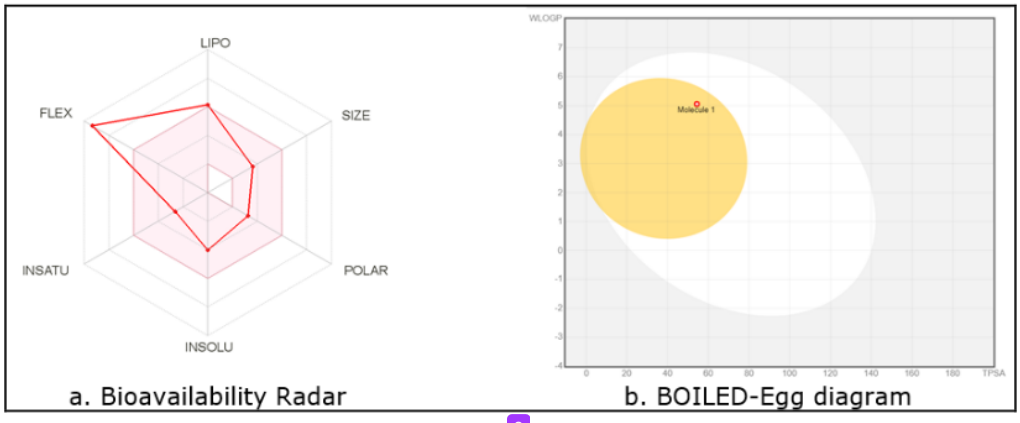

Figure 7. Pharmacokinetics properties of 9-Oxo-10(E),12(E)-octadecadienoic acid.

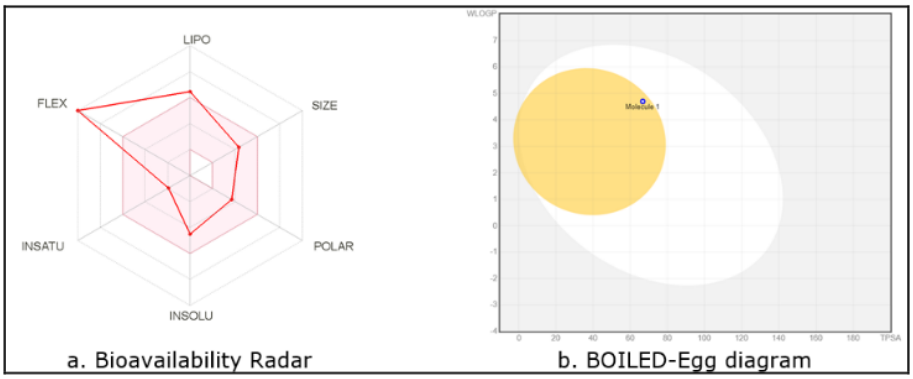

Figure 8. Pharmacokinetics properties of 1-Linoleoyl glycerol.

Figures 1 to 8 show most compounds having high gastrointestinal absorption, except choline. The boiled egg diagram in Figure 1 shows that choline is outside the yolk and white. It indicates that the gastrointestinal absorption value is low. The high value of gastrointestinal absorption indicates that the compounds are easily absorbed by the body. As it is more easily absorbed, the compound is better. High gastrointestinal absorption can reduce the amount of nutraceutical administration, can reduce the risk of side effects and toxicity. Low gastrointestinal absorption can result in low efficacy and variability among individuals and, therefore, can lead to an unexpected response to a nutraceutical. Most compounds show an excellent bioavailability.

The physicochemical characteristic from the hydrolysate of Nile tilapia viscera waste are shown in Tables 2 and 3.

Table 2

Physicochemical properties from the hydrolysate of Nile tilapia viscera waste using SwissADME

Compound	*MW*	*HA*	*AHA*	*RB*	*HBA*	*HBD*	*MR*	*TPSA*	*L*
Choline	104.14	7	0	2	1	1	29.69	20.23	1.38
Eicosapentaenoic acid	302.45	22	0	13	2	1	97.88	37.30	5.49
4-Piperidone	99.13	7	0	0	2	1	30.95	29.10	0.20
Ethyl palmitoleate	282.46	20	0	15	2	0	89.45	26.30	5.59
L-Phenylalanine	165.19	12	6	3	3	2	45.50	63.32	0.01
Anacardic acid	348.52	25	6	15	3	2	107.69	57.53	6.37
9-Oxo-10(E),12(E)-octadecadienoic acid	294.43	21	0	14	3	1	89.66	54.37	4.56
1-Linoleoyl glycerol	354.52	25	0	18	4	2	105.72	66.76	4.84

Note: MW - molecular weight (g mol^{-1}); HA – number heavy atoms; AHA – number aromatic heavy atoms; RB – number rotatable bonds; HBA – number hydrogen bond acceptor; HBD – number hydrogen bound donor; MR - molar refractivity (m^3 mol^{-1}); TPSA - topology polar surface area (Å²); L – lipophilicity (LogP).

Tables 2 and 3 indicate that all compounds meet the rules of Lipinski or drug-likeness. Drug-Likeness is a term used to describe how physiochemical properties of compounds affect molecular properties *in vivo*. This analysis suggests that the compound can spread well to all parts of the body to play an active role as a drug (Aristyani et al 2018). Most rules to test drug-likeness use the physicochemical properties obtained from molecular structures and to match those properties with the medicines that have been registered. One of the most used rules is the rule of Lipinski (Lipinsky et al 1997). The chemical components of the Nile tilapia viscera waste hydrolysate have excellent potential as drug candidates. This estimate is based on the molecular weight (MW) value, which is less than 500 g mol^{-1}, the hydrogen bond acceptor is less than 10, the hydrogen bond donor is less than 5, the topology surface area (TPSA) is less than 140 Å, and the LogP is less

than 5 (Sehgal et al 2016). Compounds that have a molecular weight exceeding 500 g mol^{-1} will present a weak bioavailability, low fraction absorption, high bound fraction, and weak renal clearance. TPSA is a surface image of a molecule that emerges from polar atoms such as oxygen, nitrogen, or hydrogen bond to an oxygen or nitrogen atom. The bioactive compounds with a TPSA value higher than 140 Å will difficultly enter cells (Pajouhesh & Lenz 2005). Conversely, if the bioactive compound has a TPSA value less than 140 Å, it will easily enter cells (Aristyani et al 2018). ADME analysis suggests that the nile tilapia viscera waste hydrolysate has potential as a moderately good medicinal material based on the analysis of the Lipinski rules and the pharmacokinetic properties.

Table 3

Druglikeness properties of the Nile tilapia viscera waste hydrolysate using the Lipinski Rule of Five

Compounds	*A*	*B*	*C*	*D*	*E*	*F*
Choline	Yes	Yes	Yes	Yes	Yes	Yes
Eicosapentaenoic acid	Yes	No	Yes	Yes	Yes	Yes
4-Piperidone	Yes	Yes	Yes	Yes	Yes	Yes
Ethyl palmitoleate	Yes	Yes	Yes	Yes	No	Yes
L-Phenylalanine	Yes	Yes	Yes	Yes	No	Yes
Anacardic acid	Yes	Yes	Yes	Yes	No	Yes
9-Oxo-10(E),12(E)-octadecadienoic acid	Yes	Yes	Yes	Yes	Yes	Yes
1-Linoleoyl glycerol	Yes	Yes	Yes	Yes	Yes	Yes

Note: A - molecular mass less than 500 Dalton; B - high lipophilicity (expressed as LogP less than 5); C - less than 5 hydrogen bond donors; D - less than 10 hydrogen bond acceptors; E - molar refractivity should be between 40-130; F - conclusion.

One of the requirements in obtaining compounds for nutraceuticals is material safety. The safety of the material in question concerns mainly the toxicity of the compound. The toxicity of Nile tilapia viscera hydrolysate is presented in Table 4. Table 4 shows that 8 compounds from the Nile tilapia viscera waste hydrolysate are not toxic. Analysis of toxicity based on Pro Tox's predictions suggests that there is no potential for hepatotoxicity, carcinogenicity, immunotoxiticity, mutagenicity, or cytotoxicity of the Nile tilapia viscera waste hydrolysate.

Table 4

Oral toxicity prediction results from the hydrolysate Nile tilapia viscera waste using Pro Tox II

Compounds	*LD_{50}*	*Class*	*HE*	*CA*	*IM*	*MU*	*CY*
Choline	1391	4	(-)	(-)	(-)	(-)	(-)
Eicosapentaenoic acid	10000	6	(-)	(-)	(-)	(-)	(-)
4-Piperidone	338	4	(-)	(-)	(-)	(-)	(-)
Ethyl palmitoleate	5000	5	(-)	(-)	(-)	(-)	(-)
L-Phenylalanine	2400	5	(-)	(-)	(-)	(-)	(-)
Anacardic acid	481	4	(-)	(-)	(-)	(-)	(-)
9-Oxo-10(E),12(E)-octadecadienoic acid	2610	5	(-)	(-)	(-)	(-)	(-)
1-Linoleoyl glycerol	20000	6	(-)	(-)	(-)	(-)	(-)

Note: LD_{50}-Lethal Dose 50% of response *(mg kg^{-1})*; HE - hepatotoxicity; CA - carcinogenicity; IM - immunotoxiticity; MU - mutagenicity; CY - cytotoxicity; (-) - inactive; (+) - active; class 4 - slightly toxic; class 5 - practically nontoxic; class 6 - relatively harmless.

Conclusions. These results indicate that the 8 compounds with high levels in Nile tilapia viscera waste hydrolysate can act as an anti-inflammatory nutraceutical, according to PASS and ADMET analyses. Based on these results, the development potential of the compounds form Nile tilapia viscera waste hydrolysate can be further studied.

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