

Fish Scale Rich in Functional Compounds and Peptides: A Potential Nutraceutical to Overcome Undernutrition

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21

22 1 Introduction

23 Child undernutrition remains an important global health problem. Undernutrition increases the
24 susceptibility to illness and fatality and is related to 45% of child deaths (World Health Organization,
25 2016). Undernourished children also have severe short-term (e.g., delayed cognitive development),
26 medium-term (e.g., lower school achievement), and long-term implications (e.g., lower earnings and
27 higher probability of adult noncommunicable chronic diseases) (Leroy and Frongillo, 2019). Child
28 undernutrition is often a consequence of inadequate intake of vitamins and minerals such as vitamin
29 A, iron, iodine, and zinc but also by poor quality or insufficient proteins ([Ahmed](#), Hossain, & Sanin,
30 2012; Jee, 2021). The manifestations are low weight for height (or wasting) and low height for age (or
31 stunting). Furthermore, the incidence of stunting is greatly influenced by early life undernutrition since
32 growth faltering frequently starts while a child is still in the womb and lasts for at least the first two
33 years after birth (Black & Heidkamp, 2018; de Onis & Branca, 2016). In addition to these determinants,
34 the availability of health services is important (Sambo et al., 2022). The rates of stunting or chronic
35 protein energy malnutrition are increasing in certain parts of the world. One of the proposed solutions
36 is producing food or supplements rich in nutrition from the conversion of food by-products high in
37 good-quality proteins.

38 Fish is a healthy food with a high nutritional value which makes it extremely important for human
39 chain food (Fauzan *et al.*, 2020). Mass quantities of fish waste are produced annually during fish
40 processing, where fish waste, including fish scales, is discarded (Maktoof, Elherarlla, and Ethaib,
41 2020). To date, fish waste is partly used for the production of fishmeal, fertilizers, and fish oil with low
42 profitability or utilized as raw material for direct feeding in aquaculture while the rest are thrown away
43 (Coppola *et al.*, 2021). Fish scales are frequently regarded as abandoned waste from the aquaculture
44 industry, including fish canning, filleting, salting, and smoking processes (Qin *et al.*, 2022). An
45 estimated 7.2–12 million tons of fish waste are thrown away globally each year, with the 5 most utilized
46 species being *Oreochromis niloticus*, *Sardinella brasiliensis*, *Pogonias comes*, *Labeo rohita*, and
47 *Leporinus elongatus* (Qin *et al.*, 2022). The fish scale yields various functional applications originating
48 from its valuable components such as hydroxyapatite, collagen, and chitin (Coppola *et al.*, 2021; Wang,
49 2021). Furthermore, the collagen in fish scales can be utilized into bioactive peptides with various
50 health benefits (Nuñez et al., 2020; Ahmed, Verma, & Patel, 2020). Many efforts and research are
51 being carried out to exploit the potential of the fish scale, starting from the potential in the fields of
52 nutrition and food to medicine (Sreelakshmi *et al.*, 2022; Yamaura *et al.*, 2022). However, the

53 development of functional food from the fish scale to contribute to nutritional problem solutions is
54 currently underdeveloped.

55 Fish-derived peptides exhibit various biological activities such as an angiotensin-I-converting
56 enzyme (ACE) inhibitory activity, antioxidant, antimicrobial as well as anticancer activity, and
57 immunostimulant activity (Zaky *et al.*, 2021). Peptides, in addition to their nutritional characteristics
58 as sources of amino acids, are known to also have beneficial health effects, as they can present the
59 ability to interact directly with human metabolism routes, acting as health promoters and in the
60 mitigation of the aging process (Tacias-Pascacio *et al.*, 2021). Previous studies identified many types
61 of bioactive peptides derived from the fish scale. Four types of bioactive peptides from the sea bream
62 (*Sparus aurata*) scale have been showing antihypertensive activity with various efficacy. Other
63 bioactive peptides from different fish scales yielded antioxidant activities (Coppola *et al.*, 2021; Sierra-
64 Lopera and Zapata-Montoya, 2021). Regulation of oxidative stress and immunity plays an important
65 role in the growth and physiological metabolism. Eventually, it could lead to the prevention of
66 malnutrition, especially undernutrition conditions including stunting. A preclinical study by Sabrina *et*
67 *al.*, (2022) showed that bioactive peptides could improve nutritional status biomarkers such as serum
68 protein, hemoglobin, and IGF-1 levels. Stunting is a condition in which a child has a below-average
69 height, which is two standard deviations lower than his age on the standard growth chart (Prendergast
70 and Humphrey, 2014; Beal *et al.*, 2018). With its abundance in protein and bioactive peptides, fish
71 scales showed interesting potential as a nutraceutical that could act to fulfill the unmet needs of the
72 stunting population.

73 Therefore, this article aims to interpret the latest findings about the potential application of fish
74 scales as a functional food that has functional compounds and peptides, which may have the potential
75 to overcome undernutrition as a nutraceutical.

76 **2 Fish scale**

77 Fish scales are composed of type I collagen and hydroxyapatite (Yamaura *et al.*, 2022)
78 Identification of fish scale's major components revealed that moisture and protein share the majority
79 of fish scale weight. Maktoof, Elherarlla, and Ethaib (2020) analyzed the scales of *Cyprinus carpio*
80 fish, finding that between 22.1% to 23.9% of the scales' weight consists of protein with a low lipid and
81 carbohydrate content. The proportion of protein tends to increase associated with the increase in weight
82 and length of the fish (Maktoof, Elherarlla, and Ethaib, 2020). Due to its nutritional value, especially

83 its high protein, some researchers were able to develop nutritional food and meals from fish scales
84 (Sreelakshmi *et al.*, 2022).

85 Fish scales are the source of many valuable products. Fish scales consist of a type I collagen
86 multilayer with orderly orientation, adequate mechanical strength, transparency, and good
87 biocompatibility (Li *et al.*, 2019). Fish scales collagen gained advantages because it is considered a
88 safer collagen source compared to other animal-derived scaffolds due to the absence of zoonotic
89 infections and religious issues (Yamaura *et al.*, 2022). Alongside collagen, gelatin is also a component
90 of interest in fish scales. Gelatin belongs to a class of protein fractions derived from collagen, by
91 thermal hydrolysis which involves breaking hydrogen bonds between polypeptide chains of collagen
92 molecules. Due to its characteristics, gelatin has the most significant application in the food industry
93 field, pharmaceutical, and cosmetics industries (Ideia *et al.*, 2020). Gelatin supplementation can
94 enhance joint and bone health (Schauss *et al.*, 2012). Fish-based gelatin also encourages tissue
95 regeneration, raising bone marrow density and offering an alternate benefit for osteoporosis patients
96 (Lv *et al.*, 2019).

97 Aside from collagen, the fish scale also contains hydroxyapatite with various utilization values.
98 Hydroxyapatite is the hydroxylated representative of phosphate minerals known as apatites
99 ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$). Hydroxyapatite from fish scales has emerged as an alternative to substitute
100 synthetic and bovine hydroxyapatite, due to the similarity of chemical properties that simple and
101 inexpensive methods can achieve (Figure 1). Results from studies have shown that fish scales
102 hydroxyapatite demonstrated no cytotoxicity, increased mineralization *in vitro*, and tolerable
103 biocompatibility in murine models (Granito *et al.*, 2018). Hydroxyapatite constituent from fish scale
104 was also developed as a calcium-binding peptide which promotes calcium cellular uptake (Lin *et al.*,
105 2020). Those pieces of evidence suggested a significant role of hydroxyapatite in bone metabolism.

106 Chitin also can be found in fish scales. Chitin is a very attractive item owing to its biological
107 properties and therapeutic feature via antibacterial and antifungal activities. Chitin is a long chain
108 odorless or tasteless amino polysaccharide of white or off-white color in its pure state, composed of *N*-
109 acetyl- β -D-glucosamine units and monomers (Figure 1). The utilization of chitin derivatives is
110 numerous, ranging from medical, pharmaceutical, food, and cosmetic industries, to nutraceuticals,
111 bioremediation, gene therapy, and cosmetics (Coppola *et al.*, 2021). Chitin has many beneficial
112 properties as an antioxidant, prebiotic, dietary fiber, and hypocholesterolemic agent (Harkin *et al.*,

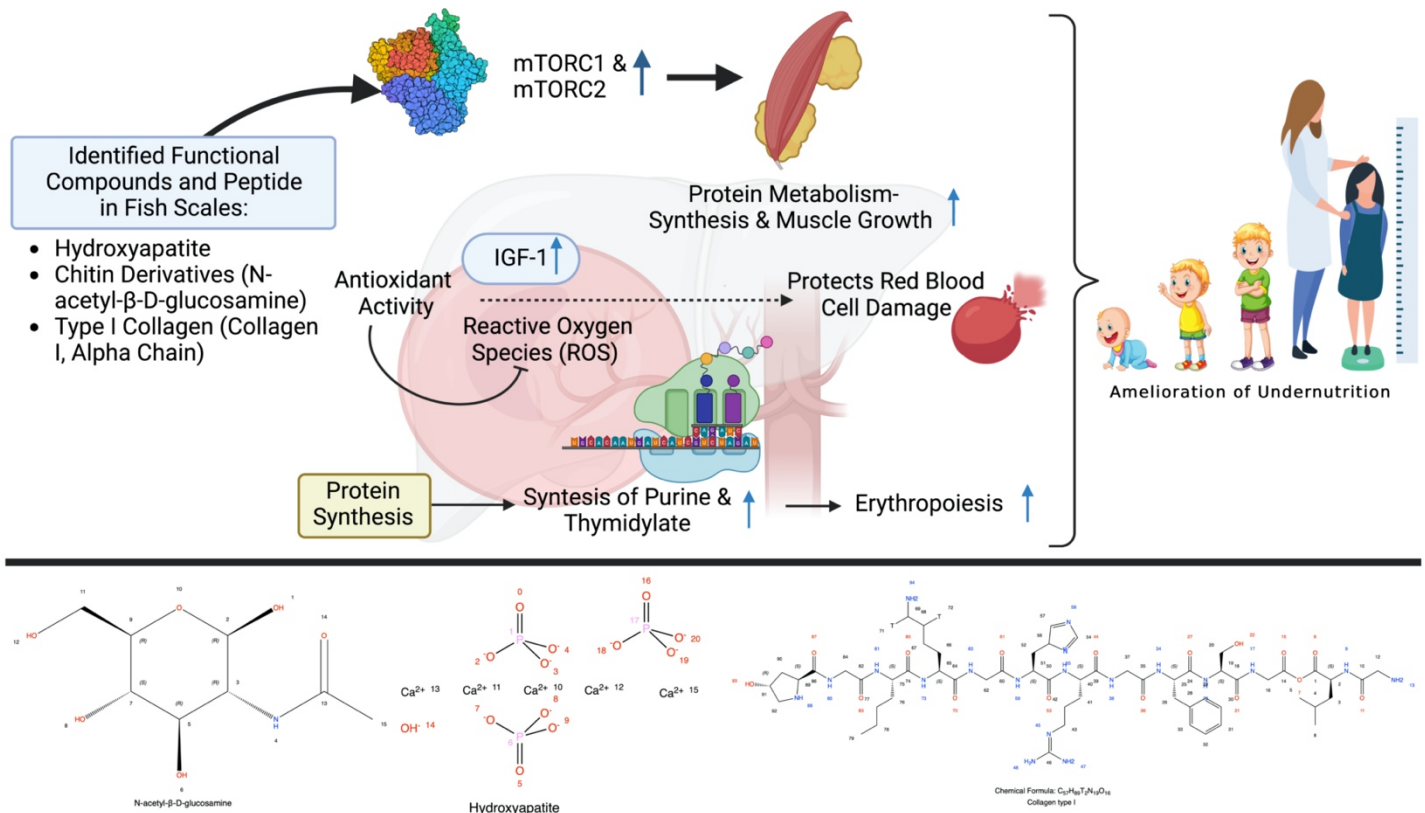
113 2019). Incorporating chitin into a protein-based meal was also shown to improve growth, increase fatty
114 acid production, and modulate gut microbiota (Khempaka *et al.*, 2011).

115 **3 Fish scale supports growth and prevents malnutrition through various mechanisms**

116 Food that is rich in protein show many health benefits which are influenced by the presence of
117 bioactive peptides (Chakrabarti, Guha, & Majumder, 2018). The antioxidative, anti-inflammatory,
118 anticancer, antimicrobial, immunomodulatory, and antihypertensive properties of bioactive peptides
119 derived from dietary proteins are only a few of their important roles in the living body (Zaky *et al.*,
120 2022). Fish scale, which is a potential source of bioactive peptides, can be utilized to synthesize chitin
121 and chitosan, which have antioxidant, antimicrobial, and antiviral properties (Takarina & Fanani, 2017;
122 Mutalipassi *et al.*, 2021). These properties may contribute to the incidence of growth retardation since
123 it involves immune dysfunction, antioxidant, and metabolic (hormonal) system (Qi *et al.*, 2019).
124 Antioxidant was shown to enhance the activity of insulin-like growth factor-1 (IGF-1; Figure 1) and
125 its receptors (Masodsai *et al.*, 2019) while growth hormones also reduce oxidative stress
126 (Mohammadjafari *et al.*, 2019). An improvement in immunity will result in a good cellular metabolism
127 through the activation of rapamycin (mTORC1 and mTORC2; Figure 1) which promote protein
128 synthesis, glycolysis, mitochondrial functions, and lipid synthesis (Linke *et al.*, 2017). Bioactive
129 peptides also upregulate calcium uptake, which is associated with healthy bone growth (Liu *et al.*,
130 2013). Collagen peptides from the fish scale also showed immunomodulatory activity by protecting
131 cells from cytotoxicity and inflammation (Subhan *et al.*, 2017; Fatma *et al.*, 2020). Collagen peptides
132 made from fish scales contain a unique amino acid composition with a high concentration of proline,
133 hydroxyproline, and glycine (Hu *et al.*, 2017). Due to its ability to control cellular redox equilibrium,
134 proline, a non-essential amino acid, plays important role in protein structure or function and the
135 regulation of illnesses through extensive metabolic networks (Vettore *et al.*, 2021). Collagen contains
136 57% of the total amino acids, mostly glycine, proline, and hydroxyproline which is necessary to
137 preserve the strength and regular structure of connective tissue, including bones, skin, cartilage, and
138 blood vessels (Li & Wu, 2018).

139 The antimicrobial activity derived from the fish scale may also play a role in preventing
140 malnutrition, which is supported by a systematic and meta-analysis study that found that antibiotics –
141 which treated infections and might modulate intestinal microbiota – promoted growth in children
142 (Gough *et al.*, 2014). Diarrhea, water supply, sanitation, and hygiene practices were significantly
143 associated with the incidence of malnutrition (Soboksa *et al.*, 2021). Preventing infection and diarrhea

144 through the use of antimicrobial agents against *Shigella*, *Vibrio*, *Salmonella*, *Campylobacter*, and many
 145 others is genuinely recommended (Cohen *et al.*, 2017). A considerable amount of micronutrients, such
 146 as calcium, iron, magnesium, and phosphorus were identified in fish scales (Begum *et al.*, 2021).
 147 Calcium and magnesium had a significant contribution to bone and muscle health (Capozzi *et al.*,
 148 2020). Next to that, multiple micronutrient supplementation had shown good results by improving
 149 growth and reducing the risk of anemia in infants (Albelbeisi *et al.*, 2020). Looking at the big picture,
 150 this strategy may give a significant contribution to preventing anemia (a risk factor for stunting) in
 151 teenage girls or pregnant mothers (Tampy *et al.*, 2020) while also potentially resolving the dual-
 152 occurrence of anemia and stunting in children (Gosdin *et al.*, 2018). Hemoglobin levels were positively
 153 correlated with growth hormone levels (such as insulin-like growth factor I (IGF-1)) which emphasized
 154 the role of hemoglobin in preventing growth retardation (Zhang *et al.*, 2021; Zhao *et al.*, 2020). These
 155 facts highlight the fish scale as a wonderful source of both collagen and bioactive peptides which is
 156 rich in amino acid and micronutrients, supports growth, and prevent malnutrition through various
 157 mechanisms (Figure 1).
 158



159 **Figure 1.** Possible Scheme to Alleviate Stunting via the Modulation of the Metabolism by Fish Scale
 160 Peptides Supplementation. Created with BioRender.com premium license by Fahrul Nurkolis.

161 4 Nutraceutical products and developments based on fish scale bioactive peptides

162 The processing and utilization of fish scales into a food product of health value (nutraceuticals) is
163 a challenge for researchers. This opinion article attempts to interpret the latest findings about the
164 potential application of fish scales as a functional food that has the potential to overcome
165 undernutrition. However, we also aim to stimulate researchers in the exploration of bioactive peptides
166 derived from fish scales. Therefore, there is a need for further research that focuses on this research
167 topic. Unutilized fish scales may affect the realization of Sustainable Development Goals Number 14
168 (Life Below Water) since their waste can cause environmental pollution. Therefore, fish scales can be
169 developed as functional food products through various technologies and methods, which may also
170 reduce fish scale waste. Isolation, encapsulation, nanotechnology, and possibly fermentation are some
171 of the alternative methods that can be used to achieve the purpose of utilizing fish skin bioactive
172 peptides. More interestingly, fish scales have collagen composed of bioactive peptides.
173 Supplementation of food products containing bioactive peptides in rats was shown to improve
174 nutritional status biomarkers such as serum protein, hemoglobin, and IGF-1 levels (Sabrina *et al.*,
175 2022). Collagen contained in fish scales will undergo a hydrolysis reaction to produce gelatin. Fish
176 scale gelatin is a class of biopolymers containing abundant and potential bioactive amino acids and
177 peptides, which can be utilized in savory products such as fish scale crispy (Sreelakshmi *et al.*, 2022),
178 cookies (Abdullah, 2019), and protein hydrolysate (Lin *et al.*, 2020). The natural characteristics of fish
179 gelatin indicate that this fish scale gelatin product can be used as an ingredient in making jelly or agar-
180 agar, both types of food are favored by children. This will be an added value in the intervention of
181 malnourished children or lead to stunting. So, in addition to being able to overcome environmental
182 problems, the use of fish scales can also overcome nutritional problems.

183 5 Conclusion

184 As explained previously, there is the potential for processing fish scales into a functional food
185 product rich in bioactive peptides, which can not only overcome environmental problems, but this can
186 also overcome nutritional problems, especially to overcome undernutrition (Figure 1). Natural
187 processes in the body are modulated almost exclusively by the interaction of certain amino acid
188 sequences, either as peptides or as subsections of proteins or polypeptides. In connection with growth,
189 proteins and peptides are involved in the modulation of cell proliferation, cell migration, inflammation,
190 metabolism (hormonal), and protein synthesis and regulation. Research on the therapeutic peptide or
191 bioactive analogs of specific interactive sequences derived from fish scales has opened the door to a

192 diverse new field of pharmaceutical ingredients and functional foods for the food industry. These facts
193 form the basis that fish scales have the potential to be a source of collagen and bioactive peptides rich
194 in amino acids, and micronutrients, support growth, and prevent malnutrition through various
195 mechanisms. It is suitable to be applied in nutritional interventions in children with stunting. Further
196 clinical trials related to these benefits are expected to be conducted by many researchers.

197 **6 Conflict of Interest**

198 The authors (NAT, FN, WBG, MY, NM, AT, NS, JM, LM) declare that the article study was conducted
199 in the absence of any commercial or financial relationships that could be construed as a potential
200 conflict of interest.

201 **7 Author Contributions**

202 All listed authors (NAT, FN, WBG, MY, NM, AT, NS, JM, LM) have made substantial, direct, and
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213 **10 Data Availability Statement**

214 There is no data related to this opinion article. The data is only sourced from the literature that has
215 been listed in this article.

216 **11 Reference Styles**

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