REVIEW ARTICLE

Trends and applications of food protein-origin hydrolysates and bioactive peptides

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Abstract

It was reported that protein hydrolysates or derived peptides have more functionalities than their parent protein. Most functional protein hydrolysates or peptides are identified from various food products, including plant, fish, and land-animal protein sources. Within a few decades, the application of food protein-origin functional hydrolysates or peptides could be divided into two main categories according to their applied intentions: 1) preservatives and bioactive packing materials; 2) nutraceutical ingredients. According to the literature, the applications of food protein-origin functional hydrolysates or peptides on food preservative and nutraceutical ingredients have attracted much attention. However, the approach method should be changed. Multi-activities, compound formulation, comprehensive evaluation, and the added value of by-products are possible strategies. Although there have been great results and findings in the functionalities of food protein-origin bioactive hydrolysates or peptides, there is still a big gap between the lab-scale results and practical applications. Via this narrative review on the current research, scientists, the food/health industry, and government authorities should cooperate to dig into the new material sources and the possible practical application.

Keywords: Bioactive packing materials, Nutraceuticals, Peptides, Preservatives, Protein hydrolysates

1. Introduction

Amino acids joined by covalent bonds, also known as amide or peptide bonds, form bioactive peptides, which could positively impact body functions or health conditions [1]. Besides, bioactive peptides play crucial roles in the metabolic functions of living organisms, especially human beings. In many studies, antihypertension, antithrombotic, anti-cancer, antimicrobial, antioxidant, immunomodulatory, and agonist/antagonist properties of bio-peptides and protein hydrolysates have been reported [2]. Many bioactive peptides are identified from protein hydrolysates of various food products, including soybean, cereals, potatoes, nuts, vegetables, dairy products, eggs, and meat proteins [2]. It was mentioned that the protein hydrolysates or peptides produced from various protein sources possess some, or better, beneficial bioactivities compared to those found in the parent proteins [3,4]. Most food protein does not show specific biological activities in the naive sequences, though some biological activities of that food protein can be triggered by enzymatic, chemical, or microbial hydrolysis [5]. Enzymatic hydrolysis is the most effective method of producing functional hydrolysates or peptides. However, different factors, such as processing condition, protein source, amino acid sequence and compositions, molecular weight, charge distribution, pH, and certain chemical treatments, could directly affect the functionalities of generated bioactive hydrolysates or peptides [6].

Regarding bio-functional peptides, Sánchez and Vázquez indicated that many bioactive peptides have a peptide residue length of between 2-20 amino acids in addition to proline, lysine, or arginine groups [1]. Interestingly, bioactive peptides have also been shown to resist the further action of digestion peptidase [7]; therefore, the bioactive peptides could be absorbed under the current bioactive form. Moreover, the correlation between structure and functional properties is still not well understood; therefore, the crude extract, known as

Received 29 November 2021; revised 7 March 2022; accepted 14 March 2022.
Available online 15 June 2022.

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https://doi.org/10.38212/2224-6614.3408

hydrolysates, is often acceptable and used widely in practice [8–10].

There always exists a pervasive doubt in the absorption and bioavailability of bioactive peptides or hydrolysates. According to metabolic physiology, the protein is digested and absorbed in the gastrointestinal tract while gastric and pancreatic proteinases conduct luminal digestion. The resultant end products (mostly large peptides) undergo a further hydrolyzation by various peptidases present in the intestinal epithelium brush border membrane [11] Interestingly, several scientific pieces of evidence revealed that luminal amino acids are present as a peptide form (about 80%) rather than the free form (about 20%), and most peptides are 2–6 amino acids [12]. Ganapathy reported that the transport of free amino acids contributes relatively less; meanwhile, the protein digestion products enter the enterocytes in dipeptides or tripeptides via specific peptide transport systems [11].

Recently, bioactive peptides or hydrolysates from food by-product proteins have attracted much attention. According to a report from Food and Agriculture Organization of the United Nations (FAO) [13], the global meat output in 2018 is 336.4 million metric tons, in which there are mainly 123.9, 71.1, and 120.5 million tons for poultry, bovine, and pig meats, respectively. As a result, huge amounts of by-products are generated, including feathers, fish scales, blood, bones, skin, and viscera [14,15]. Hence, many researchers should be drawn to the question of how to maximize the utilization of those by-products from livestock, poultry, and aquaculture. It seems that the development of functional protein hydrolysates or bioactive peptides is one of the possible strategies; thus, this article also includes cases generated from food by-product protein. In this article, the application of food protein-origin bioactive peptides or hydrolysates would be discussed as following two major categories according to their applied intentions: 1) preservatives and bioactive packing materials and 2) nutraceutical ingredients (Fig. 1).

2. Preservatives and bioactive packing materials in the market

2.1. Antioxidative protein hydrolysates and peptides

Excessive free radicals could produce oxidants, which may reduce the quality of oleaginous foods, cause lipid oxidation, and shorten the shelf life of food [16]. Lipid oxidation always causes a great problem for the food industry and consumers because it leads to undesirable off-flavors, odors, and potentially toxic reaction products [17]. Because it is very practical to retard lipid peroxidation occurring in foodstuffs to maintain the quality and extend the shelf life of foods [18], many synthetic antioxidants, such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tertiary butylhydroquinone (TBHQ), are used as food additives to prevent rancidity. Antioxidants for use in food processing must be inexpensive, nontoxic, effective at low concentrations (0.001–0.02%), capable of surviving processing (carry-through), stable in the finished products, and devoid of undesirable color flavor and odor effects [18]. Generally, antioxidants in food products could normally

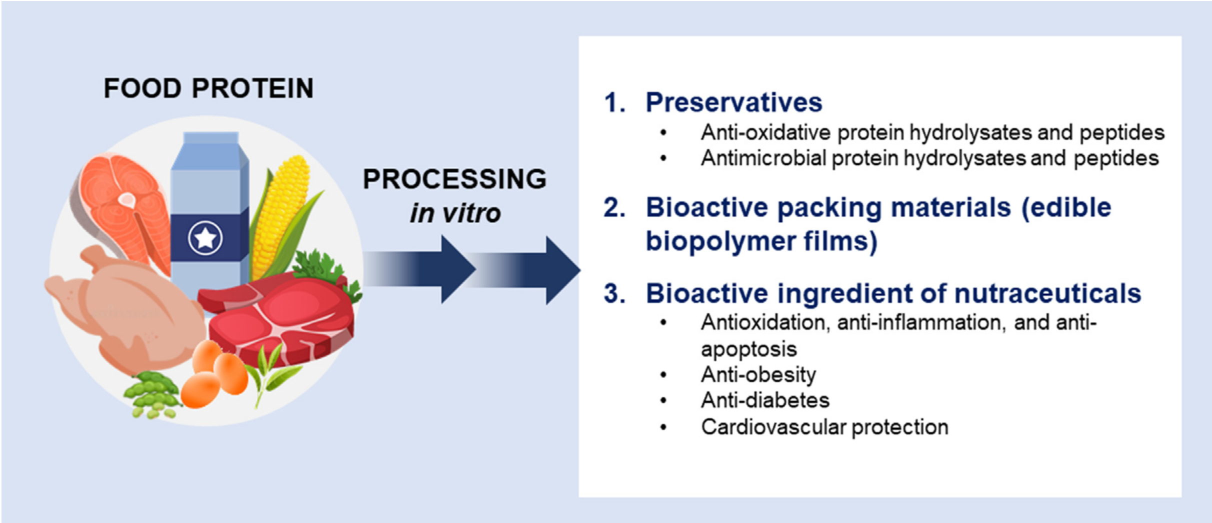

Fig. 1. Trends and applications of food protein-origin bioactive peptides and hydrolysates.

be added as either direct additives or indirectly through diffusion from packaging materials [19] (Fig. 2). Although synthetic antioxidants show stronger antioxidant activities than natural ones, such as α-tocopherol and ascorbic acid, there is still a doubt that these chemical compounds may cause health concerns due to the induction of DNA damage and toxicity [20–23]. Hence, there is a credit to looking for a natural source of antioxidants in applying food products.

Notably, natural antioxidant peptides originating from food proteins have captured scientists' attention due to their advantages of eco-friendliness, sustainability, and a lack of toxic side effects [24]. Plant proteins have been considered a new source of antioxidant peptides or hydrolysates, which delay the lipid peroxidation of food, save energy, and strengthen the treatment of oxidation-related diseases, thus decreasing food waste and improving the quality of life, respectively [25]. Decades ago, the antioxidative properties of whey and soy hydrolysates were revealed [26] (Table 1). Recently, some agricultural by-products, such as tea dregs and *Phoenix dactylifera* L. seed, were also found to be good sources of antioxidative hydrolysates [27,28] (Table 1). It was reported that peptide- and polyphenol-rich dark red kidney bean (*Phaseolus vulgaris* L.) hydrolysates could reduce the oxidation process of plain yogurt products during storage at room temperature for 3 days, and their antioxidative stability is higher than that of ascorbic acid [29]. Moreover, Gomes and Kurozawa reported that the rice protein hydrolysate as an encapsulated matrix in linseed oil microparticles enhances the stability of the unsaturated fatty acid-rich lipid [30]. Nowadays, antioxidative plant protein hydrolysates successfully apply to various food systems, i.e., beverages, yogurt, oil, and meat (Table 1).

Fish can serve as a source of functional materials, such as polyunsaturated fatty acids, polysaccharides, minerals and vitamins, antioxidants, enzymes, and bioactive peptides. Recently, a topic focused on identifying and characterizing bioactive murine peptides' structure, composition, and sequence. Antioxidant peptides and hydrolysates from marine sources and their by-products are also revealed [18,31]. 3% caplin-protein-hydrolysate addition in porcine meat increased cooking yield by 4% and inhibited oxidation [32]. The concentration of hydrolysates was up 3% in cases where the opposite effects occurred. Nikoo et al. also revealed similar results as the anti-oxidative-peptide study. The antioxidative peptide from Amur sturgeon skin gelatin was effective in the minced Japanese sea bass muscle model system [33]. Processed meat foods were also chosen for further application, as indicated in Table 1. Among those meat models, the optimal addition levels of antioxidant hydrolysates are different [34,35]. These cases indicated that addition levels were crucial factors, and meanwhile, the addition levels also depended on the various properties of different food systems. Although antioxidants from fish and their by-products were effective, their usage was limited due to their flavor and odor. Therefore, the solid results of antioxidative hydrolysates or peptides should be developed in a specific food system, and the influence on the sensory evaluation of the final product should also be included.

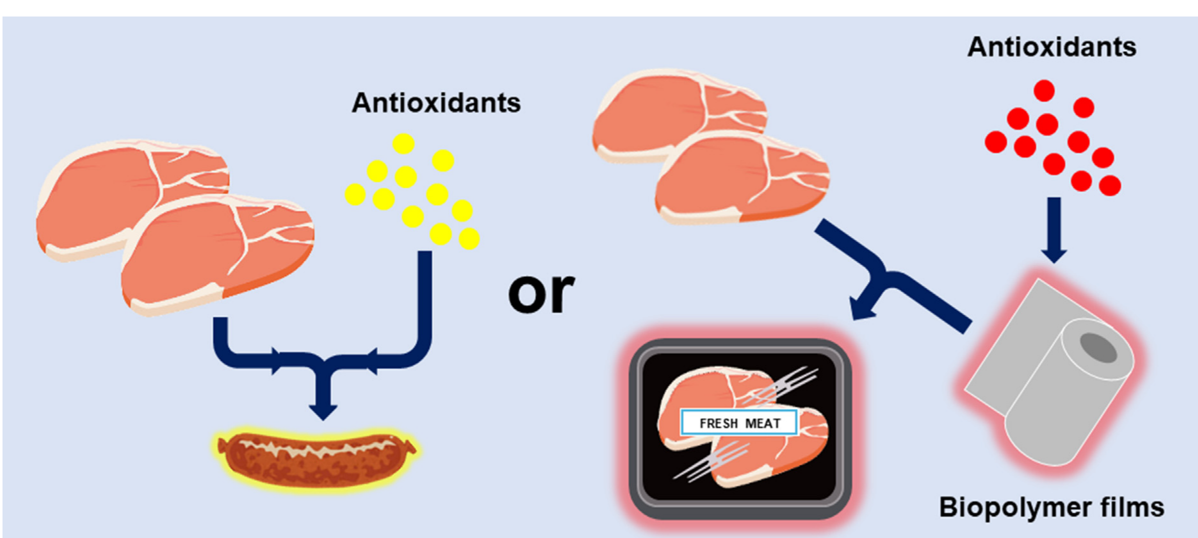

Fig. 2. Direct and indirect strategies of antioxidants in food-product preservation.

Table 1. Application of antioxidative protein hydrolysates and peptides as a preservative in the food system.

Protein source	Hydrolysates or peptides	Incorporated food system	Amount of active ingredients	References
Plant protein				
Date seed protein	Hydrolysates	Ground salmon	200 ppm	[28]
Dark red kidney bean (*Phaseolus vulgaris* L.)	Hydrolysates	Plain yogurt	3 g/L	[29]
Tea residue protein	Hydrolysates	Chicken surimi	0.1, 0.5, and 1.0%	[27]
Zein	Hydrolysates	Oil-in-water emulsions prepared by myofibrillar protein	1.25, 2.5, 5, and 10 mg/mL	[95]
Fish protein				
Amur sturgeon (*Acipenser schrenckii*) skin gelatin	Peptides	Japanese sea bass (*Lateolabrax japonicus*) mince	25 ppm	[33]
Capelin (*Mallotus villosus*) protein	Hydrolysates	Cooked meat	3%	[32]
Gelatin from blacktip shark (*Carcharhinus limbatus*) skin	Hydrolysates	Cooked comminuted pork	100, 500, and 1000 ppm	[34]
Goby (*Zosterissessor ophiocephalus*) muscle	Hydrolysates	Turkey meat sausage	0.01–0.04%	[35]
Land-animal protein				
Camel milk	Hydrolysates	Minced fish	5% and 10%	[39]
Casein	Peptides	Ground beef/deboned poultry meat	20 mg/g	[37]
Deboned chicken residue	Hydrolysates	Cantonese sausage	2%	[40]
Milk protein	Peptides	Cooked beef	200 and 800 μg/g	[38]
Porcine blood	Hydrolysates	Pork meat emulsion	900 μg/g	[41]
Camel milk	Hydrolysates	Minced fish	5% and 10%	[39]
Whey protein isolate and soy protein	Hydrolysates	Meat patties	2%	[26]

In addition, land-animal protein is a good source for deriving antioxidant hydrolysates or peptides because its proteins contain plenty of essential amino acids with a high bioavailability that defeats plant proteins. The well-known antioxidant dipeptides of carnosine (β-alanyl-L-histidine) and anserine (β-alanyl-3-methylhistidine) endogenously exist in muscle tissue, acting as free radical scavengers and metal ion chelators [36]. As seen in Table 1, the land-animal protein sources were milk protein and slaughter remnant protein. Rossini et al. found that casein peptides exhibited a good antioxidative capacity in the 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical method [37]; a similar result was displayed in studies of bovine milk protein-derived peptides and camel milk hydrolysates [38,39]. Sun et al. reported that deboned chicken-residue hydrolysates decrease oxidation and Mallard reaction products in Cantonese sausage without significant influences of sensory properties [40].

Furthermore, Verma et al. proved that porcine-blood hydrolysate has possible antioxidant and antimicrobial abilities in pork meat emulsion [41]. The hydrolysate incorporation may have more opportunities to maintain multi-functional characteristics, i.e., antioxidation, antimicrobial, and physic-chemical property enhancements, than a single bioactive peptide. Thus, it has high potential in practice, especially in the food industry. Overall, those studies indicated that the antioxidative protein hydrolysate could be used to retard lipid peroxidation in oxidizable products, such as the unsaturated fatty acid-rich product. However, the optimal application should be further measured depending on the properties of the individual food system.

2.2. *Antimicrobial protein hydrolysates and peptides*

Microbial intrinsic antimicrobial peptides, known as bacteriocin, have been an interesting research subject for a long time and developing the foundation of modern antibiotics [42]. Nowadays, microbial peptides from probiotics are also applied to the entire food system [43], though food protein hydrolysates and peptides were not emphasized in this study. Pane et al. proclaimed that antimicrobial peptides could also be produced by enzymatic hydrolysis of food proteins *in vitro* [44]. The isolation and characterization of antimicrobial peptides from food proteins have also been well studied. Moreover, various antimicrobial agents, such as food protein-origin bioactive peptides and protein hydrolysates, are applied as bio-preservatives for different food products (Table 2). The antimicrobial activity of porcine blood protein hydrolysates was also observed against spoilage microbes, such as *Listeria monocytogenes*, *Staphylococcus aureus*, *E. coli*, and *Bacillus cereus* in the pork emulsion during storage [41]. It was reported that the whey acidic protein-derived peptide has good antimicrobial activity against *Staphylococcus aureus* in milk [45].

In most research cases, the antimicrobial activity of peptides was demonstrated only *in vitro* and not shown on any trials in commercial practices because food ingredients, such as proteins, proteases, fats, and metal ions, may limit the interaction of antimicrobial peptides with their target pathogens [42,46]. Therefore, before peptidic preservatives are introduced to the market, their stability during food processing and storage requires further assessment; potential safety and sensory problems also warrant an evaluation [47]. Moreover, the clean-label requirement in the market could push the industry or government to develop natural-origin (non-synthetic) food additives. From this point of view, food hydrolysates or peptides with an antimicrobial ability still require comprehensive study, and the real commercial application still has a long way to go.

2.3. Protein hydrolysates and peptides as food preservatives of edible biopolymer films

Recently, protein hydrolysates and bioactive peptides as food preservatives on green packaging materials, biodegradable and edible films and coatings have attracted much attention from food scientists. Rangaraj et al. reported that edible bioactive packaging materials had been applied to food storage and preservation [48]. The main function of food packaging systems is to separate food from the surrounding environment, thereby reducing interaction with spoilage factors, such as microorganisms, water vapor, oxygen, and off-flavor, and avoiding losses of desirable compounds, for example, flavor volatiles, thus extending the shelf life of food products [49]. Although coatings and edible films are not expected to replace conventional wrapping materials fully, they can retain food stability by reducing the exchange of moisture, lipids, volatiles, and gasses between the food and the surrounding environment. As we know, avoiding surface contamination increases the efficiency of food packaging, thus reducing the need for petroleum-derived polymers. The main components of biodegradable and edible films are usually an animal or vegetable proteins, polysaccharides, fats, and waxes. Meanwhile, they are primary packaging made from edible ingredients. Moreover, it is possibly used directly in the food system by coating, immersion, and spraying [50,51].

It has been reported that hydrolysates from fish by-products can be a source of biologically active peptides with high antioxidative activity (Table 3). The raw materials are mainly from cuttlefish, rainbow trout, silver carp, squid, and tilapia. An active two-layer coating consisting of furcellaran and gelatin hydrolysates from carp skins had been fully discussed [52–54]. Interestingly, many cases use hydrolysates and gelatin film from the same origin, which may be due to the concept of full application [55–59] (Table 3). It was demonstrated that milk protein-based edible films could be applied to preserve food products [56,57]. These selective films are effective oxygen, fat, and aroma barriers but are still permeable to moisture. Hence, they could be applied to various forms of high-protein dairy preparations, such as total milk protein powder, skim milk powder, caseinates, and whey protein concentrates [60,61]. Mukherjee and Haque (2016) proclaimed that antioxidative coatings incorporating cheddar whey casein hydrolysates could reduce the protein carbonylation in steak and fish fillet systems.

Various antimicrobial compounds incorporated into edible films have also been interesting, while integrating natural derivatives in edible films was

Table 2. Application of antimicrobial protein hydrolysates and peptides as a preservative in the food system.

Protein source	Hydrolysates or peptides	Incorporated food system	Amount of active ingredients	References
Snakin-1-derived from potato tubers	Peptides	Fanta orange, cranberry juice, and apple juice	50, 100, 200, and 400 μg/mL	[96]
Porcine blood	Hydrolysates	Pork meat emulsion	900 μg/g	[41]
Whey acidic protein	Peptides	Milk	31.2 and 15.6 μg/mL	[45]

Table 3. Effect of edible biopolymer films with the addition of protein hydrolysates and biopeptides on the quality of food products during their storage.

Source of bioactive hydrolysate or peptide	Type of biopolymer matrix	References
Carp skin gelatin hydrolysates	Polysaccharide-furcellaran film	[54]
Casein hydrolysates	Cheddar whey-based coating film	[56,57]
Cuttlefish (*Sepia Officinalis*) protein hydrolysates	Cuttlefish skin gelatin film	[58]
Gelatin hydrolysate extracted from *Scomberomorus commerson* skin	Fish skin gelatin, commercial gelatin, commercial bovine gelatin film	[59]
Rapeseed protein hydrolysates	Chitosan film	[97]
Squid gelatin hydrolysates	Squid skin gelatin films	[55]

successfully executed (Table 3). Although scientific results are abundant and remarkable, the gap between laboratory to commercial practices still warrants investigation. There is no individual natural polymer to provide all the desired edible film properties, so the challenge is to select integrated and synergistic composite ingredients to fulfill the desired film properties. Furthermore, there are difficulties in up-scaling the laboratory research to industrial applications. Consumer acceptance, industrial interests, and governmental regulations would be other challenges.

3. Bioactive ingredient of nutraceuticals

The global nutraceutical market was valued at USD 382.51 billion in 2019 and is expected to expand at a Compound Annual Growth Rate (CAGR) of 8.3% from 2020 to 2027 [62]. A favorable outlook toward increasing cardiovascular disorders and malnutrition application is observed [62]. The consumers' positive attitude toward functional foods fuels market growth because these added health and wellness benefits. Overall, rising concern about healthcare costs and the growing elderly population worldwide assist the global functional food industry. Besides, the rising disposable income, changing lifestyle, and shifting preferences for healthier dietary intake are expected to drive nutraceuticals in the Asia Pacific area, where the major market share was 31.01% in 2019 [62]. Jakubczyk et al. mentioned that bioactive protein hydrolysates or peptides are a trend as new sources of therapeutic strategy [63]. The main research targets on the biofunctions of bioactive protein hydrolysates or peptides could be divided into two categories: (1) antioxidation, anti-inflammation, and anti-apoptosis; (2) metabolic factor-related targets including anti-obesity, anti-diabetes, cardiovascular protection, and hypolipidemic effect. As we know, cardiovascular disease (CVD) and diabetes mellitus (DM) are two popular research topics, while metabolic syndrome is a crucial issue and challenge in human health worldwide. A summary of recent research is shown in Table 4.

3.1. Antioxidation, anti-inflammation, and anti-apoptosis

Antioxidation, anti-inflammation, and anti-apoptosis were proven to be highly correlated in organisms; thus, those bioactivities were summarized jointly [64–66]. According to a report from Chou et al. [67], the antioxidant activities of chicken-liver hydrolysates have been successfully developed. Continuously, the *in vivo* antioxidant activity of chicken-liver hydrolysates was displayed in a D-galactose-induced mouse model in which chicken-liver-hydrolysate supplementation performed the universal antioxidant activities, especially in the brain and liver (Table 4). This is a good example linking the *in vitro* and *in vivo* antioxidative effects, and it further indicates why *in vitro* antioxidative capacity analysis is still included in many studies of protein hydrolysates or bioactive peptides. Furthermore, the food-origin protein hydrolysates or bioactive peptides were proven to be tissue-specific protective effects in recent *in vivo* studies (Table 3), such as hepatic [68] and cardiac tissues [69,70]. Incidentally, chicken egg-derived peptides for their biological multi-activities, especially antioxidation, anti-inflammation, and hypoglycemic effects have been attracted much attention [71–74]. It was demonstrated that trypsin-digested ovalbumin hydrolysates show anti-inflammatory activity in LPS-treated RAW 264.7 cells [75]. In addition, the antioxidative peptides, VYLPR, derived from egg-white protein, protected HEK-239 cells from H_2O_2 exposure [76]. Finally, some cases showed both biofunctional and processing capabilities. For example, Wang et al. proclaimed that alcalase-hydrolyzed scallop protein hydrolysate exhibited high antioxidative activity in the PC-12 cell model as well as good foaming and emulsifying properties [77]. In addition, it effectively inhibited lipid oxidation in the emulsifying system. This means that food-origin bio-active hydrolysates or peptides could incorporate various functional products that fulfill both bio-functionalities and product quality control requirements.

Table 4. Recent research targets the functionalities of protein hydrolysates and biopeptides.

Protein resources	Hydrolysates or peptides	Functionality	Details	Ref.
Anti-oxidation, anti-inflammation, & anti-apoptosis				
Chicken liver	Hydrolysates	*In vivo* antioxidative effects in serum and organs in D-galactose injected mice	1.2 g D-galactose kg^{-1} BW + 50 and 250 mg CLH kg^{-1} BW on male C57BL/6 mice for 6 weeks	[67]
Chicken liver	Hydrolysates	*In vivo* antioxidation and anti-inflammation in thioacetamide-induced mice	100 mg TAA kg^{-1} BW + 200 and 600 mg CLH kg^{-1} BW on male Wistar rat for 10 weeks	[68]
Chicken liver	Hydrolysates	Cardiac muscle anti-inflammation in high-fat-diet-induced mice	HFD (46.5% energy as fat) + 170 and 510 mg CLH kg^{-1} BW on male C57BL/6 mice for 20 weeks	[70]
Potato protein	Hydrolysates	Cardiac muscle apoptosis attenuation in high-fat-diet-fed hamsters	HFD (60% of energy as fat) + 15, 45, and 75 mg CLH kg^{-1} BW on male hamster for 50 days	[69]
Ovalbumin	Hydrolysates	Anti-inflammatory activity in LPS-induced RAW264.7 macrophages	0.1, 0.5, and 2 mg OVA mL^{-1} in LPS-induced (100 g mL^{-1}) RAW 264.7 cells	[75]
Egg white protein	Peptides	Antioxidative effect in H_2O_2-induced cells	20 μm peptide (VYLPR) in HEK-293 cells	[76]
Scallop protein	Hydrolysates	Antioxidative activity and protective effect in H_2O_2-induced cytotoxicity *in vitro*	10 mg mL^{-1} SPH in DPPH and ABTS assays	[77]
Anti-obesity				
Chicken liver	Hydrolysates	Body weight gain decreases in HFD-induced mice	HFD (46.5% energy as fat) + 170 and 510 mg CLH kg^{-1} BW on male C57BL/6 mice for 20 weeks	[83]
Chicken breast raw materials	Hydrolysates	Mitochondrial β-oxidation enhancement and anti-inflammation in HFD-fed mice	HFD (59% of energy as lard) + CPH-contained diet (12.5%, w/w) on male C57BL/6JBomTac mice for 12 weeks	[81]
Crude chalaza of egg	Hydrolysates	Lipolysis and bile-acid biosynthesis enhancement and cholesterol clearance ability upregulation in high-fat-diet-fed hamsters	HFD (12% lard and 0.2% cholesterol, w/w) + 240, 480, and 960 mg CCH kg^{-1} BW on male hamster for 10 weeks	[82]
Alaska Pollack fillets	Hydrolysates	Hypothalamic neuropeptide Y reduction White adipose tissue weight decreases Muscle hypertrophy attenuation	AIN-93 control diet (7% fat, w/w) + 100 and 300 mg APP kg^{-1} BW on male Sprague–Dawley rats for 3 days	[79]
Yeast	Hydrolysates	Weight and body fat reduction in obese women	Asia–Pacific region women aged 20–60 years with BMI>25 kg m^{-2}/0.25 g YH-500 twice a day for 8 weeks	[80]
Anti-diabetes				
Chicken liver	Hydrolysates	Insulin sensitivity enhancement in HFD-induced mice	HFD (46.5% energy as fat) + 170 and 510 mg CLH kg^{-1} BW on male C57BL/6 mice for 20 weeks	[83]
Camel milk	Hydrolysates	Hyperglycemic, hyperlipidemic, and antioxidative effects in STZ-induced rats	100.500, and 1000 mg CMPH kg^{-1} BW in male STZ-induced diabetic rats for 8 weeks	[88]
Silver carp swim bladder	Hydrolysates	DPP-IV inhibition *in vitro* Insulin secretion improvement in INS-1 cells	INS-1 cell treated with 4 mM bioactive peptides (IPGSPY or WGDEHIPGSPYH) for 60 min	[87]
Egg white	Hydrolysates	Glucose homeostasis improvement *in vitro*	Insulin secretion by isolated Zucker rat pancreas islets (Experimental groups: Zucker lean rats, control Zucker fatty rats, and Zucker fatty rat treated for 12 weeks [750 mg HEW1 kg^{-1} BW per day])	[72]

(*continued on next page*)

Table 4. (continued)

Protein resources	Hydrolysates or peptides	Functionality	Details	Ref.
Egg white	Hydrolysates	Insulin sensitivity improvement in skeletal muscle cells	L6 cell treated with 5 mg mL^{-1} EWH or 11 μM IRW for 4 h	[89]
Grey triggerfish muscle protein	Hydrolysates	Hypoglycemic and hypolipidemic activities in diabetic rats	400 mg BPH kg^{-1} BW in male alloxan-induced diabetic Wistar rats for 21 days	[84]
Pasteurized liquid egg white	Hydrolysates	Insulin mimetic and insulin-sensitizing actions in 3T3-F442A cells	3T3-F442A cell treated with 5 mg mL^{-1} EWH for 72 h	[78]
Pasteurized liquid egg white	Hydrolysates	Glucose homeostasis improvement in Zucker fatty rats	Plasma glucose and insulin (Experimental groups: Zucker lean rats, control Zucker fatty rats, and Zucker fatty rat treated for 12 weeks [750 mg HEW1 kg^{-1} BW per day])	[72]
Liquid egg white	Hydrolysates	Insulin sensitivity enhancement in HFD-induced rats	HFD (20% fat, w/w) + EWH-contained diet (1, 2, and 4%, w/w) on male Sprague–Dawley rats for 6 weeks	[90]
Sea cucumber (*Holothuria Nobilis*)	Hydrolysates	Hypoglycemic, hypolipidemic, and insulin-sensitizing effects in STZ and HFD-induced diabetic rats	HFD (45% energy as fat) + 200 and 400 mg SCH kg^{-1} BW on STZ-induced male Sprague–Dawley rats for 8 weeks	[86]
Norwegian spring-spawning herring by-products	Hydrolysates	Hypolipidemic effect and glucose homeostasis improvement in obese Zucker rats	Fish protein (Herring or salmon) hydrolysate-contained diet (25%, w/w) in male obese Zucker fa/fa rats for 4 weeks	[85]
Cardiovascular protection				
Chicken blood	Hydrolysates	Anti-hypertensive effect *in vivo* ACE inhibition *in vitro*	100, 300, and 600 mg BCH kg^{-1} BW in male spontaneous hypertension rats for 4 weeks	[94]
Chicken liver	Hydrolysates	Hypolipidemic effect in high-fat-diet-induced hamsters	HFD (12% lard and 0.2% cholesterol, w/w) + 100, 200, and 400 mg CLH kg^{-1} BW on male hamster for 8 weeks	[98]
Chicken liver	Hydrolysates	Cardiac muscle anti-fibrosis in high-fat-diet-induced mice	HFD (46.5% energy as fat) + 170 and 510 mg CLH kg^{-1} BW on male C57BL/6 mice for 20 weeks	[70]
Chicken skin protein	Hydrolysates	Renin and ACE activity inhibition *in vitro*	1 mg mL^{-1} CTSH in ACE-inhibitory activity assay	[91]
Egg white	Peptides	Angiotensin II type I receptor downregulation *in vitro*	A7r5 cell treated with 5 mg mL^{-1} EWH or 100 μM synthetic peptides for 24 h	[92]
Egg white	Hydrolysates	The hypotensive effect in rats	EWP or EWH-contained diet (1%, w/w) in male spontaneous hypertension rats for 4 weeks	[93]

3.2. Anti-obesity

An anti-obesity property of food-origin hydrolysates or peptides was well reported as well, but the underlying mechanisms are various and inconclusive. Many researchers are still striving to clarify bioactive compounds and trying to connect structures and physiological outcomes. Jahandideh et al. revealed that bioactive peptides from egg white hydrolysate had an adipogenic-differentiating effect on the 3T3-F422A pre-adipocyte model [78]. Although the results are opposite and doubtful for its physiological meaning, they indicated the trend of structure–function studies of bio-functional food-origin peptides.

Table 4 contains the recent representative studies. Mizushige et al. found that Alaska-pollock-protein-hydrolysate supplementation decreases an energy intake in rats by reducing the mRNA expression of hypothalamic neuropeptide Y, which may reduce the appetite [79]. In another clinical case, low-dose yeast-hydrolysate supplementation was used as an obesity and weight-loss treatment among obese Korean women [80]. Although a further study for its mechanism is still needed, the anti-obesity effect was presented. The anti-obesity effects of poultry hydrolysates (i.e., egg chalaza, breast meat, and liver) were also reported, and the common mechanism was enhancing the lipolysis, fatty-acid β-oxidation, and energy expenditure in mitochondria [81–83]. Overall, the formulation of multiple bio-hydrolysates or peptides may be another exploration for future scientists.

3.3. Anti-diabetes

Diabetes is a dread for human beings because it directly damages patients' life quality. Certainly, there is a craving for anti-diabetic peptides. In Table 4, aquatic, egg white, chicken liver, and milk-derived hydrolysates or peptides are listed. It was indicated that Grey triggerfish (*Balistes capricious*) muscle protein hydrolysates can alleviate hyperglycemia and reduce HbA1c levels in diabetic rats [84]. Drotningsvik et al. obtained similar outcomes in their study of salmon hydrolysates [85]. Sea cucumber (*Holothuria Nobilis*) hydrolysates showed insulin-sensitizing effects in streptozotocin (STZ) and high-fat diet (HFD)-induced diabetic rats [86] while silver carp swim bladder hydrolysates inhibited dipeptidyl peptidase IV (DPP-IV) activity and enhanced insulin secretion *in vitro* [87]. In addition, the hyperglycemic effects of chicken-liver hydrolysates [83] and camel-milk hydrolysates are illustrated by a glucose tolerance test [88].

Remarkably, Garcés-Rimón et al. indicated that egg-white hydrolysates are a potential supplement to control complications associated with metabolic syndrome due to their DPP IV-inhibitory activity [72]. Moreover, egg white hydrolysates showed insulin-mimetic and sensitizing effects in the 3T3-F442A pre-adipocyte and skeletal muscle cell model [78,89]. Furthermore, the *in vitro* findings were verified in the *in vivo* studies. Egg-white-hydrolysate supplementation improved glucose metabolism and attenuated insulin resistance in diabetic rats via Akt activation [72,90]. All results indicated that egg-white hydrolysates had potential as a therapeutic diabetic agent.

3.4. Cardiovascular protection

In Table 4, Onuh et al. indicated that chicken-skin protein hydrolysates own an inhibitory ability on angiotensin-converting enzyme (ACE) activities *in vitro* [91]. In the cases of egg-white hydrolysates, Chen et al. successfully purified and identified the angiotensin receptor downregulating peptide, which was proven in the A7r5 cell model [92]. Moreover, the hypotensive effect of egg-white hydrolysates was confirmed in spontaneously hypertensive rats [93]. Besides, an *in vivo* anti-hypertensive property of chicken-blood hydrolysates was also demonstrated in the study of Wongngam et al. [94]. For bio-peptides, the lipid-lowering and hypolipemic properties may be concurrent with the anti-obesity property, and the details of lipid metabolic modulating hydrolysates or peptides were mentioned in the former paragraph. Wu et al. investigated the cardioprotective effects of chicken-liver hydrolysates in a long-term high-fat dietary habit [83]. Their study indicated that the cardioprotective effect of chicken-liver hydrolysates could be attributed to its synergistic hepatic lipid-lowering effect and systemic antioxidation. In the histological analysis, chicken-liver hydrolysate supplementation could attenuate cardiac pathological progression under long-term HFD induction. Meanwhile, the hypolipidemic, anti-obesity, and renal protective effects of chicken-liver hydrolysates against HFD were summarized. In addition, the anti-inflammatory and anti-fibrotic effects of chicken-liver hydrolysates on cardiac muscular tissues were confirmed. Those effects may be related to the early blockade of the autophagy pathway to prevent HFD-induced autophagosome accumulation. All works of evidence showed that the protective outcomes of the chicken-liver hydrolysates are due to systemic and synergistic effects. This study revealed the multi-activities and synergistic effects of hydrolysates, and a further application of bio-active hydrolysates and peptides need a comprehensive investigation.

Although several biofuncionalities of protein hydrolysates and peptides have been listed in this report, the delivery and stability of these benefits is still not clearly understood. In 2016, Rao et al. [99] also reported that the biofunctional availability and stability of the bioactive hydrolysates/peptides during postproduction still is a need to verify *in vivo*. They suggested two aspects on these two points: 1) the quality changes in different food protein hydrolysates during storage; (2) the resulting changes in the structure and texture of three food matrices. Hence, it is worthy for further investigation for the future commercial application. Meanwhile, those who possesses the key technology in following decades will get the ticket for global nutraceutical market, which is one of rapid growth industries nowadays.

4. Conclusion

Food preservation and nutraceutical ingredients are recent research targets of food protein-origin bioactive hydrolysates or peptides. However, the approaching method should be dynamic. Multi-activities, compound formulation, comprehensive evaluation, and the added value of by-products are possible strategies. Within the past few decades, there have been great results and findings regarding the functionalities of food protein-origin bioactive hydrolysates or peptides, but there are still efforts that are required to bridge laboratory studies with practical applications. Besides, there is a great need for the delivery and storage ability during the storage. Understandings and solutions for these two questions could benefit for future commercial application in the global nutraceutical market. Perhaps it is time to deal with these outcomes from different points of view, approaching the goal more comprehensively, creatively and with more novelty.

Conflict of interest

There are no conflicts of interest to declare.

Acknowledgements

We acknowledge funding of this research from the Great Billion Biotech, Co., Ltd. (New Taipei City, Taiwan), and partially from Ministry of Science and Technology, Taiwan (Project: NSC 102-2313-B-002-039-MY3 and MOST 109-2313-B-002-007-MY3), Council of Agriculture, Executive Yuan, Taiwan (Project: 106AS-1.3.2-AD-U4, 109AS-12.1.1-ST-a1, 110AS-2.2.2-AD-U1(1), and 110AS-17.1.4-ST-a1).

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