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Chapter

Food-Derived Opioids: Production and the Effects of Opioids on Human Health

Sevda Arısoy, Işık Çoban and Özlem Üstün-Aytekin

Abstract

Traditional opioids have been used for the people who suffer from cancer, burns, surgery, HIV/AIDS, and other serious illness pains for years. However, numerous side effects like dizziness, apnea, physical dependence, tolerance, addiction, nausea, and vomiting push the researchers to look forward to the new opioid options. The opioid peptides which derived from foods provide significant advantages as the safe and natural alternative. The researchers reported that it is also promising a new functional food and nutraceutical. In this chapter, the type of food-derived opioids, their origins, possible receptors, their amino acid sequences, opioid effects, production techniques, and health benefits are reviewed.

Keywords: food opioids, exogenous opioid peptides, bioactive peptides

1. Introduction

Opioids have been acting on endogenous and exogenous opioidergic systems of the human. Endogenous opioids are generated in the human body. The system consists of mu (μ), delta (δ), kappa (κ), and nociception receptors (**Figure 1**) and their ligands (β-endorphins, enkephalins, dynorphins, and nociceptin/orphanin FQ) [1, 2]. The amino acid sequence of these opioids is almost the same as YGGF, except nociception/orphanin FQ [3].

Exogenous opioid peptides can bind act like endogenous. The most popular sample of exogenous opioids is morphine. It is a strong opioid isolated from plants and produced synthetically [3]. The chemical structure of morphine consists of a benzylisoquinoline alkaloid with two additional ring closures (**Figure 1**). Morphine, in both injectable and oral fast-acting formulations, can be used for acute and chronic pain and acts directly on the central nervous system (CNS). The most common application area is pain due to cancer, burns, surgery, HIV/AIDS, and other serious illnesses [4].

During the past two decades, morphine consumption reached almost record level 523 tons in 2013 followed by codeine and thebaine as 361 tons and 246 tons, respectively. The United States was the leader with 57.3% of global morphine consumption and followed by European countries (22.5%) and Canada (7.7%) [5].

Increasing of morphine and/or other opioid consumption has parallel increases in opioid overdoses. Because of the adverse effects of the exogenous opioids on human health such as dizziness, apnea, physical dependence, tolerance, nausea, vomiting, and addiction, interest in morphine-like food-derived

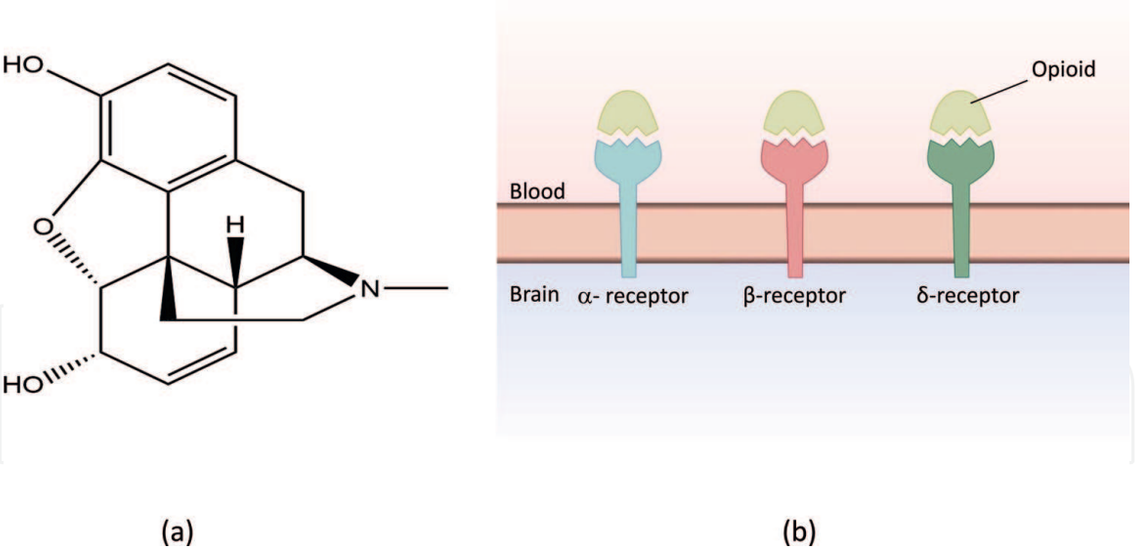

Figure 1.
(a) Chemical structure of morphine, (b) The opioid receptors in human body.

Opioid peptide	Source	Amino acid sequence	Opioid receptor	Opioid effect	Reference
β-casomorphine-4	β-Casein/milk	YPFP	μ	Opioid agonist	[6, 7]
β-casomorphine-5	β-Casein/milk	YPFPG	μ	Opioid agonist	[6, 7]
β-casomorphine-6	β-Casein/milk	YPFPGP	μ	Opioid agonist	[6, 7]
β-casomorphine-7	β-Casein/milk	YPFPGPI	μ	Opioid agonist	[6, 7]
Lactoferroxin A	Lactoferrin/milk	YLGSGY	μ	Opioid antagonist	[8, 9–11]
Lactoferroxin B	Lactoferrin/milk	RYYGY	κ	Opioid antagonist	[8, 9–11]
Lactoferroxin C	Lactoferrin/milk	KYLGPGY	κ	Opioid antagonist	[8, 9–11]
α-Lactorphin	α-Lactalbumin/milk	YGLF	μ	Opioid agonist	[12, 13]
β-Lactorphin	β-Lactoglobulin/milk	YLLF	μ	Opioid agonist	[12, 13]
Casoxin A	κ-Casein/milk	YPSYGLN	μ	Opioid antagonist	[6, 14, 15]
Casoxin B	κ-Casein/milk	YPYY	μ	Opioid antagonist	[6, 14, 15]
Casoxin C	κ-Casein/milk	YIPIQYVLSR	μ	Opioid antagonist	[6, 14, 15]
Casoxin D	α-Casein/milk	YVPFPPF	μ	Opioid antagonist	[6, 14, 15]
Serorphin	Bovine serum protein	YGFQNA	δ	Opioid agonist	[16, 17]
Hermorphin	Hemoglobin	YPWT	μ	Opioid agonist	[16, 17]
Gluteomorphine A4	Wheat protein	GYYP	δ	Opioid agonist	[6, 18]
Gluteomorphine A5	Wheat protein	GYYPT	δ	Opioid agonist	[6, 18]
Gluteomorphine B4	Wheat protein	YGGW	δ	Opioid agonist	[6, 18]
Gluteomorphine B5	Wheat protein	YGGWL	δ	Opioid agonist	[6, 18]
Gluteomorphine C5	Wheat protein	YPISL	δ	Opioid agonist	[6, 18]
Gluteomorphine 7	Wheat protein	YPQPQPF	δ	Opioid agonist	[6, 18]
Soymorphine-5	Soy protein	YPFVV	μ	Opioid agonist	[19–21]

Opioid peptide	Source	Amino acid sequence	Opioid receptor	Opioid effect	Reference
Soymorphine-6	Soy protein	YPFVVN	μ	Opioid agonist	[19–21]
Soymorphine-7	Soy protein	YPFVVNA	μ	Opioid agonist	[19–21]
Rubiscolin-5	Spinach protein	YPLDL	δ	Opioid agonist	[22–24]
Rubiscolin-6	Spinach protein	YPLDLF	δ	—	[22–24]
Oryzatensin	Rice protein	GYPMYPLPR	μ	Opioid antagonist	[8, 25, 26]
Ovalulin	Ovalbumin/egg	YPLDLF	δ	—	[8, 9–11]

Table 1.
Food-derived opioid peptides, amino acid sequences, opioid receptors, opioid effects, and production method.

opioid peptides, exorphins, has been increased by researchers. Exorphins are generated from exogenous proteins, such as milk, meat, cereal, plant, or egg by enzymatic digestion [3, 8]. They across the blood-brain barrier, interact with opioid receptors, and stimulate analgesic activity and sedative effect on the nervous system. Most of the food-derived exorphins were tested for the opioid activity, and amino acid sequences were identified. The results showed that the exorphins generally have a tyrosine (Tyr; Y) residue at the amino terminal end (except α-casein opioids) (**Table 1**).

On the other hand, due to the lack of digestive enzymes in some people and their sensitivities on opioids, food-derived opioid peptide consumption might be involved in some important diseases. For example, the increase in β-casomorphin formation from β-caseins of either human or cow milk has a correlation with the sudden infant death (SID) syndrome [27, 28]. After the penetration of β-casomorphins into the infants' immature central nervous system, the respiratory center in the brain stem may be inhibited, resulting in breathing abnormality, hypercapnia, apnea, and mortality [29]. Moreover, in atopic eczema (a relapsing skin disease prevalent on infants' face, knees, and elbows), induced immune cells form β-casomorphin from breast milk β-caseins, resulting in histamine secretion that causes allergic skin reactions. The reason for this is the lack of DPPIV enzyme which is negatively correlated with the amount of β-casomorphin [30]. The DPPIV enzyme is also effective on autistic children on the treatment of some symptoms (e.g., insensitivity to pain, digestion problems, attention problems) which are caused by the effects of β-casomorphins and gluteomorphins [31]. β-casomorphins may also cause depression which is a significant risk factor for cardiac patient men [32].

2. Bioactive peptides and generation of the opioid peptides

Food proteins provide numerous important biologically active peptides. These peptides can be released by gastrointestinal digestive enzymes during digestion, ripening processes or fermentation with proteolytic starter culture and hydrolyzing with commercial protease derived from microorganisms or plants [6, 33]. Many recent articles have been focused on the effect of bioactive peptides on human health. Generally, these peptides are known as specific peptide fragments that have a positive effect on human body systems, functions, and conditions depending on their amino acid composition and sequence [7, 34]. Oral administration of the bioactive peptides may affect the nervous, cardiovascular, immune, and digestive system. Opioid peptides are one of the most studied bioactive peptides (**Figure 2**).

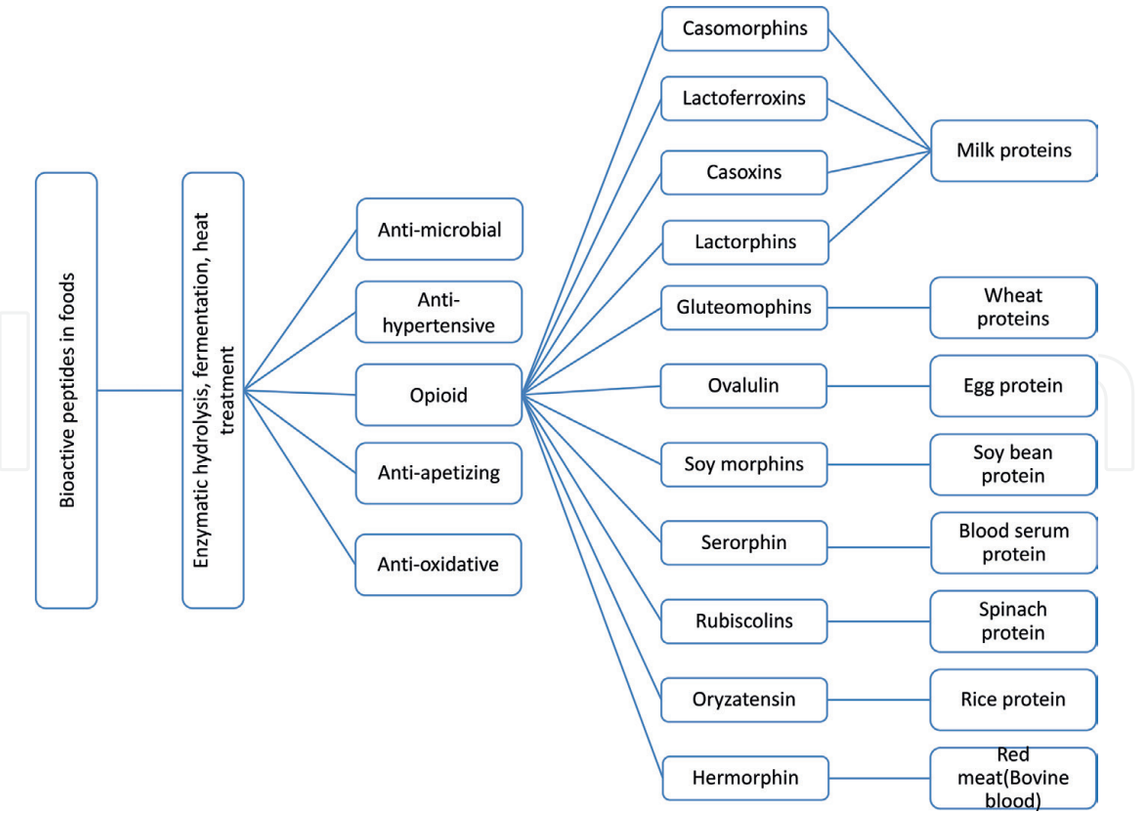

Figure 2.
Generation of bioactive peptides from foods and opioids.

3. Opioid peptides derived from animal protein

Because of the protein structures, milk proteins (80% casein; αS1-casein, αS2-casein, β-casein, and κ-casein and 20% whey protein; α-lactalbumin, β-lactoglobulin, serum albumin, immunoglobulins, and lactoferrins) have a great potential to occurrence of opioid peptides by fermentation, heat treatment, or enzymatic hydrolysis [35, 36]. Hydrolysis of these milk proteins lead to generate peptides that may have opioid activity. The milk-derived opioids have been named as β-casomorphins (β-casein), lactoferroxins (lactoferrin), casoxin (κ-casein, α -casein), α-lactorphin (α-lactalbumin), and β-lactophin (β-lactoglobulin) [9, 37]. β-casomorphins, the milk origin opioid peptides, were firstly detected in the infant's gastrointestinal system and blood plasma [10]. Then, the same structure was found in raw, processed sheep, buffalo, and human milk and fermented dairy products. The β-casomorphin group derived from β-casein consists of short-chain peptides such as β-casomorphin-4,-5,-6, and-7, and they act as opioid agonists on μ-type opioid receptors [9–11]. Researchers indicated that β-casomorphin is responsible for the calming effect of milk and stimulation of insulin and somatostatin release [12].

Lactoferrin is an iron-binding glycoprotein and known as a whey protein. It can be found not only in milk but also in secretion fluids such as tears, saliva, and synovial fluids. Lactoferrin is involved in many biological activities in human-like antimicrobial and anti-inflammatory effects and stimulating iron absorption [13]. After digestion, lactoferroxin A, B, and D forms are produced (**Table 1**). While lactoferroxins B and C act as an opioid antagonist to the κ-type receptor, lactoferroxin A acts opioid antagonists on μ-type opioid receptors. All lactoferroxin forms have weak opioid activities [8, 14–16].

α-lactorphin and β-lactorphin are derived from α-lactalbumin (bovine and human) and β-lactoglobulin (bovine), respectively. These two lactorphins are

opioid agonist to the μ-type receptor; they inhibit the angiotensin-converting enzyme activity (ACE) and have been shown to have a smooth muscle contracting effect [17, 38].

All κ-casein fragments are known as casoxins that are produced by digestion of bovine casein with pepsin and trypsin. Casoxins A, B, and C were obtained from κ- casein by the enzymatic digestion, and casoxin D was produced from α-casein in bovine milk. Casoxins are the opioid antagonist to μ-type receptor-like lactoferrins, and casoxin C have the highest biological potency, and researchers reported that it can inhibit the ACE activity [9, 39, 40].

Other opioid peptides from animal sources are serorphin, historphin, valentorphin, kapporphin, hemorphin, and ovalulin. Serorphin has a δ-type opioid receptor ligand with agonist activity and generated from bovine serum proteins by digestion with pepsin. Historphin (YGFGG) and valentorphin (YGFIL) are structurally similar to the serorphin which are derived from histone H4 and carboxypeptidases A and B, respectively. An effective opioid on peristaltic movement, bladder spasm, and pain management, hemorphin is derived from digested hemoglobin, passes the blood-brain barrier, and acts as an opioid agonist to μ-type receptors [41, 42]. Researchers have reported that there is very limited knowledge about the last two opioid peptides: ovalulin and kapporphin. The origin of ovalulin is ovalbumin that is an egg protein and synthesized as a homolog of rubiscolin (spinach opioid) [43]. Kapporphin (YSFGG) is derived from immunoglobulin κ-chain [18].

4. Opioid peptides derived from plant/cereal protein

Among the possible opioids in plants, the major opioids are gluten exorphins (gluteomorphins, gliadorphins) that consist of a combination of gliadin and glutenin proteins and are found in some grains such as wheat, rye, barley, and oats. Studies have shown that gluteomorphins act as opioid agonists on δ-type opioid receptors and consist of gluteomorphin A4, A5, B4, B5, C, and 7. These are resistant to the intestinal and enterobacterial proteinases, cross the human intestinal epithelium, enter the bloodstream, and interfere with the central nervous system [9, 43–47]. Gluteomorphin A5 has been associated with antinociceptive effect and modulation of memory process and affects peripheral nervous system and central nervous system. Takahashi et al. [19] and Fanciulli et al. [44] revealed that gluteomorphin B5 induced prolactin secretion after peripheral injection in rats. Gluteomorphin C reduced anxiety and developed learning ability after consumption [9]. Casomorphins and gluteomorphins are associated with autism spectrum disorder because these opioid peptides found in the urine samples of autistic patients and removing casein and gluten proteins from autistic children's diet may improve learning abilities, concentration, attention and language problems, eye contact, and digestion problems [21, 31].

Soy protein is one of the widely used cereals in foods for gelation, emulsification, and viscosity [3]. Soymorphins are derived from the soybean β-conglycinin β-subunit by digestion with pancreatic elastase and leucine aminopeptidase and act as opioid agonists' anxiolytic-like activity on μ-type opioid receptors. The opioid activity of the soymorphin is twice than β-casomorphin. Soymorphin fractions consist of soymorphin-5, soymorphin-6, and soymorphin-7 had anxiolytic effects with oral administration at doses of 10–30 mg/kg in mice [23]. Oral administration of soymorphin suppresses food intake, especially soymorphin-7 which is more effective in suppressing food intake than soymorphin-5 and soymorphin-6 [24]. Soymorphins inhibit anxiety and overeating and are also effective on glucose and lipid metabolism. Soymorphin-5 associated with decreasing triglycerides both the plasma and liver in diabetic mice [25].

Rubiscolins are derived from spinach protein by digestion with pepsin. Rubiscolin-5 and rubiscolin-6 are opioid agonist to δ-type receptor. Oral administration at different doses of rubiscolin-6 may have an analgesic effect and anxiolytic effect and stimulate food intake and memory consolidation in mice [26, 48, 49].

Oryzatensin is derived from digestion of rice albumin with trypsin and acts as opioid antagonists on μ-type opioid receptors, and also oryzatensin has an affinity to C3a receptors and immunomodulating activities [8, 50, 51].

5. Production of food-derived exogenous opioid peptides

Although food sources do not exhibit opioid activity in their own right, the peptide products of the proteins of these foods can exhibit opioid activity. For the efficient production of opioids by using food proteins as substrate, three different production methods were mentioned: chemical digestion, enzymatic gastrointestinal or commercial hydrolysis, and microbial production.

5.1 Chemical digestion

On the purpose of improving protein digestion and peptide formation, acid hydrolysis is applied to food protein-rich substrate. For cheeses (e.g., Mozzarella), the profile of produced bioactive peptide might be affected from the type of acid used for hydrolysis [52]. Conventional conditions for acid hydrolysis (6 M HCl treatment at 110° C for more than 24 h) can cause the destruction of amino acids (e.g., tryptophan) [53]. On the other hand, in the food industry, alkali treatment is quite rarely applied for protein hydrolysis because of the loss of protein digestibility [52] and it can reduce arginine, cystine, serine, threonine, lysine, and/or isoleucine content and form unexpected amino acid residual forms such as lanthionine or lysinoalanine. Because of the difficulty of controlling chemical processes and yielding products with modified amino acids, the other treatment methods (enzymatic, fermentation) are preferred in bioactive peptide productions [53].

5.2 Enzymatic hydrolysis

A common way to produce opioid bioactive peptides is enzymatic hydrolysis, and the production of opioid peptides via enzymatic hydrolysis is mostly carried out by using microbial enzymes (e.g., thermolysin, alcalase) and gastrointestinal enzymes (e.g., trypsin, chymotrypsin, pepsin, and pancreatin) [54–56]. In some studies, an increase in opioid activity was reported by using a combination of gastrointestinal enzymes and microbial enzymes [54, 55]. Moreover, the components of these combinations are also significant in opioid types and concentrations. For example, food proteins are hydrolyzed by pepsin to produce opioids. Besides, pepsin-thermolysin combination produces gluten exorphins A5, B5, A4, and B4, while trypsin-chymotrypsin-pepsin hydrolysate forms gluten exorphin C [54, 55]. The pepsin-elastase hydrolysate, with its 250 μg/g concentration, has almost 5 times higher gluten exorphin A5 concentration than pepsin-thermolysin hydrolysate (40 μg/g) [57]. Soymorphin-4 and soymorphin-5 are released from soy protein by the activity of elastase and leucine aminopeptidase; however, soymorphin-6 is released by pepsin and pancreatic elastase activity [43]. Enzymatic hydrolysis is carried out by the following method regardless of the food protein used (**Figure 3**): preparation of raw material for enzymatic hydrolysis (size reduction, etc.), homogenization in buffer, temperature, and pH adjustment to the optimum values of the enzyme, and hydrolysis of food product by enzyme (ultrasonic-assisted hydrolysis

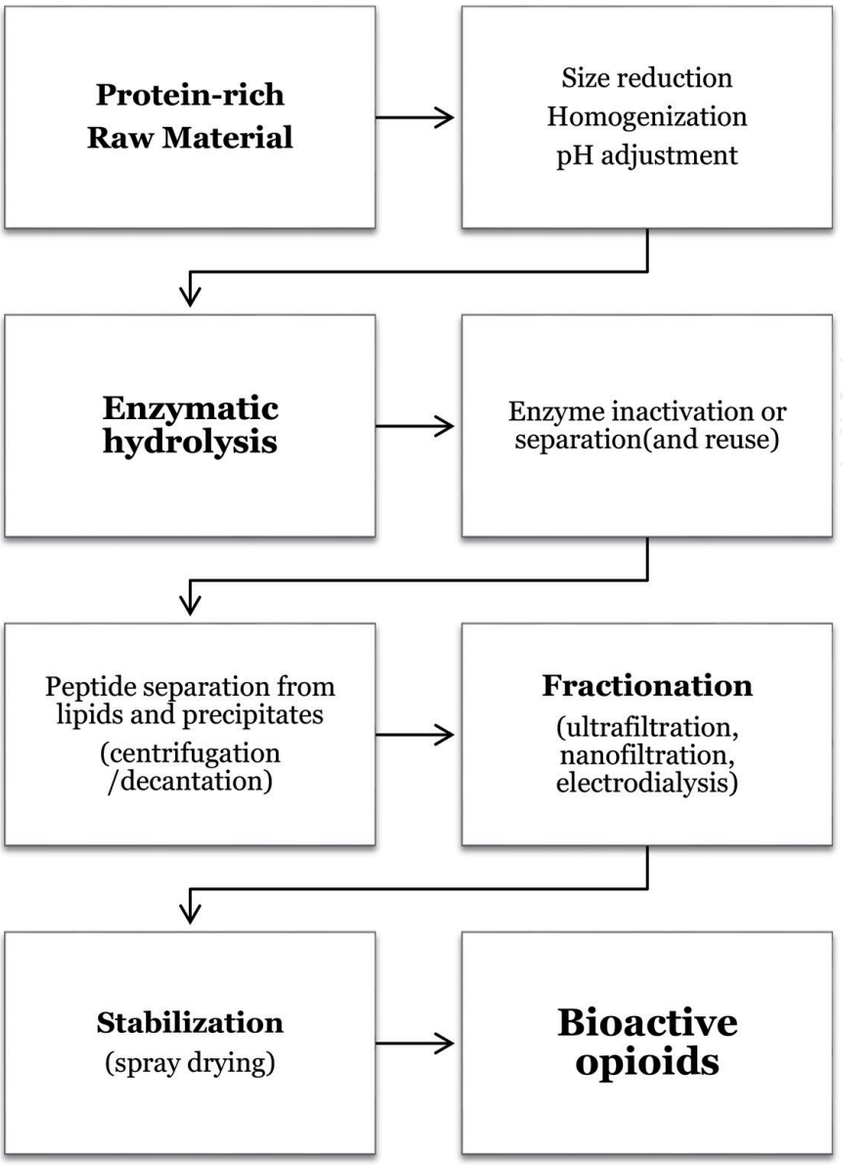

Figure 3.
Flow diagram to produce bioactive opioids.

for low molecular weight peptide production) [58, 59]. After inactivating or separating enzymes from hydrolysate, bioactive peptides are separated from the non-product residuals (e.g., lipids and precipitate) by centrifugation and decantation, subsequently fractionated (e.g., ultrafiltration, nanofiltration, electrodialysis), and then stabilized (e.g., spray drying) [60–62].

For producing desired peptides, using a proper enzyme and optimizing reaction conditions (e.g., time, pH, amount of the enzyme, temperature) are highly important [62]. For example, thermolysin enzyme obtained from *Bacillus thermoproteolyticus* has an optimum activation temperature range between 65 and 85°C and optimum pH between 5 and 8.5, while *Bacillus licheniformis* alcalase is active around 50°C and pH 8.

5.3 Microbial production

The use of protease-secreting microbial strains is an alternative method for chemical proteolysis and enzymatic hydrolysis for hydrolysis of food protein-rich substrates [63]. Enzymes secreted from microorganisms depending on the type of microbial production provide the secretion of opioids by hydrolyzing a protein-rich substrate [9]. The peptides produced during fermentation exhibit a high bioactivity

and better opioid functions. For the fermentation of protein-rich sources to produce bioactive peptides, *Lactobacillus* is one of the most widely employed genera [9–26, 38–63]. Due to the use of lactic acid bacteria, protein-rich substrates become acidified because of lactic acid production. Lactic acid existence in the production media provides a microbiologically safe environment for production and extent shelf life of the opioid product because of the organic acid feature of lactic acid [63]. *Lactobacillus helveticus* L89 X-prolyl dipeptidyl aminopeptidase (Pep X)-deficient mutant strain was used for milk fermentation to produce β-casomorphin-4 [64].

Enzymatic proteolysis of *Lactobacillus* GG-fermented ultra-high temperature milk substrate by pepsin and trypsin resulted in the release of some opioid sequences (RYLGYLE, YPFP, YPFPGPIPNSL, YGLF) [65]. *L. delbrueckii* ssp. *bulgaricus* and *S. salivarius* ssp. *thermophilus* produce β-casomorphin precursors from fermented yogurt. But they cannot produce β-casomorphin because of an inability of these bacteria to hydrolyze β-casein to β-casomorphin. *Bacillus cereus* and *Pseudomonas aeruginosa* are also able to produce β-casomorphin from the fermentation of milk. *Kluyveromyces marxianus* var. *marxianus* can produce β-lactorphin from whey [9].

In addition, it is possible to produce opioid peptides from fungi fermentation. In Brie, Gouda, Gorgonzola, Cheddar, and Fontina cheeses, β-casomorphin was also detected in different concentrations.

To sum up, opioid peptides are promising new exogenous opioids because they are free from adverse effects on human health. Due to this feature, there is a growing interest to elucidate the function of food-derived opioid peptides in the human body. The production techniques of food-derived opioid peptides are mostly based on hydrolysis of food proteins by using commercial or/and gastrointestinal enzymes. Also, some of the researchers conclude that food-derived opioid peptides may be carefully considered as new nutraceutical candidates.

Conflict of interest

No potential conflict of interest was reported by the authors.

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