Enzymatic protein hydrolysates in human nutrition

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Protein hydrolysates constitute an alternative to intact proteins and elemental formulas in the development of special formulations designed to provide nutritional support to patients with different needs. The production of extensive protein hydrolysates by sequential action of endopeptidases and exopeptidases coupled with the development of post-hydrolysis procedures is considered the most effective way to obtain protein hydrolysates with defined characteristics. This paper reviews the development and use of protein hydrolysates for dietary treatment of patients with phenylketonuria, food allergy and chronic liver failure. © 2001 Published by Elsevier Science Ltd. All rights reserved.

Medical diets are designed to provide complete or supplemental nutritional support to individuals who are unable to ingest adequate amounts of food in a conventional form, or to provide specialised nutritional support to patients with particular physiological and nutritional needs [1]. They supply all the required protein, fat, carbohydrates, vitamins and minerals in quantities sufficient to maintain the nutritional status of individuals receiving no other source of nourishment. Such formulations are designed to reduce or control diet-related chronic diseases such as atherosclerosis, cancer or liver failure, and also form the basis of special foods designed for the treatment of very different diseases such as phenylketonuria (PKU), cystic fibrosis, Crohn’s disease, food allergy and intolerance [2].

Great interest has been shown in the role played by dietary proteins in clinical diets and their use in specific formulations. Progress in the knowledge of food composition and biochemical analysis permitting validation of dietary methods has been extensively reported [3]. However, there are still significant difficulties in defining the relationships between protein requirements, nutrition and disease. Specific diseases affect protein requirements to different extents, and each disease process varies in intensity from individual to individual. It is known that adequate amounts of intact proteins cannot be administered to patients with impaired luminal hydrolysis, reduced absorptive capacity and specific stomach or hepatic failure. In allergic patients, the presence of intact or partially hydrolysed proteins can provoke immunemediated hypersensitive reactions. Two main ways to supply tailored amounts of amino acids are available: enzymatic protein hydrolysates [4] and a mixture of synthetic amino acids [5]. Enzymatic hydrolysis seems to be the most appropriate method for preparation of tailor-made peptides, not only because of their large-scale commercial availability and moderate cost, but also because of the high quality of such products [6].

Enzymatic protein hydrolysates containing short-chain peptides with characteristic amino acid composition and defined molecular size are highly desired for specific formulations. They show important advantages with respect to elemental diets, in which the protein component consists exclusively of a mixture of free amino acids. Protein absorption can occur as peptides as well as amino acids, indeed absorption as short-chain peptides (mainly, di- and tripeptides) is considered a more efficient method of amino acid absorption compared with an equivalent amount of free amino acids [7]. This is due to the availability of peptide specific transport systems and the subsequent terminal phase of peptide digestion into amino acids by the action of cytoplasmic peptidases within the enterocytes, before transport to the circulation [8,9]. On the other hand, peptides are less hypertonic than free amino acid mixtures, enabling good absorption of other dietary components and eliminating osmotic problems [10,11]. Moreover, because of chemical instability or insolubility in water, several amino acids...
(e.g., glutamine, tyrosine, cysteine) cannot easily be given in the free form.

The inclusion of protein hydrolysates in specific formulations is an area of growing interest (Table 1). Uses include clinical applications, such as geriatric products, high-energy supplements, weight-control and therapeutic or enteric diets [12]. The use of protein hydrolysates for the clinical treatment of patients with specific disorders of digestion [13], absorption [14,15] and amino acid metabolism [16] has been extended to patients with malnutrition associated with cancer, trauma and burns [13,17], and hepatic encephalopathies [18,19]. Because of their reduced antigenic activity, the development of hydrolysates for use in peptide-based hypoallergenic infant formulas, has been also extensively reported [20,21]. This paper describes the uses of enzymatic protein hydrolysates in specific formulations, their clinical applications and the current progress of food technology to supply these products assuring suitable food quality and safety.

**Enzymatic hydrolysis as a technological process**

Proteins, as a result of the cleavage of peptide bonds, are broken down into peptides of different sizes and free amino acids. This degradation, termed hydrolysis, can be carried out by enzymes, acids or alkali. Acid and alkaline hydrolysis tends to be a difficult process to control and yields products with reduced nutritional qualities. Chemical hydrolysis can destroy L-form amino acids, produce D-form amino acids, and can form toxic substances like lysino-alanine [22]. Enzymatic hydrolysis is developed under mild conditions of pH (6–8) and temperature (40–60°C), avoiding the extremes usually required for chemical and physical treatments and minimising side reactions. The overall amino acid composition of enzymatic protein hydrolysates is similar to that of the starting material [23]. Besides, protein hydrolysates show technological advantages such as improved solubility, heat stability and relatively high resistance to precipitation by many agents, such as pH or metal ions [24].

To develop commercial protein hydrolysates with defined physical, chemical and nutritional characteristics, many different factors must be taken into account.

**Table 1. Dietary uses of protein hydrolysates in human nutrition**

<table>
<thead>
<tr>
<th>Protein supplementation</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energetic drinks</td>
<td>Phenylketonuria (PKU)</td>
</tr>
<tr>
<td>Geriatrics products</td>
<td>Hypoallergenic infant formula</td>
</tr>
<tr>
<td>Sport nutrition</td>
<td>Acute and chronic liver disease</td>
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<tr>
<td>Weight-control diets</td>
<td>Short bowel syndrome</td>
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<td></td>
<td>Crohn’s disease</td>
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<td></td>
<td>Pancreatitis</td>
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<td></td>
<td>Ulcerative colitis</td>
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</tbody>
</table>

Among them, choice of suitable protein source, proteolytic enzyme/s and the development of post-hydrolysis processes have special relevance (Fig. 1).

**Protein source**

Cow’s milk protein is the most important protein source used in the development of protein hydrolysates designed for nutritional support of patients [7,16,21,25–28]. They are produced from isolated casein or from whey protein concentrate by using food-grade proteases. Because of their outstanding nutritional value, amino acid composition, commercial availability in large quantities and moderate cost, casein and whey hydrolysed formulas have been marketed for several decades.

Recently, plant proteins are finding commercial application in a number of formulated foods as an alternative to proteins from animal sources. Many studies have shown the interest of plant protein hydrolysates as functional foods and flavour enhancers [29–30]. However, it is only in recent years that the commercial applications of plant protein hydrolysates in supplementation of liquid foods or high energy beverages, production of hypoallergenic foods and development of medical diets for the treatment of specific illness have been remarkably increased [23]. According to criteria of nutritional quality and cost, many plant sources have been investigated for the production of protein hydrolysates in medical foods. Among plants, soybean is the source most widely used in special nutritional formulations [31]. Other legumes such as peas [30] and chickpeas [6,32] are becoming increasingly important as a source of edible proteins with interesting functional and nutritional properties [33]. Additional sources, including under-utilised by-products of the oil industry extraction, such as sunflower [34] and rapeseed [35] have been recently reported.

Plant proteins need to be processed prior to enzymatic hydrolysis. The excellent properties of plant protein concentrates and isolates as substrates for proteolytic enzymes are well known [32,36]. A high protein content and low levels of polyphenols, sugars and protease inhibitors facilitate the control of the hydrolytic process, increasing the effectiveness of proteolytic enzymes and the yield of the process. The main drawback of plant protein hydrolysates with respect to casein or whey hydrolysates is the low level of some essential amino acids (e.g. sulphur-containing amino acids in hydrolysates derived from legumes). They must be added to the formulation to reach the necessary standard amino acid profile.

**Proteolytic enzymes**

The use of enzymes allows good control of the hydrolysis and thereby the properties of the resulting products. Proteolytic enzymes hydrolyse the peptide linkage between amino acids, yielding a mixture of
peptides of different molecular size and free amino acids. The ability of enzymes to hydrolyse a protein substrate is highly variable. Therefore, the selection of suitable enzymes to produce compounds with defined physicochemical and nutritional characteristics is essential. Proteolytic enzymes are classified by their hydrolysing mechanism into endopeptidases or exoproteases. Endopeptidases hydrolyse the peptide bonds within protein molecules at random to produce relatively large peptides. Exoproteases systematically remove amino acids from either the N terminus or the C terminus by hydrolysing the terminal peptide bonds. Protein hydrolysates used in special formulations are composed of free amino acids, short peptides (di- and tripeptides) and normally do not contain any peptide longer than 12 amino acid residues (molecular mass ≈1500). To obtain such hydrolysates, a sequential reaction of endopeptidases and exoproteases is preferred. The initial use of endopeptidases facilitates the action of exoproteases in a second step to achieve a more complete degradation (Fig. 2).

Post-hydrolysis processes

In general, enzymatic hydrolysis can not provide per se a suitable product without the need for additional post-hydrolysis modifications. Many different post-hydrolysis processes have been successfully introduced into the production of protein hydrolysates (Table 2). The most common procedures are related to the control of molecular size and the elimination/reduction of bitterness in the resulting hydrolysates.

Control of the molecular size of resultant peptides constitutes an essential step in the development of protein hydrolysates for dietary use. In this context, ultrafiltration (UF) is known to be the most efficient post-hydrolysis procedure to remove residual high-molecular weight peptides and proteins. Besides, retention of the proteolytic enzymes in the ultrafiltration system eliminates the need for heat inactivation procedures at the end of the reaction. The use of UF membranes with a specific molecular weight cut-off value to reduce the antigen content of hypoallergenic formulas has been extensively reported [21].

A major hindrance to the use of protein hydrolysates is the unpleasant bitter flavour of some peptides, which can result in refusal by the patient. The bitter flavour of such peptides is attributed to their hydrophobic amino acid content. Bitterness is a critical parameter for the application of protein hydrolysates in special formulations and many procedures aimed at debittering protein hydrolysates have been reported. Examples include the removal of bitter peptides by adsorption or extraction, masking with other flavours, formation of plastein as

Fig. 1. Flow diagram for the development of enzymic protein hydrolysates used in clinical nutrition (modified from [21]).

![Flow diagram for the development of enzymic protein hydrolysates used in clinical nutrition (modified from [21]).](image)

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Addition of endopeptidase

Addition of exoprotease

Degree of Hydrolysis (%) vs Reaction time (min)

Fig. 2. Hydrolysis curve of chickpea protein isolate obtained by sequential treatment of endopeptidase (Alcalase) and exoprotease (Flavourzyme) enzymes (reproduced with permission from [32]).
well as release of hydrophobic amino acids from bitter peptides by exopeptidases [37]. Specific procedures have been reported to provide specialist nutritional support to patients with particular needs such as phenylketonurics or those suffering encephalopathias. These procedures will be discussed specifically in the next section.

**Main uses of protein hydrolysates in clinical nutrition**

At present, there are more than 100 formulas used in clinical nutrition. Some of them contain protein hydrolysates as the major protein component and are commonly used in the dietary management of phenylketonuria, food allergy and chronic liver disease.

Phenylketonuria (PKU)

Phenylketonuria, or hyperphenyl-alaninemia, is one of the most well known disorders of amino acid metabolism. It is caused by the autosomal recessive deficiency (less than 2% of normal activity) or absence of the hepatic enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine. Lack of this enzyme leads to phenylpyruvic acid accumulation in the blood. In the absence of treatment or when treatment is started late (after 3 weeks of age) intellectual and neurological damage is inevitable. However, when dietary treatment with phenylalanine restriction is started early, the child can achieve close to normal development [38]. Current data suggest that dietary restriction should be lifelong.

Dietary treatment of PKU was introduced in the early 1950s. Initial treatments indicated that young infants had a greater need for phenylalanine than had been previously recommended, recognising that the requirements were near normal [39,40]. At present, it is known that the majority of infants require a low-phenylalanine controlled diet to reduce phenylalanine intake to 50–70 mg kg⁻¹ body weight day⁻¹ and reduced levels to the interval 10–40 mg kg⁻¹ body weight day⁻¹ from 7 years through adulthood [41]. However, although general patterns are established, PKU patients show a broad spectrum of clinical and biochemical phenotypes which correlate with the phenylalanine hydroxylase genotype [42]. The importance of individualised diagnosis of PKU patients to provide objective and effective criteria for the dietary treatment of each particular case has been recently recognised [43].

The dietary management of PKU patients includes two different kinds of protein substitutes: (i) a mixture of free amino acids fortified with carbohydrates, vitamins and minerals, or (ii) infant formula which has a similar nutritional composition to normal infant formula milks using phenylalanine-free enzymatic protein hydrolysates as the main protein component. The use of such substitutes permits the addition of normal foods with low levels of phenylalanine to the daily diet, such as fruits, vegetables, juices and certain cereals [44]. Phenylalanine-free protein hydrolysates or protein hydrolysates with low levels of this amino acid have been used for treatment of phenylketonurics infants, with satisfactory physical growth and mental development [45,46]. They supply the majority of the protein requirements to PKU patients. Since PKU patients have the inability to convert phenylalanine to tyrosine, protein hydrolysates need to be supplemented to provide 100–120 mg tyrosine kg⁻¹ body weight daily. Rectification of such hydrolysates is possible according to European Community Regulation 231/91 [47] which states that amino acids may be added to improve the nutritional value of infant formula, but their addition is allowed only in a proportion that is considered useful to this purpose.

The development of protein hydrolysates for patients with PKU include post-hydrolysis procedures to remove phenylalanine such as the treatment by activated carbon or the use of ionic exchange resins [48,49]. Cogan et al. [50] developed a sequential enzymatic procedure (papain + pepsin) followed by activated carbon treatment to obtain protein hydrolysates with a substantial reduction of bitterness accompanied by a selective loss of phenylalanine (36%). Arai et al. [16] tested a series of enzymes on whey protein and achieved excellent results for phenylalanine removal using a pepsin–pronas system, followed by separation on G-25 Sephadex. Lopez-Bajonero et al.
[25] reported a sequential hydrolysis of casein using the protease 2A from *Aspergillus oryzae* and papain. These hydrolysates were passed through an activated carbon column to remove 92% of the total phenylalanine. The degradation of phenylalanine through its deamination with phenylalanine ammonia lyase (PAL) has also been reported [51].

Several infant formulas containing protein hydrolysates with null or low amounts of phenylalanine are commercially available. Lofenalac® (Mead Johnson, Evansville, USA) is widely used as a protein substitute for cow’s milk proteins in infants with PKU. This formula has as the protein ingredient an enzymatic protein hydrolysate of casein with levels of phenylalanine between 0.06 and 0.1% (approximately 75 mg/100 g of product). Acosta et al. [52] investigated growth and nutrient intake in 88 treated infants with phenylketonuria using Lofenalac as the major protein source. These authors found that such formula provided adequate essential amino acids and nitrogen to support normal growth in infants with phenylketonuria. A comparative studied showed no major differences using a phenylalanine-free protein hydrolysate in the treatment of children with PKU [45].

Food allergy

It is well known that allergy to cow’s milk protein is a serious problem for a particular population of infants, especially those genetically predisposed to develop an allergic reaction. In developed countries, the estimated prevalence of cow’s milk allergy ranges from 0.5 to 7.5% in children, resulting from the use of cow’s milk as the main source of protein [53]. Clinical manifestations include angioedema, urticaria, atopic dermatitis, respiratory symptoms, colic, diarrhoea, vomiting and anaphylaxis.

The basic and only effective treatment of cow’s milk allergy is complete elimination of cow’s milk proteins from a patient’s diet. In allergic infants and young children, alternative hypoallergenic substitutes are recommended. For more than 50 years, protein hydrolysates have been used as successful substitutes for cow’s milk proteins. Protein hydrolysates show a reduced or eliminated antigenic potential and are used together with other non-sensitising ingredients to develop specialised hypoallergenic products [54]. They have been reported to be safe for infants with documented cow’s milk allergy or intolerance, and sufficiently nutritious to allow normal growth and development. Another advantage is that protein hydrolysates are more palatable for a long period of time than a mixture of free amino acids.

Casein is considered the main protein source to develop hypoallergenic protein hydrolysates. For several decades, extensive protein hydrolysates of casein have been successfully used in the treatment of cow’s milk allergy. As cited above, to obtain such hydrolysates sequential enzymatic procedures are preferred to individual treatment with endopeptidases. The main drawback of such hydrolysates is its unpleasant odour and taste. The use of whey protein hydrolysates has been also used with success in the treatment of infants allergic to cow’s milk proteins [28]. They have shown a quite acceptable flavour for long-term consumption. Although concentrations of sulphur-containing amino acids, especially cysteine, are greater in whey than in casein, no nutritional advantage of whey protein hydrolysates over casein hydrolysate has been reported. The choice of casein or whey proteins in the development of formulations for infants allergic to cow’s milk proteins seems somewhat surprising given the fact that casein and whey proteins are the major allergens in cow’s milk [55,56]. The development of infant formulas based on protein hydrolysates from other sources has been suggested that may eliminate risk of adverse reactions in highly sensitive cow’s milk allergic infants [21].

The composition and immunologic properties of protein hydrolysates can not be controlled by hydrolysis alone. Additional procedures such as heat treatment and/or use of ultrafiltration membranes have been reported in order to develop true hypoallergenic protein hydrolysates. Heat treatment alone has only a moderate effect on allergenicity of cow’s milk proteins [57,58]; however, its use prior to hydrolysis affects the conformation of proteins, improving the access of proteolytic enzymes to yield hypoallergenic protein hydrolysates [59]. Ultrafiltration has been reported to be the most successful post-hydrolysis method to reduce the antigen content of hypoallergenic formulas [60]. Casein hydrolysates have been also subjected to extensive pre-clinical testing, demonstrating the non-antigenic nature of peptides of <1200 Da molecular weight [63]. The elimination of intact whey proteins and large peptides from a whey hydrolysate by UF treatment has been reported [61]; the process resulted in a six-fold reduction of allergenicity. Van Beresteijn et al. [27] found the minimum molecular mass required for whey derived peptides to elicit an immune response was between 3000 and 5000. Van Hoeyveld et al. [62] reported the minimal molecular mass for IgE-binding *in vitro* to be between 970 and 1400; however, the significance of this result to *in vivo* sensitisation and subsequent IgE cross-linking required for an immune response is unclear. The improvements in the ultrafiltration technique and the knowledge of the minimum size of peptides required to elicit an allergic reaction have allowed the development of a ‘new generation’ of hypoallergenic protein hydrolysates. These hydrolysates have reduced levels of free amino acids and a main protein fraction of short peptides improving the organoleptic characteristics of the end product [7].

Recently, the Subcommittee on Nutrition and Allergic Disease of the American Academy of Pediatrics [64] recommended that a formula be designated hypoallergenic
when the base protein has been modified to reduce antigenicity such that 90% of subjects with proven allergy to the base protein can tolerate the formula without symptoms. Although, using this criterion milk-based infant formulas classed as hypoallergenic are safe for ingestion by most children with cow’s milk allergy, they may still cause sensitisation or reaction in some allergic individuals. Indeed circulating IgE antibodies recognising protein fragments present in hypoallergenic formulas have been found in allergic children [65]. This may explain the occasional occurrence of severe reactions to hydrolysed formulas and raises doubts about their absolute safety [66]. Therefore, the use of hypoallergenic formulas in highly allergic patients should be initiated with caution and preferably under close clinical supervision so that appropriate therapy can be administered in the unlikely event of an allergic reaction [28,67]. Further studies will be necessary to investigate the presence of residual immunogenic epitopes in so-called hypoallergenic protein hydrolysates. Such epitopes can trigger severe anaphylactic reactions in children with cow’s milk allergy.

Liver diseases

The liver plays a key role in the metabolism of the nutrients essential for well being and for life. Complex alterations in the metabolism of proteins occur in patients with acute and chronic liver failure. Disturbances in protein synthesis and changes in the plasma amino acid composition have been extensively investigated [68]. These patients show a plasma amino acid imbalance characterised by high levels of aromatic amino acids (AAA: tyrosine and phenylalanine) and methionine, and low levels of branched-chain amino acids (BCAA: valine, leucine and isoleucine) [69,70]. Plasma molar ratio of BCAA to AAA, named Fisher ratio, has been used as an indicator of abnormalities in protein metabolism during liver disease as well as a guide in the clinical therapy of these patients. In normal individuals, this ratio is 3.5-4.0. In hepatic disease the ratio falls below 2.5, in hepatic coma it drops below 1.2, and in profound coma it is usually less than 0.8 [71].

Nutritional support plays an essential role in the pathogenesis and treatment of patients with chronic liver disease. Adequate provision of protein is necessary to enable protein synthesis and hepatic regeneration, as well as to supply metabolic substrate for immunologic host defence [72] and normalisation of plasma amino acid profile [18]. Protein requirements for patients with hepatic encephalopathy include high levels of BCAA, amounts of AAA below 2% by weight and a Fisher ratio higher than 20 [73]. Since no natural protein sources with these characteristics are available, patients are forced to take defined amino acid mixtures. Several investigators have reported the beneficial effects of BCAA-enriched solutions in the management of hepatic encephalopathy [18, 74–76]. These solutions provide a useful energy source, reduce plasma concentration of AAA, as well as preventing brain uptake through direct competition for a common carrier. BCAA act via two distinct mechanisms: firstly, by inhibiting transport of AAA across the blood brain barrier; and, secondly, by reducing AAA and ammonia outflow from muscles as a consequence of their regulatory effects on muscular protein turnover [77]. Cerra et al. [78] reported the therapeutic efficacy of modified amino acid mixtures enriched with BCAA to a level of 36% and deficient in AAA and methionine, in comparison with a standard treatment with neomycin in patients with chronic alcoholic cirrhosis. The group receiving the modified amino acid mixture demonstrated a statistically faster and more complete recovery as compared to the neomycin group, while maintaining nitrogen equilibrium. This improvement in patients with hepatic encephalopathy seems to be correlated with a normalisation in the plasma amino acid molar ratio [79].

Although synthetic amino acid mixtures are used in the dietary management of hepatic patients, alternative supplies of enzymatic protein hydrolysates with suitable characteristics are highly desired. To develop such hydrolysates, a complex strategy including the use of specific proteases and post-hydrolysis processes to separate peptides with an appropriate profile of amino acids is necessary (Table 3). Tanimoto et al. [80] reported a sequential reaction carried out by pepsin and pronase to increase the Fisher ratio of zein protein hydrolysates. Pepsin hydrolysed the protein fraction so as to localise aromatic amino acids at the N terminus or C terminus of the resulting peptides and, subsequently, pronase liberated the aromatic amino acids. Other specific proteases, such as actinase [80,81] and carboxypeptidase A [82] have been used to liberate terminal AAA. To remove AAA, liberated during the hydrolytic process, and AAA-rich peptides from protein hydrolysates, Sephadex G-15 adsorption chromatography might be carried out [19,80,81]. Removal of AAA decreases the bitterness of protein hydrolysates and increases the BCAA/AAA ratio.

Casein is the protein source most commonly used to develop enzymatic hydrolysates for nutritional applications. However, in the case of protein hydrolysates for patients with hepatic failure, protein sources with a higher level of BCAA amino acids are desirable. Zein [80] and sunflower globulins [82] have been proposed as excellent starting materials for the development of protein hydrolysates with high levels of BCAA and low content of AAA. In both cases, the resulting protein hydrolysates exhibited a high Fisher ratio (20 and 75, respectively), showing suitable characteristics to be included in the formulation of specific parenteral diets for patients with liver diseases.
Table 3. Changes in the Fisher ratio (BCAA+/AAA) during the development of sunflower protein hydrolysates for dietary treatment of patients with liver failure [82]

<table>
<thead>
<tr>
<th></th>
<th>Sunflower protein isolate</th>
<th>Globulin fraction + hydrophobic chromatography</th>
<th>Chymotrypsin hydrolysis + ultrafiltration 3 kDa</th>
<th>Carboxypeptidase-A hydrolysis + Sephadex G-15 chromatography</th>
<th>Flavourzyme hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCAA</td>
<td>19.2 ± 1.2</td>
<td>32.1 ± 1.7</td>
<td>33.0 ± 2.3</td>
<td>37.4 ± 2.2</td>
<td>37.6 ± 3.1</td>
</tr>
<tr>
<td>AAA</td>
<td>10.6 ± 0.8</td>
<td>5.3 ± 1.1</td>
<td>5.1 ± 1.3</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Fisher ratio</td>
<td>1.8</td>
<td>6.1</td>
<td>6.5</td>
<td>74.8</td>
<td>75.2</td>
</tr>
</tbody>
</table>

a BCAA, branched-chain amino acids (Val + Leu + Ile).
b AAA, aromatic amino acids (Phe + Tyr).

Future research needs

Protein hydrolysates with defined characteristics are major ingredients in special formulations to support specific clinical needs of patients. Although the manufacture of protein hydrolysates is a well-established process, there are a great number of clinical and technological issues to be clarified. They are summarised in the following points:

- To develop a better understanding of the structure–function relationship of peptides as well as their interactions with other components in the formula.
- New sources of proteins with suitable amino acid composition for use as starting material in the development of protein hydrolysates are required.
- Improvement of the palatability of protein hydrolysates, while maintaining nutritional value and safety, is required.
- A better knowledge of specific epitopes will be an essential step in explaining allergic reactions to hypoallergenic formulas.
- A need exists to increase the communication between food technologists and medical professionals; this will contribute to the development of more effective nutritional products for the management of specific disease conditions.

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