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Nutritional profiling of foods for Phenylketonuria

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A phenylalanine (Phe)-restricted diet is the only effective treatment in patients with classical phenylketonuria (PKU) in Latvia. This study analysed the protein and Phe content of 28 foods, including some Latvian-specific foods, aiming to expand the range of foods given to the Latvian PKU population. After consultation with Latvian parents and patients a list of preferred foods for analysis was collated. Preference was given to local foods and products were no or limited information about protein and Phe content was available. All food samples were collected from November 2023 until May 2024. Foods were analyzed by protein and amino acid content and compared with international databases. Phe content is reported as mg Phe/100 g of product. The highest amounts were found in microgreens from peas 200 mg/100 g, nettle 210 mg/100 g, wild garlic 140 mg/100 g.The Phe amount in garden cress and sunflower seed microgreen was 150 mg and 140 mg/100 g. A lower Phe content was found in radish 100 mg/100 g and broccoli microgreens: 97 mg/100 g. This study demonstrates that microgreens, and traditional products like sorrel and nettles should be measured within a Phe restricted diet. Rhubarb, celery stalk, raisins and leeks can be eaten without measurement or restriction.

Keywords Phenylketonuria, Diet, Amino acid, Inherited metabolic disorder, Nutrient

Inherited metabolic disorders (IMD) represent a diverse group of genetic conditions characterized by disruptions in metabolic pathways[1]. Phenylketonuria (PKU) is the most prevalent amino acid-related IMD, but other aminoacidopathies, such as tyrosinemia, homocystinuria, glutaric aciduria type 1, and maple syrup urine disease, also result from enzyme deficiencies affecting amino acid (AA) metabolism. Managing these IMDs typically involves adherence to a Phe-restricted diet, in PKU restriction of dietary Phe is essential to prevent the build up of toxic byproducts[2,3].

PKU is a rare IMD caused by defects in the phenylalanine-hydroxylase (PAH) gene, catalyzing the conversion of phenylalanine to tyrosine[4]. PAH impairment causes phenylalanine accumulation in the blood and brain, with a broad spectrum of pathophysiological and neurological consequences. If PKU is left untreated, it causes severe intellectual disability – intelligence quotient (IQ) < 50/developmental quotients < 20–40, epilepsy, psychotic behaviours such as severe hyperactivity, destructiveness, self-injuring behaviours, and agoraphobia. Anxiety, depression, speech difficulties, and neurological impairments (movement difficulties, tremor) also occur[5–9]. According to European Society of Phenylketonuria and Applied Disorders (ES.PKU) guidelines, treatment should be started as soon as possible, ideally before 10 days from birth. A 4 weeks' delay in starting treatment may lead to a decline in IQ score by approximately 4 points[10,11].

In Europe, PKU prevalence rates vary widely, in Latvia is approximately 1:6190 newborns[12], while the worldwide prevalence is 1:23,930[13]. The main treatment for PKU is a Phe-restricted diet; dietary restriction is severe with avoidance of foods such as meat, fish, eggs, lentils and peas, dairy products, grains, and aspartame-containing foods and medicine[14]. Patients with classical PKU have a low Phe tolerance of approximately 4 to 6 g of protein (200 to 300 mg Phe)/day; patients with mild PKU may tolerate approximately 7 to 10 g of protein and in case of mild hyperphenylalaninemia protein tolerance can be as high as 30 g/day of protein[10,14]. Around 85% of the Latvian PKU population have classical PKU, with approximately 15% with mild PKU[15]. A diet composed of < 30 g of protein will lead to nitrogen, vitamin and mineral deficiencies and to prevent this a Phe-free protein substitute, providing a comprehensive supply of vitamins, minerals and AA except Phe is taken 3 or 4 times a day. In classical PKU, they may provide up to 75% of total nitrogen requirements[14].

The dietary recommendations of PKU in Latvia, are based on the ES.PKU guidelines, with foods divided into three groups:

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- foods that are unmeasured or allowed without restriction i.e. specialized low protein foods and fruits, vegetables, with a Phe content of ≤ 75 mg/100 g,
- foods that can be consumed in limited quantities i.e. potatoes, green peas, corn, sour cream these are given in controlled amounts as part of an exchange system (Phe content > 75 mg/100 g and < 200 mg/100 g).
- foods that are high in protein/Phe are prohibited i.e. meat, fish, dairy products (cheese, cottage cheese), legumes, cereals, nuts, seeds, eggs, gelatine, aspartame (Phe content of > 200 mg/100 g)[10,14].

Based on E.S.PKU guidelines and the PKU dietary handbook, the Latvian dietary system uses indirect Phe calculation, where 1 g protein is equivalent to 50 mg Phe from fruits and vegetables[10,14].

The PKU diet is strict and limiting, so knowledge and reliable dietary information about the Phe content of food is crucial for optimal dietary control. It is important to validate which foods can be incorporated into the diet safely and which should be consumed in limited and measured amounts[14,16].

Dietary diversity is important, allowing variability, flexibility, and increasing the capacity to eat more foods socially[17]. Unfortunately, there is insufficient information about the Phe content of some specific Latvian foods, such as wild garlic, nettle, sorrel, and microgreens; these are used in substantial amounts in the diet and are not limited to food flavouring functions only.

Adherence to a low protein diet is frequently poor, and it is recognized as a challenge across most inherited metabolic disorders and different age groups, often worsening with age, especially in puberty[17,18]. This issue tends to be more pronounced in chronic conditions where the risk of acute metabolic decompensation is minimal, such as PKU, homocystinuria and tyrosinemia type I and type II. In contrast, for disorders like urea cycle disorders and maple syrup urine disease, poor dietary compliance can quickly lead to metabolic instability and its associated complications[19,20].

A comprehensive database on the Phe content of all fresh vegetables/fruits commonly consumed in Latvia is lacking, and so the protein content is used as a proxy measure of Phe content. For example, there are two food databases - FRIDA is the Danish food composition database maintained by the National Food Institute at the Technical University of Denmark, and Fineli is Finland's national food composition database, maintained by the Finnish Institute for Health and Welfare. Both databases are widely used for dietary assessment and research. For example, kohlrabi in the Fineli database contains information only about the protein content, but there is no data on the Phe content[21]. In the FRIDA database there is information on the Phe content in raw kohlrabi, but no information about when it is cooked or fried[22].

The use of microgreens has increased worldwide, including Latvia, in recent years due to their impressive nutritional content[23]. The microgreens can be added to salads and desserts. Larger quantities are often consumed by adding them to drinks like to smoothies. Unfortunately, there is no data about their Phe composition.

This study aimed to analyze the amino acid (including Phe) content of common Latvian foods (such as a variety of mushrooms, nettle, sorrel, rhubarb, leek, and microgreen), assessing their suitability for inclusion in a Phe-restricted diet for PKU.

Methods

Food selection for nutrition analysis

Caregivers and patients with PKU were invited to identify foods lacking sufficient compositional data via an online form. Ten caregivers and five individuals submitted responses, listing foods ($n = 55$) that present challenges for adhering to the dietary management of PKU. Subsequently, a team of four dietitians and three pediatricians, one internist reviewed the list and, following discussions with the caregivers, reached a consensus on which Latvian foods should be analyzed for their Phe content. A total of 28 foods were selected, with preference given to locally grown products. The study was conducted between November 2023 and May 2024.

Foods were collected (wild, tinned or frozen), vacuumed, and stored at a temperature − 18 C till analysis. For the analysis one kg of food was prepared. Methods of collection and preparation techniques of foods are mentioned below: (Table 1)

Amino acid analysis

All foods were analysed by *J.S. Hamilton Poland Sp. z o.o.* (LVS EN ISO/IEC 17025:2017). Fourteen of the AA were analysed by PB-53/HPLC - determining the profile of AA (in total - with peptide bonds and free AA) using pre-column reverse-phase high-performance liquid chromatography ranging from 0.005 to 10%.

Phe was determined in the unoxidized sample, which was hydrolyzed with a hydrochloric acid solution (C = 6 N). The AAs were converted to the corresponding phenyl thiocyanate derivatives and determined by reverse phase high-performance liquid chromatography with ultraviolet or diode array detector detection (wavelength 254 nm). The content of each AA in the test sample was determined by the internal standard method. The result was expressed as a mass fraction, in a percentage to two decimal places. Samples were analyzed according to the following norms and regulations: *PB-116 ed. III of 11 August 2020* for crude protein. The protein content of all 28 chosen foods was given by their total nitrogen content. The study analyzed the full amino acid composition of foods, which is a key strength, offering valuable insights into protein quality and nutrition.

Other nutrients (total energy, protein, fat and carbohydrates) concentrations were analysed using those methods (Table 2).

Results

After analysis, all 28 foods were divided into two groups: foods with a Phe content < 75 mg/100 g (Table 3), which is considered low-Phe concentration and foods can be consumed without measurement or restriction, and foods containing more than 75 mg/100 g, so should be measured and controlled as a source of natural Phe in the diet.

	Food	Methods of collection	Preparation
1	Aquafaba	Manufactured	From cane
2	Arugula	Manufactured	Fresh
3	Boletus edulis	Picked in harvest season	Frozen, tempered, cooked
4	Broccoli microgreens	Manufactured	Fresh
5	Celery root	Manufactured	Boiled
6	Celery stalk	Manufactured	Fresh
7	Champions mushroom (brown)	Manufactured	Cooked
8	Champions mushroom (white)	Manufactured	Cooked
9	Chanterelle	Picked in harvest season	Frozen, tempered, cooked
10	Coriander	Manufactured	Fresh
11	Garden cress microgreens	Manufactured	Fresh
12	Leeks	Picked in harvest season	Fresh
13	Nettle	Picked in harvest season	Frozen
14	Peas microgreens	Manufactured	Fresh
15	Poertabello mushroom	Manufactured	Cooked
16	Radish microgreens	Manufactured	Fresh
17	Raisins (black)	Manufactured	Dried
18	Raisins (gold)	Manufactured	Dried
19	Raisins (jambo)	Manufactured	Dried
20	Rhubarb	Picked in harvest season	Frozen
21	Russula emetica, boiled	Picked in harvest season	Boiled, frozen
22	Shiitake mushroom	Manufactured	Boiled
23	Sorrel, boiled	Picked in harvest season	Boiled, frozen
24	Sorrel, fresh	Picked in harvest season	Fresh, frozen
25	Spring onions	Picked in harvest season	Fresh
26	Sugar snap peas	Manufactured	Fresh
27	Sunflower microgreens	Manufactured	Fresh
28	Wild garlic	Picked in harvest season	Frozen

Table 1. Methods of collection and Preparation techniques of foods.

Chemical components	Source of method
Energy	Regulation (EU) No 1169/2011 of the European Parliament and of the Council
Sugars	Regulation (EU) No 1169/2011 of the European Parliament and of the Council
Fiber	AOAC 991.43:1994
Protein	PB-116 ed. III of 11.08.2020
Fat	PN-A-82100:1985 (withdrawn)
Fatty acid	PN-EN ISO 12966-1:2015-01; PN-EN ISO 12966-2:2017-05 except p.5.3 and 5.5; PN-EN ISO 12966-4:2015-07;

Table 2. Applied methods of laboratory analyses.

Low Phe concentration was observed in foods like prepared wild mushrooms, such as cooked chanterelle, contained 56 mg/100 g of Phe and 1.8 g/100 g of protein. Cooked *Boletus edulis* (contained 52 mg/100 g of Phe and 2.6 g/100 g of protein. Very low Phe content was observed in frozen rhubarb (9 mg/100 g), fresh celery stalk (21 mg/100 g), boiled celery root (28 mg/100 g) and fresh leeks (37 mg/100 g).

Phe content in raisins depended on the variety. Black and Jambo raisins had a Phe content of ≤ 75 mg/100 g, so they could be given in a Phe-restricted diet without measurement. However, golden raisins contained a higher Phe content of 86 mg/100 g.

All other amino acid analysis is given in Supplement 1. (Table 3)

From our analysis microgreens peas (200 mg/100 g) and nettles (210 mg/100 g) had the highest Phe content (See Table 2). A high Phe content > 75 mg/100 g was also identified in wild garlic (140 mg/100 g), and sorrel (fresh and cooked 120 mg/100 g). Garden cress and sunflower seed microgreens contained 150 mg/100 g and 140 mg/100 g respectively, while radish and broccoli microgreens contained 100 mg/100 g and 97 mg/100 g. The highest concentration of Phe between cultivated mushrooms was observed in cooked Champignon (both

Foods	Energy (kcal/100 g)	Carbohydrates (g/100 g)	Fat (g/100 g)	Protein (g/100 g)	Phe (mg/100 g)
Spring onions, fresh	18.2	1.9	0.2	2.2	71
Raisins (black)	329.2	74.9	1.6	3.8	69
Shiitake mushroom, boiled	20.5	2.3	0.5	1.7	64
Sugar snap peas, fresh	29.3	4.1	0.1	3.0	63
Aquafaba (Chickpea cooking water)	28.6	3.1	1.0	1.8	57
Chanterelle, frozen, tempered, cooked	23.3	0.2	1.7	1.8	56
Boletus edulis (cep), frozen, tempered, cooked	27.8	1.2	1.4	2.6	52
Raisins (Jambo)	330.6	76.7	1.8	1.9	42
Leeks, fresh	29.3	5.9	0.1	1.2	37
Celery root, boiled	18.3	3.0	0.3	0.9	28
Celery stalk, fresh	16.5	3.4	0.1	0.5	21
Rhubarb, frozen	13.8	2.1	0.2	0.9	9

Table 3. Nutritional data of foods with phe content below 75 mg/100 g.

Foods	Energy (kcal/100 g)	Carbohydrates (g/100 g)	Fat (g/100 g)	Protein (g/100 g)	Phe (mg/100 g)
Nettle, frozen	41.4	3.8	0.6	5.2	210
Peas microgreens, fresh	33.3	0.8	0.5	6.4	200
Garden cress microgreens, fresh	18.8	0.3	0.4	3.5	150
Champignon mushroom (brown), cooked	89.9	0.8	7.5	4.8	150
Sunflower microgreens, fresh	55.5	1.5	3.9	3.6	140
Wild garlic, frozen	34.2	4.0	0.6	3.2	140
Portobello mushroom, cooked	87.3	0.2	7.7	4.3	120
Sorrel, fresh, frozen	21.9	1.5	0.3	3.3	120
Sorrel, boiled, frozen	18.6	0.2	0.6	3.1	120
Arugula, fresh	13.4	0.2	0.2	2.7	110
Coriander, fresh	15.8	0.8	0.2	2.7	110
Radish microgreens, fresh	23.8	1.4	0.6	3.2	100
Champignon mushroom (white), cooked	67.1	1.1	5.5	3.3	100
Broccoli microgreens, fresh	21.1	0.7	1.1	2.1	97
Raisins (golden)	329.2	78.4	0	3.9	86
Russula emetica, boiled, frozen	29.2	2.3	1.2	2.3	81

Table 4. Nutritional data of foods with Phe content above 75 mg/100 g.

brown and white): 150 mg and 100 mg per 100 g, respectively; Portobello mushrooms are also high in Phe: 120 mg/100 g. (Table 4)

Discussion

This is the first publication to describe the AA analysis of foods chosen by patients with PKU and caregivers in Latvia. These include specific foods like nettles and sorrel, which are used in traditional Latvian dishes, and microgreens, which have become more popular in recent years. The detailed analysis, including Phe, leucine, methionine, and tyrosine, might benefit other amino acidopathies requiring an amino acid-restricted diet.

Nutritional data describing the AA content in traditional foods not only helps to ensure safety and diversity of dietary treatment for patients with disorders of AAs but can also contribute to greater dietary accuracy and support. This allows people with PKU and other aminoacidopathies to safely eat traditional foods.

Expanding data on the nutritional value of local foods means that these foods can be safely incorporated into the Phe-restricted diet and can be used to provide healthy nutrition. One of the most difficult challenges for patients and their caregivers is to exclude high-protein foods from the diet, reducing their food choices. Another issue (particularly in Latvia) is the limited variety of special low-protein food available at the market. Also, there are concerns about the nutritional value of low-protein foods, which are high in carbohydrates and sugars[20]. Including low-Phe nutritious-rich products like rhubarb, and different types of mushrooms, celery root and stalk, leek, nettle, sorrel, and microgreens in limited amount helps to enrich both dietary variety and the micronutrient content[24].

Microgreens are eaten fresh and frequently used as garnishes. They add vibrant colour, texture, and flavour to dishes while also offering health benefits[25,26].

The microgreens contain an abundant amount of different phytonutrients, varying according to the nature of the plants that are selected to produce the microgreen. They are source of micronutrients such as magnesium, potassium, calcium, iron, vitamin A, vitamin B, C and vitamin K[27]. They also have reported antioxidant activity, anti-obesity, diabetic and cholinergic activity[26,28,29]. There is limited information about microgreen's protein and AAs content. For example, in the FRIDA[22], there is no available information, but in the USDA, only data about the protein content of broccoli microgreens is available. This information is controversial because they contain 0 g/100 g protein according to the USDA[30], which is different from our data (the protein content is 2.1 g/100 g, and Phe content is 97 mg/100 g). More testing of microgreens is necessary[28,31]. Our data describing the protein content of broccoli and radish microgreens is like data that was published by Dereje et al. in 2023, who described the protein content as 2.23–3 g/100 g and 1.81–2.58 g/100 g respectively[26]. Recently published data by Boyle et al. also reported that broccoli microgreens contained Phe > 75 mg/100g[32].

Surprisingly a high protein and Phe content was observed in golden raisins, Phe content was 86 mg/100 g. A mean for 3 different types of raisins was protein content 3.2 g/100 g and mean Phe concentration 65 mg/100 g. Similar results were reported by Boyle et al., where mean Phe content of raisins (all types) was 59 mg/100g[32] This is also similar to the USDA, with available information describing their Phe content as 65 mg/100 g and protein content 3.07 g/100 g. Previously, it was reported that protein quantity was 2.2 g/100 g and Phe content was 97 mg/100g[21,33], although in the PKU dietary handbook, raisins are included in the list of fruits and vegetables that are allowed without measurement in PKU[14]. The PKU diet is already very challenging, so it is important that any dietary advice should be practical and straightforward. It may cause confusion if there are different rules for different types of raisins, but at the same time it may underestimate the amount of Phe eaten[34].

As we report, the Phe content of leeks is 37 mg and protein is 1.2 g per 100 g; in the FRIDA, Phe concentration was 50 mg/100 g, and protein content there is also reported higher – 2 g per 100 g, there is also data available about protein content in USDA about leeks – 1.57 g per 100 g, but there is no data about Phe concentration, data of protein in our study is similar to USDA information.

Mushrooms have a unique nutritional composition with positive health benefits. Mushroom's dry matter is rich in carbohydrates, including both digestible (trehalose, glycogen, mannitol, and glucose) and non-digestible carbohydrates (chitin, mannans, and β-glucan). They are a complete protein source, containing all essential AAs, and are high in polyunsaturated fatty acids. As the only vegetative source of vitamin D, mushrooms also provide a good amount of B vitamins and various minerals, making them a powerhouse of nutrients for human physiological functions[35–38]. There is a wide range of Phe concentrations among different types of mushrooms. For example, boiled shiitake mushrooms contain only 64 mg of Phe/100 g, while cooked Portobello, white, and brown Champignon mushrooms contain 120 mg, 100 mg, and 150 mg per 100 g, respectively, and should be counted in a Phe-restricted diet. Traditional mushrooms for Latvian PKU patients, such as *Boletus edulis* and chanterelles, are low in Phe. However, there is limited information on the Phe content of *Boletus edulis*. Our data indicate a protein content of 2.6 g/100 g, which aligns with findings published by Jaworska et al.[39] As of January 2025, there was no published information about the Phe content of *Boletus edulis mushrooms*, White mushrooms, and brown mushrooms in USDA and FRIDA databases. Previously, in Latvia, mushrooms like shiitake and white and brown Champignons were allowed without measurement, but *Boletus edulis* and Chanterelles were allowed in limited amounts in the PKU diet. The latest data on the Phe content of mushrooms suggests that repeated testing is needed to verify the Phe content in different types of mushrooms.

A low-protein diet can lead to a reduced feeling of satiety, which may cause individuals to consume larger quantities of other foods, such as potatoes, potentially impacting metabolic control. Incorporating various mushrooms into the diet could help individuals with PKU experience a greater sense of fullness due to their fibre content[40]. Many people with PKU often express that it is challenging to achieve satiety with low-protein foods and vegetables[41–44].

Nutritional data about Latvian traditional foods like sorrel, wild garlic, and nettle are also very limited in international food databases; for example, there is no data about the Phe content of nettles in the USDA, FRIDA or Fineli.

A comparison of the data from our study with food databases is presented in Table 5 .

Without AA data, dietitians are unable to advise about the suitability of these products. Confidence in the Phe analysis is essential for patients with PKU. Reliable measurements ensure that dietary treatment maintains safe Phe concentrations, preventing neurological damage and supporting optimal cognitive and physical development. This confidence is vital for long-term management, where consistent monitoring is required to adapt to changes in a patient's age, metabolism, and lifestyle.

Unfortunately, patients with PKU often exhibit neophobia, which makes introducing new products and flavours into their diets a challenging task. Therefore, it is crucial to incorporate as many allowed products as possible early in life, particularly during the first few years[45]. This strategy aims to expand the child's menu to include items from both the allowed and in limited amount consumed food lists[46–48].

One limitation of the study is that the nutrient analysis was conducted during just one season, which could be influenced by climate; therefore, it is recommended to evaluate the same local products collected across different seasons. Another limitation of this study is that the nutritional value of the products was analyzed in a single

Food Item	Phe (mg/100 g) –	Protein (g/100 g)	FRIDA (Phe/protein)	USDA (Phe/protein)
Broccoli microgreens	97	2.1	N/A	0 g protein
Radish microgreens	100	3.2	N/A	N/A
Golden raisins	86	3.2	N/A	65 mg Phe, 3.07 g protein
Raisins (mean of 3 types)	65	3.2	N/A	65 mg Phe, 3.07 g protein
Leeks	37	1.2	50 mg Phe, 2.0 g protein	1.57 g protein

Table 5. Comparison of Phe and protein content with food Databases.

laboratory. To ensure confidence in the nutritional analysis, it is essential to repeat the analyses in a different laboratory.

The way foods were stored, duration of storage, and cooking technique can affect the nutrient content. For example, sorrel dries very quickly and consequently, it was not possible to deliver it raw to the laboratory. Therefore, it had to be frozen to ensure transportation, and this will affect the amount of water, protein and Phe in the product. Comparing fresh, frozen, and cooked forms of each food could help assess the impact of storage and preparation methods on protein and Phe content. Also standardized protocols for sample handling and transportation should be established to minimize nutrient loss.

By actively involving patients with PKU and their caregivers, our study ensures that the research is based on the real-life experiences of patients and the needs of the PKU community. It also helps develop practical dietary recommendations that can improve the quality of life for individuals with PKU.

This research expands the range of dietary options available to PKU patients, allowing them to maintain nutritional balance while adhering to the strict and limiting Phe-restricted diet.

Our work advances PKU dietary research, enhances patient support, and promotes healthier food choices tailored to specific medical needs.

Conclusion

It is important for patients with PKU to expand the range of foods, that can be added to their diet. Such foods like rhubarb, celery root, stalk and leek have the lowest Phe concentration and can be consumed without measurement, while foods like nettle, peas microgreens and champignons mushrooms have the highest Phe levels and should be counted in the low-Phe diet.

It is essential to continue assessing the nutrients in both traditionally used products and new foods entering the global market. This will provide patients with reliable and current information about the nutritional composition of food products. Also, it will improve patients' adherence to a Phe-restricted diet; it is crucial to provide accurate and comprehensive information about the nutritional content of food products, including not only protein but also their phenylalanine concentration.

Data availability

All data supporting the findings of this study are available within the paper and its Supplementary Information. Methods of collection and preparation techniques of foods are available in Supplement 1. Information about applied methods of laboratory analyses is available in Supplement 2 and data about amino acid content in foods are provided in Supplement 3.

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Author contributions

O.Lubina wrote the main manuscript text. M.Auzenbaha design and reviewed the work.S.Laktina and L.Gailite worked on the interpretation of data, and L.Gailite also reviewed the manuscript.A. MacDonald and A. Daly substantively revised the manuscript.

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