

Evaluation and acceptability of alternative food recipes for patients with phenylketonuria

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Summary

Phenylketonuria (PKU) is an inborn error of metabolism, treatment of which is based on phenylalanine restriction diet. This study aimed to identify studies with developed recipes and food products as well as sensory analysis for patients with PKU. The search was performed in Coordination Agency for Advanced Training of Graduate Personnel (Capes – Brasília, Distrito Federal, Brazil), National Library of Medicine (PubMed – National Institutes of Health, Bethesda, Maryland, USA), Latin American and Caribbean Health Science Literature (Lilacs – São Paulo, Brazil) and Cochrane Library (Cochrane – London, United Kingdom). Articles were selected in these databases without date restrictions. After the filter addition and through the selected articles' list of references, 12 articles were included in this study with recipes and food for patients with PKU (bakery products, dairy beverages and juices). The results suggest that the production of PKU foods was feasible and could be made at home, since these food preparations were easy and contained low-cost ingredients. Results also suggest that more food surveys are carried out in periphery countries, where special products are difficult to find and expensive to purchase, besides improving viable food preparations in the family environment.

Keywords

phenylketonuria; phenylalanine restriction; phenylketonuria recipes; sensory evaluation

Phenylketonuria (PKU) is an inborn error of metabolism which is caused by the deficiency of the enzyme phenylalanine hydroxylase (PAH). PKU is the most common inborn error of metabolism, with a global prevalence of approximately 1:15000 live births and is considered a rare disease. Statistics may vary depending on the analysed population [1]. Patients with this condition have increased plasma concentration of phenylalanine (Phe) and low concentration of tyrosine (Tyr), as Tyr is the product of PAH-Phe interaction. Phe is an essential amino acid and its intake is important for protein synthesis, besides forming other compounds in the human organism. Tyr is the precursor of multiple metabolic products, as catecholamines, melanin and thyroxine [2], which makes its plasma concentration levels an important marker to be monitored. The diagnosis of the disease is confirmed by blood test, in which

the blood Phe concentration must be higher than $120 \mu\text{mol}\cdot\text{l}^{-1}$ ($2 \text{ mg}\cdot\text{dl}^{-1}$) [3].

The mainstay of PKU treatment is a life-long diet with Phe restriction, depending on individual characteristics, namely, gender, age, tolerance, serum blood levels. Therefore, professional assistance through all life stages is essential to avoid complications related to the disease's course [4]. The foods allowed in the diet for PKU have low protein content and Phe must be controlled to not overpass the recommended limit (0–20 mg Phe per 100 g of food) [5]. Duo to such restriction, these patients frequently eat foods with low nutritional value such as candies, lollipops, honey, soft drinks, or desserts. In addition, it is necessary to have daily intake of specific protein formulae, restricted in Phe, to balance the low allowance of regular dietary protein [6]. It is advised to start the restricted diet and the Phe-free amino acid formu-

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la before the 10th day of life to avoid neurological deficiency [7].

The composition of Phe-free amino acid formula includes amino acids (except for Phe), vitamins and a number of trace elements, being adequate to substitute foods of high protein value and suitable for daily consumption of PKU patients. It is estimated that the Phe-free amino acid formula can achieve from 75 % to 95 % of the daily protein intake [8]. For a proper prescription, the Phe-free amino acid formula and the diet must be administered according to one's individual needs and tolerances. GULDBERG et al. [9] classified the individuals according to their tolerance to ingested Phe to:

- classic PKU, tolerance between 250–350 mg per day,
- moderate PKU, tolerance from 350–400 mg per day,
- mild PKU, tolerance from 400–600 mg per day.

Although the Phe-free amino acid formula is a food easy to be included in the patient's routine, it has an unpleasant odour and taste, making it difficult for adherence to treatment.

Recently, new alternative PKU treatments have emerged, namely, tetrahydrobiopterin (BH₄) and glycomacropeptide (GMP) [10]. BH₄ is a co-factor needed for the PAH enzyme, that converts Phe to Tyr, and the treatment aims to improve the enzyme's activity and Phe tolerance. GMP is a protein found in a fraction of whey, and its pure form does not contain any Phe [4].

The basic treatment for PKU patients consists of a PHE-restricted diet, which is extremely limited, and, in many countries, there is a limited supply of specific food preparations for PKU. Therefore, the present study aimed to identify studies that developed recipes for PKU and, besides the main aspects, to distinguish whether they are low in protein and Phe, or only low in Phe, whether they used GMP- in preparations, as well as the studies in which sensory analyses were conducted.

MATERIALS AND METHODS

This study is an integrative article and was evaluated by two different researchers in the following electronic databases: Coordination Agency for Advanced Training of Graduate Personnel (Capes – Brasília, Distrito Federal, Brazil), National Library of Medicine (PubMed – National Institutes of Health, Bethesda, Maryland, USA), Latin American and Caribbean Health Science Literature (Lilacs – Sao Paulo, Sao Paulo, Bra-

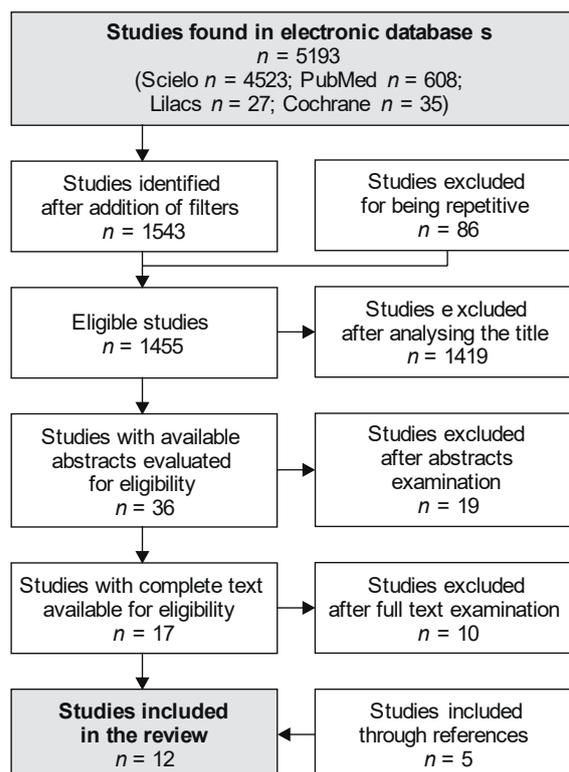


Fig. 1. Flowchart of the selection of articles.

zil) and Cochrane Library (Cochrane – London, United Kingdom), from October 2017 to December 2018. Identification of studies was also performed based on the reference list of the selected article after reading, according to a flow chart (Fig. 1). The search strategy was made with the following combination: “phenylketonuria AND food”; “phenylketonuria AND diet”; “phenylketonuria AND recipes”; “fenilcetornúria AND alimentos”. Later, the following filters were used: articles published in English, Portuguese or Spanish, with available abstract and that did not include animal interventions. The filters “gender”, “age” and “population” were not applied due to the insufficiency of articles on food production.

The articles were considered eligible when the following inclusion criteria were met:

1. the title should mention the elaboration of a food product for PKU patients,
2. human experiment with no distinction regarding gender or age and
3. sensory analysis with PKU and/or non-PKU participants.

The extracted data included authors, year of publication, country, objectives, methods and results.

RESULTS AND DISCUSSION

Considering all the results from the electronic databases, the search strategy initially found approximately 5000 articles. Adding the filters, the number of eligible studies dropped to 1543, out of which 86 were excluded due to repetition. According to the inclusion criteria, 1419 articles were excluded from the study because of their titles and 19 were excluded after reading the abstract. Finally, 17 articles were fully read, out of which 10 were not selected for not achieving the inclusion criteria. Through the list of references of the selected articles, 5 new articles were identified and they were included in the study. At the end, 12 articles were considered eligible (Tab. 1).

In the 12 selected articles, the food preparations varied from bakery products, such as breads, cookies or cakes, to dairy beverages. Tab. 2 summarizes the main data of this study. Among those, 8 manuscripts were about evaluation of food preparations with low protein and Phe, while 4 manuscripts were about low-Phe preparations with GMP.

According to the articles, 4 studies showed that GMP is suitable for developing food preparations, these articles included

- GOLDAR et al. [5] in which 4 types of yogurt were used,
- ZAKI et al. [11] which prepared a cheese made of GMP,
- ABDEL-SALAM et al. [12] elaborated a dairy beverage,
- LIM et al. [13] developed orange juice, chocolate drink, strawberry fruit leather, cookie and strawberry pudding.

The food preparations that used GMP differed from the others as an alternative that can contri-

bute to protein intake and reduce the intake of Phe-free amino acid formula. The studies from ZAKI et al. [11] ($n = 10$), ABDEL-SALAM et al. [12] ($n = 10$), LIM et al. [13] ($n = 49$) conducted sensory studies with PKU patients whereas the study by GOLDAR et al. [5] ($n = 10$) was carried out with healthy subjects.

GMP is obtained in the cheese manufacturing process, in which the rennet and whey are separated. Whey is composed of the proteins α -lactalbumin (20–25 %), β -lactoglobulin (50–55 %), immunoglobulin (10–15 %) and GMP (10–15 %). Lactoferrin and lactoperoxidase are found in lower quantity, 1–2 % and 0.5 %, respectively [14, 15]. Isolated GMP is the only natural protein that does not contain Phe. However, it is necessary to separate the GMP fraction from the other whey components, which requires a long industrial process. The isolated GMP contains essential amino acids (except the aromatic ones, namely, Phe, Tyr and tryptophan), therefore being a potential alternative to reduce the Phe-free amino acid formula intake, besides presenting sensory properties that are pleasant for consumption [10]. The commercial formulations of GMP contain trace amounts of Phe [16]. The 4 studies performed both chemical and sensory analysis, and both categories had satisfying results. When compared to the international standards, which allow 0–20 mg Phe per 100 g of food [5], the food preparations were considered safe for consumption.

LIM et al. [13] developed 5 types of food preparations using GMP, 3 solid foods (strawberry pudding, strawberry fruit leather and cookie) and 2 beverages (chocolate and orange). The ingredients used were not listed in the methodology. Sensory analysis was performed with 49 PKU patients, where a high satisfaction level on the

Tab. 1. Selected studies.

No.	Authors	Country	Year	Objective	Ref.
1	GOLDAR et al.	Iran	2016	Elaboration of yogurts with low Phe levels	5
2	ZAKI et al.	Egypt	2016	Elaboration of a type of cheese	11
3	ABDEL-SALAM et al.	Saudi Arabia, Egypt	2010	Development and evaluation of a dairy drink for PKU patients	12
4	LIM et al.	United States	2007	Development of preparations for PKU patients	13
5	YASEEN et al.	Egypt	2014	Elaboration of low Phe cookies for PKU patients	17
6	YASEEN et al.	Egypt	2012	Formulation of low Phe loaf breads	18
7	YASEEN and SHOUK	Egypt	2011	Formulation of low Phe pita	19
8	YASEEN and SHOUK	Egypt	2011	Elaboration of low Phe pasta	20
9	MOHSEN et al.	Egypt	2010	Elaboration of low Phe bread	21
10	ÖZBOY	Turkey	2002	Development of breads for PKU patients	22
11	RIBEIRO et al.	Brazil	2014	Development of breads, pizzas, pancakes, cakes	23
12	VILAR and CASTRO	Brazil	2013	Development of a passion fruit cake with chocolate syrup recipe for PKU patients	24

PKU – phenylketonuria, Phe – phenylalanine.

Tab. 2. Summary of the main data from selected studies.

No.	Product and ingredients	Type of analysis	n	Age of recipients	Groups	Results	Ref.
1	4 types of yogurt (milk, water, permeate, cream, starch, inulin, butter, transglutaminase and GMP)	Sensory, physico-chemical	10	Adults	Non-PKU	Yogurts within values considered safe, with desirable properties for consumption.	5
2	Cheese with a cream-like aspect; GMP was used in its formulation	Sensory, chemical	10	Teenagers	With PKU	The addition of GMP to food is safe and offers pleasant sensory properties for consumption, patients also reported higher satiety.	11
3	Dairy beverage with the following formulation: buffalo and cows' milk, GMP and wheat germ oil	Sensory, chemical	10	Children and adults	With PKU	After ingestion of the dairy beverage, the Phe serum levels of patients varied from 30 % to 80 %. Presented better flavour when compared to other formulations.	12
4	Strawberry pudding, chocolate beverage, orange juice, strawberry fruit leather and cookie with GMP	Sensory	49	Children and adults	With PKU	The GMP preparations are viable and present pleasant sensory properties for consumption.	13
5	5 types of cookies (wheat flour, maize starch, pectin and CMC), the samples had different contents of wheat flour and maize starch	Sensory, chemical	10	Adults	Non-PKU	All the formulated biscuits were characterized by Phe content lower by 40, 56, 68, 88 and 92 %, when compared to the control sample. The control protein content was 6.4 %, while this parameter ranged in the samples from 3.8 % to 0.65 %. All of them had satisfactory sensory acceptability.	17
6	4 loaf breads with wheat flour, maize starch, pectin and CMC base	Sensory, chemical	10	Adults	Non-PKU	The bread formulas were characterized by Phe content lower by 38, 46, 56 and 67 %, respectively.	18
7	4 breads with low-protein flour, pectin, CMC, maize starch and yeast base	Sensory, chemical	15	Adults	Non-PKU	All breads had reduced content of Phe (by 62 %) and protein (by 61 %) when compared to the control bread.	19
8	4 types of pasta with maize starch, pectin and CMC base, with different content of maize starch in each preparation	Sensory, chemical	10	Adults	Non-PKU	The pasta presented favourable sensory result, Phe content decreased by 68 %. The control sample contained 9.7 % of protein and the formulations contained from 2.9 % to 5.7 % of it.	20
9	4 types of bread with a different base each (gluten-free flour, pectin, arabic gum and CMC)	Sensory, chemical	10	Adults	Non-PKU	The breads had desirable sensory properties, the gluten-free bread presented lower Phe content compared to the control bread (43 %).	21
10	5 types of bread which were made with maize starch, 5 different types of thickening agents (one in each preparation), yeast, salt, sugar, mono and diglycerides	Sensory, chemical	5	Adults	Non-PKU	All breads had low Phe content and were accepted by the judges.	22
11	Preparations with low Phe ingredients (product datasheet)	Sensory, chemical (tables)	50	Adults	Non-PKU	The portions varied from 8 g to 110 g, all of which presented 22.08 mg of Phe, an acceptable value for PKU patients.	23
12	Cake ingredients: potato starch, oatmeal flour, maize starch, sugar, margarine, passion fruit juice, chemical baking powder, linseed, vegetable oil Syrup: water, chocolate, sugar and margarine	Sensory	50	Adults	Non-PKU	94 % of appraisers reported that they would buy the cake, the amount of Phe in each portion was 15.43 mg, within the recommended value for PKU patients.	24

n – number of samples. PKU – phenylketonuria, Phe – phenylalanine, GMP – glycomacropeptide, CMC – carboxymethylcellulose.

food preparations was revealed. It was also found out that the functional properties of GMP were adequate for the development of beverages and semi-solid foods, such as pudding. In the study performed by ZAKI et al. [11] with PKU children ($n = 10$), it was additionally observed that food preparation using GMP was better in terms of palatability and satiety when compared to the classic diet using the Phe-free amino acid formula.

GOLDAR et al. [5] described 4 yogurts that were made by adding different amounts of water, sugar, some minerals, non-protein nitrogen compounds, lactose-free cream (mixture of fats or vegetable milk), dietary protein, edible additives, corn, starch, inulin and GMP, the latter ingredients presented the same percentage in all samples. Sensory analysis performed by trained judges ($n = 10$) identified that the food preparation with the highest percentage of non-dairy creamer was the best regarding colour, flavour, taste, texture and overall acceptability.

ABDEL-SALAM et al. [12] developed a dairy drink based on a mixture of cows' and buffalo milks, to which ultrafiltration permeate (containing water, sugar, some minerals and non-protein nitrogen compounds), maize germ oil and GMP were added. Sensory analysis was performed with PKU patients ($n = 10$), demonstrating good acceptance among the judges. In addition, the drink retained the natural flavour and smell characteristics of milk. It is noteworthy that measurements of serum phenylalanine of patients before and after ingestion of a dairy drink were made in this study. A decrease to 30–80 % in serum Phe level was observed after drinking.

The remaining articles elaborated their recipes with ingredients such as maize starch, potato starch, oatmeal flour or wheat flour. Except for wheat and oatmeal flours, which are rich in Phe and protein, the other ingredients are low in Phe and protein contents. In contrast to the products developed with GMP, these food preparations had low protein value. Therefore, the use of the Phe-free amino acid formula had to be maintained. These food preparations had two positive factors, namely, the ingredients are popularly known and homemade food preparations are cheaper when compared to those that use GMP. It is recognized, however, that elaboration of such products demands time and availability from the person who will prepare it - whether a caregiver or the patient himself.

All the studies had sensory analysis as a part of the research. These were performed generally with adults and/or children that had PKU or were healthy and trained panelists. ZAKI et al.

[11] ($n = 10$), ABDEL-SALAM et al. [12] ($n = 10$) and LIM et al. [13] ($n = 49$) performed sensory analysis with PKU patients. In studies by GOLDAR et al. [5] ($n = 10$), YASEEN et al. [17] ($n = 10$), YASEEN et al. [18] ($n = 10$), YASEEN and SHOUK [19] ($n = 15$), YASEEN and SHOUK [20] ($n = 10$), MOHSEN et al. [21] ($n = 10$), ÖZBOY [22] ($n = 5$), RIBEIRO et al. [23] ($n = 50$) and VILLAR and CASTRO [24] ($n = 50$), sensory analysis was performed with healthy subjects. The evaluated attributes were flavour, colour, texture and overall acceptance.

The studies that aimed at development of products with low Phe and protein levels achieved food products with safe levels for PKU patients, besides presenting satisfying sensory properties. In studies that used GMP, the goal was not to elaborate products with low protein levels, considering that essential amino acids can be found in its composition together with vitamins and minerals. The products elaborated with GMP enabled to lower the dependence on the Phe-free amino acid formula. However, the food preparations that only used ingredients low in protein can not substitute the Phe-free amino acid formula, as protein is an indispensable macronutrient for proper physiological function of the human organism, making it necessary to use supplementation as means of ensuring the adequate protein intake. These food preparations, however, can contribute to expand and diversify food options for PKU patients, improving the quality of their diet.

It is highlighted that the majority of the found studies were performed in periphery countries [5, 11, 12, 17–22]. Such data suggest that the patients in these countries find higher challenges for access and/or acquisition of special products, which are expensive and not re-imbursed. So, the patients have higher need of new preparations that can be elaborated on the domicile level. In contrast, according to the multicentered research study performed by PENA et al. [25], a wide offer of products for these patients is available in Europe. In Italy, for example, there are at least 256 types of PKU-specific food products. Besides economic factors, there is also the necessity of studies for this public due to the high number of cases found in the region. Turkey, for example, is the country with the highest number of persons with PKU in the world, where its incidence is 1:2600 live births [1].

Regardless the recipe chosen, whether with GMP or other foods, the studies wield a fundamental role for improving the quality of life of PKU patients, as the treatment is jeopardized when there is low or no compliance of following the diet.

MACDONALD [26] performed a systematic study about diet therapy with Phe-free amino acid formula, mainly analysing the factor that affects its acceptance and adherence. The author observed that school-age children and young adults with PKU have higher difficulties in consuming the Phe-free amino acid formula when they are in school or at work. The author also verified that people with PKU probably don't have the same meal as their family, what makes it even more difficult to comply with the diet, considering that, on many occasions, there is no analogous food alternative allowed for consumption. In the study conducted by YASEEN and SHOUK [19], a pita bread with low Phe levels was developed, as it is the most consumed type of bread in Middle Eastern countries, having great importance on local food culture and diet. This study enabled PKU patients to include similar or identical food substitutes in their diet that maintain their culture and typical foods, which is the case of pita, being an important factor for both social interactions and treatment. Other studies [18, 21–23] also developed bread food preparations. For bread recipes, wheat flour is commonly used because its composition includes gluten, a protein that aggregates elastic and extensible properties, which characterize a bread of good quality. However, wheat flour has high Phe content, making it necessary to find alternatives for total or partial substitution of this ingredient [24]. In the considered studies, various techniques were found to substitute wheat flour: various types of hydrocolloid – gliadin-free flour, pectin, arabic gum or carboxymethyl cellulose [21]; various types of thickening agents and maize starch [22]; carboxymethyl cellulose and maize starch [23] or potato starch, oatmeal flour and maize starch [24].

CONCLUSIONS

It was observed that there are few studies that aimed to elaborate food products for the PKU population. The recipes contributed to a better quality of life PKU patients, since a wider offer of PKU-specific products improves adherence to the dietary treatment, enhancing clinical condition along with overall health and social relations. This study has strengths and limitations. A positive point includes filling a gap in the literature regarding articles of food preparations for patients with PKU, as well as an overview of specific foods for this population. As a limitation, due to the differences found in the studies, it was difficult to compare the findings of the articles, because of

the different methodologies. Furthermore, only a few studies evaluated also sensory attributes and acceptability with PKU patients, and those that did, worked only with a few patients and had no follow-up. It is indispensable to increase the number of studies that aim at development of food products for patients with PKU, as diet has a considerable influence in these patients' daily life.

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