

Review Article

# Contribution of Therapeutic Foods to the Nutritional Care of Malnourished Children in West Africa

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## Abstract

Undernutrition is the most common form of malnutrition in West Africa, particularly in countries in the Sahel region. It constitutes a major public health problem in Africa and in the world. Caused by deficiency of one or more nutrients, undernutrition remains a major concern around the world and especially in the West African region where it contributes to a high number of deaths in children under five. It denotes an insufficient supply of energy and nutrients to meet an individual's needs for good health. Moreover, there are more and more centers specialized in nutritional care to help solve the problem of undernutrition in children. Thenceforward, knowledge of the current situation will allow better actions to overcome this form of malnutrition which grieves many families in our African regions and particularly in West Africa. This review reports on the nutritional care of malnourished children in West Africa. To do this, scientific databases such as PubMed, ScienceDirect, Scopus and Google Scholar were used to extract publications on the nutritional care of malnourished children. The data are analyzed to assess the management of cases of undernutrition in West Africa. These results can serve as a basis for better care of malnourished children in countries with limited resources, including those in West Africa.

## Keywords

Therapeutic Food, Undernutrition, Child, Care, West Africa

## 1. Introduction

Despite targeted interventions, an estimated 150.8 million children under 5 worldwide are still stunted, more than a third of whom are in Africa [1]. Undernutrition remains a major concern especially in West Africa where it contributes to more than half of the deaths of children under five [2-4]. Undernu-

trition denotes an insufficient supply of energy and nutrients to meet an individual's needs for good health [5]. Nearly 200 million children under the age of 5 suffer from stunting, wasting, or both. At least 340 million suffer from hidden hunger from vitamin and mineral deficiencies [6]. Undernu-

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trition contributes to half of the world's child deaths, which is more than any other infectious disease [6]. Undernourishment and associated health issues are some mammoth challenges that the world currently faces [7]. In sub-Saharan Africa, and specially in West Africa, the main countries affected by stunting and undernutrition are Burkina Faso, the Gambia, Mali, Mauritania, Niger, Nigeria and Senegal [6]. Recurrent conflicts, repeated epidemics of cholera, meningitis and measles, as well as difficult climatic conditions keep the Sahel region in a situation of food insecurity [8]. In 2019 and in West, 33.1% of children under five suffered from chronic malnutrition, 9% from acute malnutrition and 20% from underweight [6]. In this sub-region, Niger records the highest rates of acute and chronic malnutrition with 19% and 43% respectively. Thus, significant efforts must be taken in capacity building (financial resources, legislative and institutional framework) for nutrition in this region [9, 10]. Malnutrition is a complex problem with several possible manifestations. The aim of this review is to show the contribution of therapeutic foods in the nutritional care of malnourished children in West Africa. It reports on undernutrition and the highlights of the therapeutic food revolution in the nutritional care of malnourished children. It opens perspectives on endogenous solutions that may be lacking in solving the problem of undernutrition, especially in the context of the COVID-19 pandemic.

## 2. Types of Undernutrition

### 2.1. Wasting

Also called acute malnutrition, wasting corresponds to a low weight for height [11]. This form of malnutrition is due to rapid weight loss, as a result of an acute infection (diarrhea, measles, malaria), or even an episode of famine (poor food availability following climatic hazards or lean periods) [12, 13]. Body mass is then reduced, vital functions are impaired, and the risk of mortality is great. Globally, wasting threatens the lives of 7.3% of children under 5, or approximately 50 million children [6]. In 2013, wasting caused about 13% of deaths worldwide among children under 5, or 875,000 child deaths and this could have been avoided [14]. In West Africa, the prevalence of acute malnutrition is 9% [14]. This type of malnutrition can be corrected quickly with the establishment of appropriate nutritional support.

### 2.2. Stunted Growth

In the case of stunted growth, the child is small for his or her age. Growth failure in sub-Saharan Africa leads to a high prevalence of child stunting starting in infancy, and is attributed to dietary inadequacy, poor hygiene, and morbidity [15]. Following repeated episodes of malnutrition, the nutritional deficit first results in weight loss, then, if not corrected,

height growth is slowed down or even stopped [14]. This means that the children did not develop well, physically and mentally, especially in the first 1000 days of their life [6]. Multiple childhood infections also affect growth and can lead to stunting. This deficit can also develop during pregnancy, when the mother herself is malnourished. Stunting hinders cognitive development in young children, which impairs their learning abilities later in life [16]. Since the causes leading to this type of malnutrition are numerous, this growth retardation is difficult to correct, even irreversible if it is not taken into account in the first years of life. Between 2000 and 2018, the number of stunted children under 5 increased by 6.5 million in West Africa [6]. In 2019, 33.1% of children under 5 were stunted in West Africa [6].

### 2.3. Underweight

It corresponds to a weight delay where the child is considered thin for his or her age [6]. However, it is not possible to determine whether the child developed acute or chronic malnutrition with this form. Underweight is a mixed form of acute and chronic malnutrition [17]. A child who is underweight may not be wasted but be stunted, or he or she may be wasted and not stunted, or he or she may be wasted with stunted growth. In West Africa, 20% of children under 5 are underweight [6]. Studies have also shown that the prevalence of underweight in developing countries is quite high [18].

### 2.4. Micronutrient Deficiencies

Micronutrient deficiencies and stunting are known as a significant problem in most developing countries [19]. In fact, low micronutrient levels in critical illness have been reported in multiple studies [20]. Among the micronutrient deficiencies, we mainly have the deficiencies of vitamins and minerals such as vitamins A and B, and iron and zinc respectively. This form of malnutrition is invisible and therefore too often ignored. Still called "hidden hunger", it robs children of their health, vitality and even their life. Vitamin A is a fat-soluble micronutrient involved in the regulation of several physiological functions, such as visual acuity and immune response, thus playing a crucial role in childhood growth and development [21]. Vitamin A deficiency remains a real problem and is the leading cause of preventable childhood blindness in developing countries [21]. It affects approximately 190 million preschool children and 10 million pregnant women in low-income countries [22]. Vitamin A deficiency is also recognized as a problem that reflects chronic dietary deficiency that can extend from infancy through adolescence and into adulthood, particularly for women of childbearing age [22]. Vitamin A deficiency remains an underlying cause of at least 157,000 early childhood deaths from diarrhea, measles, malaria and other infections each year [22]. The World Bank has suggested that the cost of micronutrient deficiencies could reach 5% of gross national product

(GNP) while the intervention could cost only 0.3% of GNP. Zinc and calcium deficiencies are also linked to stunted growth and the increasing number of patients with osteoporosis. Today, micronutrient deficiencies, such as zinc, is a real health problem in developing countries [23].

Zinc is a micronutrient of particular importance during childhood and pregnancy. Zinc deficiency has been linked to increased infection and growth retardation in children [24]. Children under 7 are the most vulnerable population group to iron deficiency [25]. Iron deficiency can induce or worsen a deficiency of other essential nutrients, which can negatively impact development of the brain and other organs in infants [25]. Vitamin B12 deficiency causes megaloblastic anemia and nervous system disorders [26]. Indeed, vitamin B12 is

essential for brain development, neural myelination and cognitive functions [27].

### 3. Causes of Undernutrition

The conceptual framework developed by UNICEF (Figure 1) and accepted at international level summarizes most of the economic, social and cultural factors linked to poverty and which are the causes of undernutrition at different socio-organizational levels [28]. The immediate causes relate to individuals, the underlying causes relate to families, households or communities while the root causes are linked at the national and regional levels [29].

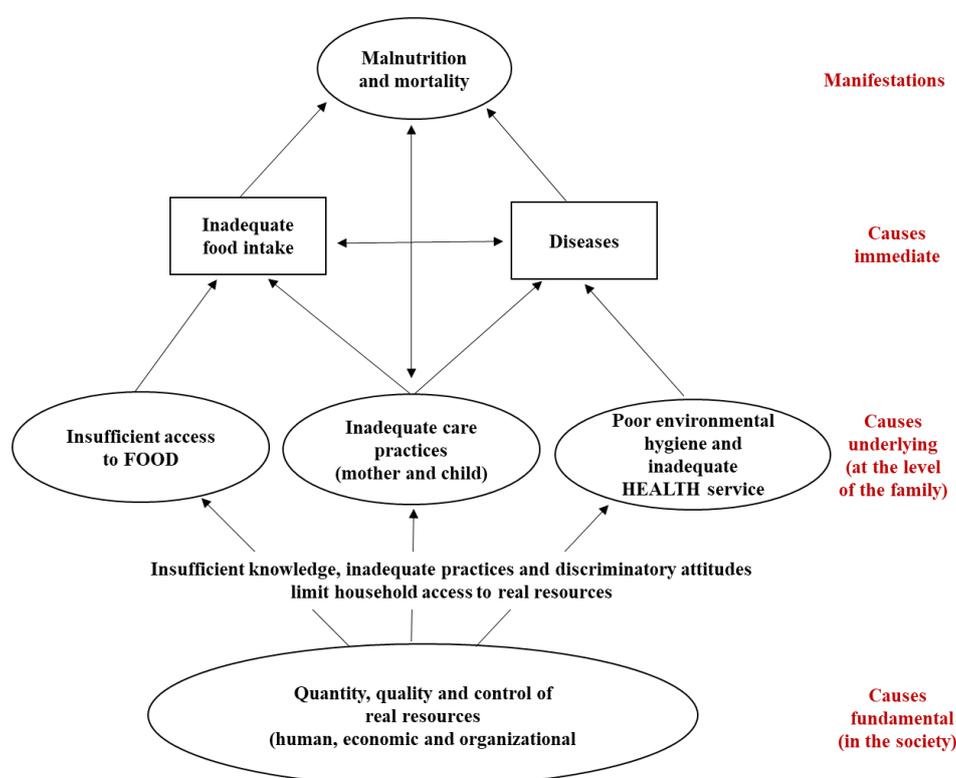


Figure 1. Conceptual Framework of Malnutrition ACC / SCN and UNICEF modified by Bayala-Ya iet al.

Framework of the relationships between poverty, food insecurity and other underlying and immediate causes of maternal and child undernutrition and its short and long term consequences; ACC / SCN, Administrative Committee on Coordination / Subcommittee on Nutrition.

#### 3.1. Immediate Causes

The two main immediate causes are inadequate food intake and disease [30]. Their interaction tends to create a vicious circle. Thus, the malnourished child is more susceptible to infections and once sick, malnutrition worsens. For example, malnutrition is a factor favoring the onset of infections such as measles (a highly contagious disease), diarrhea and acute respiratory infections, the complications of which can be fatal. These infections in turn will generate cases of undernutrition

in affected children. The immediate causes of undernutrition are influenced by the underlying ones (Figure 1).

#### 3.2. Fundamental Causes

The fundamental or structural causes are at the level of society. They concern the political, economic and social context in which the population lives [31]. Lack of financial or human resources at the level of a country is a brake on development and may explain the underlying causes mentioned above. Climate disasters are also included in this category. We

mainly distinguish the weakness of natural resources and the socio-economic and political system as well as the role of women [32]. In Sahel countries like Burkina Faso, low availability of fertile land coupled with insufficient rainfall constitutes the main weakness of natural resources [33]. This situation leads to insufficient harvests, affecting food availability, and the purchasing power of especially rural populations. Also, the high rate of illiteracy of the population and especially of women in developing countries like Burkina Faso has a negative impact on the nutritional status of children in these countries [34]. Numerous studies have shown that there is a correlation between the level of education of women and the prevalence of malnutrition, justifying the importance of making women literate [35]. Lack of knowledge about child feeding practices and poor weaning practices are also causes of undernutrition [36]. In addition, studies have shown that children born to women without access to education are twice as likely to die at an early age [37]. When they are literate, women better assimilate nutritional education programs. Educated women find it easier to obtain paid employment; they can thus contribute in taking charge of their health and that of their children.

### 3.3. Underlying Causes

#### 3.3.1. Mycotoxin-Related Underlying Causes

Weaning foods contaminated with natural toxins have been shown to play an important role in undernutrition [38, 39]. Also, there are strong associations between aflatoxin exposure and stunting and wasting [40]. Exposure to aflatoxins would have an impact on congenital malformations, birth weight, premature birth and growth disorders which are aggravating factors of infant malnutrition [41]. In fact, food diversification and the reduction of exposure to aflatoxins can reduce child malnutrition [42]. Mounting evidence suggests that exposure to aflatoxin can occur at any stage of life, including in utero through a transplacental route and in infancy through contaminated weaning food and family food [43]. Early exposure to aflatoxin is associated with adverse effects including low birth weight, growth retardation, immune suppression and damage to liver function [43]. Also, it should be noted that exposure to mycotoxins, in particular aflatoxin, fumonisin and deoxynivalenol, impairs child growth [44].

#### 3.3.2. Other Underlying Causes

The underlying causes manifest themselves at the household level. They are characterized by household food insecurity, inadequate care for mothers and children, inadequate sanitary environment and difficult access to clean water and health services as well as discrimination against women, and young girls.

Food insecurity is linked to the unavailability of food due to the lack of arable land, inaccessibility due to lack of financial means, climatic hazards and poor mechanization (unsuitable

agricultural tools). Families cannot produce or acquire enough foods that contain the energy and nutrients they need [45].

The state of a mother's health impacts the child from conception. Indeed, when pregnant women have inadequate diets, they give birth to low-weight children [46-48]. These children are affected by various health problems and more likely to die at a young age [49]. Families and communities do not devote the time and resources necessary to take charge of their health and nutrition [50].

The health environment plays a fundamental role in influencing the nutritional status of the child. In fact, insanitary conditions inside and near homes promote the spread of infectious diseases, especially diarrhea in children [51]. These infections in turn become major causes of malnutrition. Also, parents' ignorance of the importance of attending health services leads to low vaccination rates and inadequate care for sick and malnourished children [52].

## 4. Consequences of Undernutrition

Undernutrition is a real scourge that affects the health of children, the economy and the education of a country [14]. It is a major factor in mortality, disease and disability in children [53]. First, malnutrition causes 3.5 million deaths worldwide and is responsible for 35% of morbidities in children under five [54]. Undernutrition is, among other things, a source of anorexia [55], of the decline of intellectual coefficient, vulnerability of diseases [56] and severe anemia [57]. Malnutrition suffered in utero and in early childhood increases the risk of obesity and chronic non-communicable diseases in adulthood [58]. These diseases can then hamper the psychomotor and cognitive development of children, lowering their Intellectual Quotient (IQ) [59, 60]. Children with low birth weight have IQs on average five points lower than those of normal weight children [61]. For example, iodine deficiency causes stunted growth and mental disorders. The risk also exists in the fetus, especially on brain development. In addition, the risk of death is four times higher for a child with severe growth retardation and eight times higher for a child with severe wasting [62]. Malnutrition also has economic consequences [63]. Indeed, malnutrition reduces the profitability of investments made in sectors such as agriculture, education and health. Malnutrition and the diseases that result from it place a considerable burden on health systems. The costs of food-related non-communicable diseases are particularly high. Malnutrition increases the predisposition to disease and leaves people in lethargy, reducing their capacity for work [64]. Malnutrition lowers productivity, hinders economic growth and the effectiveness of investments in health and education, and increases poverty [63]. In some developing countries such as Burkina Faso, loss of life, disability and drop in productivity resulting from nutritional deficiencies cost a lot [65].

## 5. Management of Undernutrition Cases

### 5.1. Management Protocol

The goal of management of cases of malnutrition or undernutrition is to correct it and reduce its mortality (Figure 2). During the management of severe acute malnutrition (SAM),

it is advisable that the child is not separated from his mother, especially when the latter is still breastfeeding. The SAM management protocol includes: phase I or initial phase, transition phase and phase II or nutritional rehabilitation phase [66]. However, an appetite test is first done to find out which method to use for eating meals.

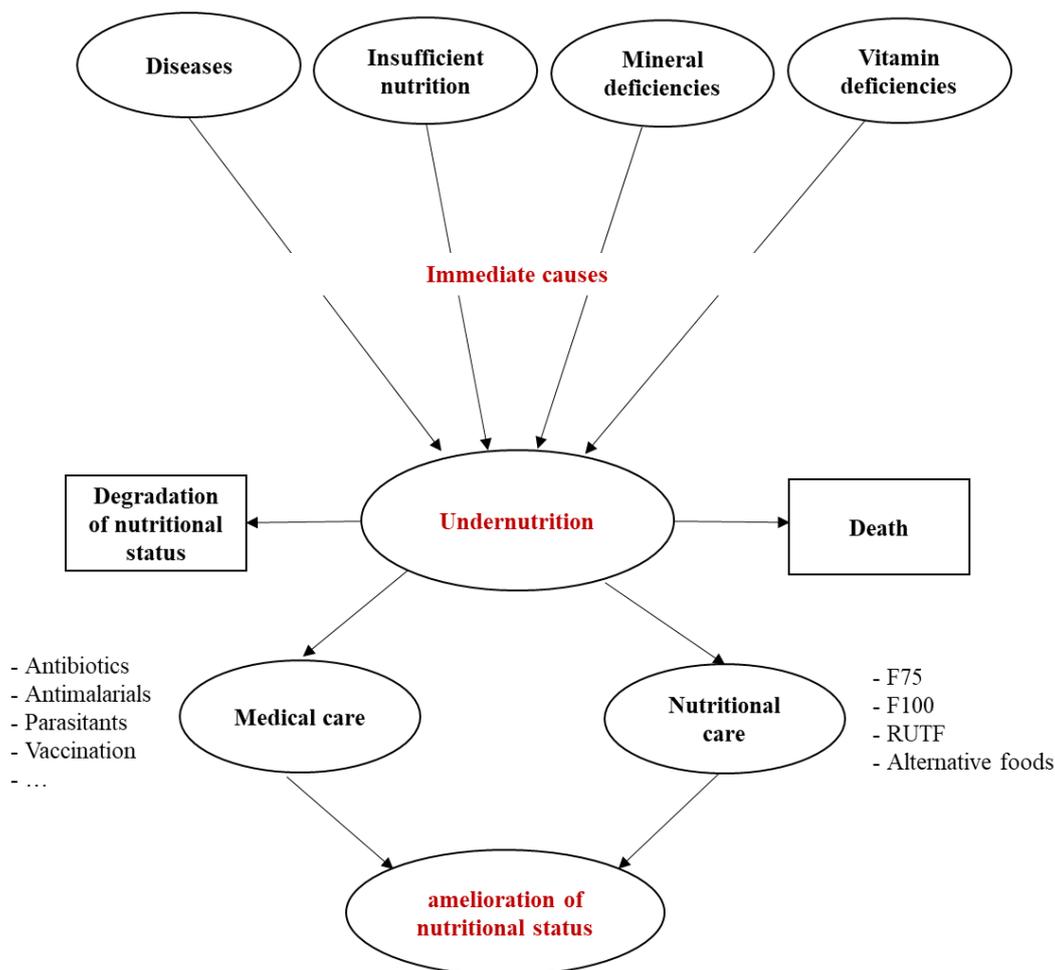


Figure 2. Factors affecting nutritional status and management of undernutrition.

#### 5.1.1. Appetite Test

Malnutrition affects the clinical condition of the child and often leads to loss of appetite. This loss of appetite is often the only telltale sign of severe complications. The appetite test is therefore the most important criterion to determine how the child can eat his meals (use of nasogastric tube or not) in sufficient quantity for better recovery. According to the National Protocol for the Management of Severe Malnutrition (2014), the appetite test should be done in a quiet place. The mother should sit the child comfortably on her lap and offer the Plumpy'nut to eat while encouraging and without straining. The test is successful when the child consumes at least half of

the ration per meal that corresponds to him or her according to his weight [67]. If, despite all efforts to encourage the child, he or she refuses to eat, or if the amount consumed is less than half of the ration per meal which corresponds to him or her according to his or her weight, the test is said to have failed [67]. In this case, the child is referred to the Hospital Support for SAM (PEC MAS) to receive the necessary medical care. Lack of appetite is a serious danger sign [68].

#### 5.1.2. Phases of Clinical and Nutritional Management

The aim of phase I is to provide only the amount of food necessary to restore the fluid and electrolyte balance, the

capacities of homeostasis and to stop the process of deterioration of the general condition. Any fluid overload is to be avoided. The stabilization phase involves systematic treatment, dietetic treatment and follow-up [66]. Systematic treatment consists of supplementation with Vitamin A, Folic Acid, the administration of antibiotics, antimalarial and anti-fungal at doses fixed by the national protocol and vaccination against measles if the child has not been vaccinated. Regarding dietetic treatment, the protocol recommends 5 to 8 meals / day, but each center according to its organizational capacities can choose the number of meals to be given daily. F75 therapeutic milk (75 kcal / 100 ml or 100 kcal / 130 ml) is specially given to children suffering from SAM in hospital. According to the protocol for the management of severe acute malnutrition in Burkina Faso, the use of the Naso-Gastric Tube (SNG) is recommended if the child takes less than 75% of the prescribed amount. Monitoring consists of observing changes in food intake, clinical status and anthropometric parameters, and this is done daily. Thus, several clinical parameters are observed. They are: degree of edema, temperature, number, appearance and color of stools, vomiting, hydration, respiratory rate, and size of the liver. The anthropometric parameters observed are weight, MUAC, and height. This makes it possible to follow the progress of the child during the care.

### 5.1.3. The Transition Phase

The criteria for moving from Phase I to the Transition Phase is the resumption of appetite, and the onset of melting edema [69]. The product used is F100 therapeutic milk (100 ml = 100 Kcal) indifferently for all age categories except for children under 6 months. 1 sachet of F100 is diluted in 2 liters of lukewarm water previously boiled. The number and times of meals as well as the volume of the diet remain the same both in the transition phase and in the stabilization phase. With the change in the type of diet, energy intake increases from 100 kcal / kg / d to 130 kcal / kg / d. This is enough to allow the child to gain weight. The expected weight gain is approximately 6 g / kg / day in the absence of edema or fluid transfer from edema to the tissues. The amount of F100 to give at each meal depends on the weight of the child. This phase, which prepares the child for phase II treatment, was introduced following analyzes of the mortality of children treated according to the WHO manual which showed an increase in mortality in the first three days of Phase II. The systematic treatment instituted during phase I continues in the transition phase. Any child in the transition phase must be put back into phase I when faced with the onset of excessive weight gain, the onset or increase of edema, a rapid increase in the size of the liver, signs of fluid overload, abdominal distension, diarrhea accompanied by weight loss, a complication that requires an infusion.

### 5.1.4. Phase II or Rehabilitation Phase

The criteria for passing from the transition phase to phase II are a good appetite and complete relief of the edema. The principle/aim is to feed children with a well-balanced diet with high-energy value and encourage them to eat as much as possible. Breastfeeding should be promoted and continued throughout treatment. Children who are still being breastfed should be put to the breast before they receive Plumpy'nut. In phase II, children can tolerate large amounts of food and can thus begin their nutritional rehabilitation. In the rehabilitation phase, the child must necessarily achieve a weight gain of 10 g / Kg / d [66]. To reduce the risk of relapse and facilitate follow-up after the release of children, patients cured of severe acute malnutrition should be referred to a service for moderate malnutrition. A child can be considered as recovered and ready to go out when his weight / height ratio (is greater than)  $\geq -2$  standard deviation of the median of the NCHS / WHO reference for 2 consecutive visits and there is no disease. To achieve this goal, it is essential that the child eats as many meals as possible per day. In some cases, a child may be out before reaching the required weight / height ratio; but as soon as he or she is not fully recovered, he or she will have to be further monitored (externally). For this purpose, the dietary treatment will consist of giving an amount of Plumpy'nut fixed by the national protocol according to the weight of the child, which can cover his ration of one week.

## 5.2. Therapeutic Foods Used in the Management of Malnourished Children

### 5.2.1. Ready-to-Use Therapeutic Foods (RUTF)

#### (i). Composition

Ready-to-use Therapeutic Food (RUTF) therapy is a standard protocol for treating children with severe acute malnutrition (SAM) admitted in Out-Patient Therapeutic Programmes (OTP) [70]. Ready-to-Use Therapeutic Foods (RUTF) are high-energy, micronutrient-enhanced pastes used in therapeutic feeding [71, 72]. These soft foods are a seamless blend of high fat foods with a nutritional profile similar to the World Health Organization recommended therapeutic milk formula used for inpatient therapeutic feeding programs. Typical primary ingredients for RUTF include peanuts, oil, sugar, milk powder, and vitamin and mineral supplements [73].

#### (ii). Importance

The invention of RUTF was a great revolution in the field of care. RUTF effectively combats undernutrition in children [74]. Indeed, it gives malnourished children who suffer from severe acute malnutrition without complications and who maintain their appetite, the essential nutrients they need to recover [12]. The most original and well-known, Plumpy'nut,

was invented in 1996 by the French pediatrician André Briand and which obtained approval as a therapeutic food from the WHO [75, 76]. RUTF is a widely used option for home rehabilitation [77]. The invention of RUTF led to a revolution in the area of care for severely malnourished people [77]. Indeed, its use at home facilitates outpatient care without close medical supervision and therefore relieves mothers who no longer have to give up their occupations for several weeks. This increases coverage and recovery rates [78]. RUTF provide all the nutrients necessary for recovery and have a good shelf life, so does not spoil easily even after opening [79]. They are not water-based and the risk of bacterial growth is very limited thus allowing its use without refrigeration at the household level [12]. In addition, the taste of RUTF is very popular with children [80]. RUTF also easily adapt in conflict areas where nutritional care centers are targets for ground and air attacks and home care is a solution to this problem [81]. Since RUTF do not need any further home preparation, the risk of contamination of the food during the preparation process is thus reduced, which further helps to preserve the health of the child. RUTF can also be used in combination with breastfeeding and other good practices for infant and young child feeding [12].

### (iii). Disponibility

The main difficulty related to the availability of RUTF is the high cost of production [82]. This is because although the production process is relatively simple, the cost of the different ingredients is significant. For example, according to Manary's work in Malawi, the total cost of producing RUTF is around \$ 2.60 / kg [82]. This is therefore beyond the reach of the poorest families where malnutrition is most widespread. This is how United Nations organizations such as WFP and UNICEF help by providing RUTF to care centers, making them accessible to all social categories.

One of the difficulties is also the poor management of stocks of available RUTF. Thus, not all the quantities of RUTF intended for the malnourished reach them in full. It happens to see these RUTF being used for other purposes such as consumption by people in good health or the sale of these foods in places of commerce.

Also, the recovery rate is low, for several reasons. Indeed, the work carried out by Hassane in Niger indicates the problem related to the service offer as the main reason [83]. In care centers, demand exceeds supply. This makes the RUTF stock insufficient. Although the rate of malnourished decreases over the years, there is an increase in the number of malnourished [12]. This is due to the strong demographic growth of the population and the high demand for care services.

These multiple difficulties lead the care centers to also turn to local foods in order to remedy the problem of availability of RUTF.

### 5.2.2. Unconventional Therapeutic Foods

In the absence of Ready-to-Use Therapeutic Foods (RUTF)

provided by WFP and UNICEF, the rehabilitation and nutritional education centers (CREN) use local foods generally used in the form of porridge made from cereals to be fortified. However, this approach requires careful monitoring as nutrient adequacy is difficult to achieve [79].

Indeed, it turns out that in cereals, amino acids such as lysine and tryptophan are limiting factors, that is to say that their proportion is low in cereals in comparison with their content in the egg [84]. For this purpose, cereals are said to be foods of low biological value and they are associated with pulses, legumes or milk to increase their biological value [85]. For example, at the CREN of Tanghin in Ouagadougou, we observe the use of rice porridge, millet, enriched either with whole milk, or with "soubala" or dried fish flour, or even with peanut or bean cake. It is also used at the CREN of the "juvénat fille" of Saint Camille in Ouagadougou, porridge commonly called by the acronym MISOLA based on millet, soybeans, peanuts, sugar, salt, the use of spirulina as a food supplement. There is also the use of other family-type foods in CRENs. They are: "tô" with sauces made from a variety of ingredients, rice with sauce or fat, and beans.

These foods must be prepared and given in good hygienic conditions to minimize the risk of contamination [86]. Indeed, bacteria and mycotoxins are potential sources of contamination both of the raw materials (mainly cereals and legumes) used for the formulations and of the finished products obtained [87-91].

It should be noted that unconventional therapeutic foods are less effective than RUTF [74, 92]. Also, in the work of Schoonees et al. [93] on RUTF, it appears that the use of RUTF would increase the rate of weight gain during treatment compared to any other alternative method [93]. However Ghosh-Jerath et al. consider this evidence on the effectiveness of RUTF compared to home foods to be inconclusive [79].

## 6. Conclusion

At the end of this study, it appears that undernutrition is the most common form of malnutrition in West Africa and the number has continued to increase over the years. The management of these cases of malnutrition is more than necessary. The efforts made by the care facilities make it possible to reduce the death rate, but better care would considerably reduce it and tend towards 0 cases of death. RUTF are of great importance in this care. However, centers for the care of severe malnutrition face difficulties in supplying RUTF and therefore resort to unconventional therapeutic foods to try to fill the gap. With the advent of pandemics such as COVID-19 resulting in the slowdown in international traffic, low-income countries such as those in West Africa should increasingly turn to increased use of unconventional therapeutic foods to combat malnutrition. The role of research should be to support actors in the field in incorporating local indigenous foods into RUTF products. This would ensure health quality and would be both culturally more acceptable

and sustainable. Subsidizing, popularizing and improving nutritional and health quality could be an alternative to improve the use of unconventional therapeutic foods, especially in the context of a pandemic such as COVID-19.

## Abbreviations

CREN	Rehabilitation and Nutritional Education Centers
F100	100 Kcal / 100 ml
F75	75 kcal / 100 ml or 100 kcal / 130 ml
GNP	Gross National Product
IQ	Intellectual Quotient
SAM	Severe Acute Malnutrition
SNG	Naso-Gastric Tube
WFP	World Food Program
WHO	World Health Organization

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## Author Contributions

**Léa Kilô Adam Bayala-Yaï:** Conceptualization, Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing

**Philippe Augustin Nikiéma:** Conceptualization, Data curation, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing

**Jacques Simpre:** Resources, Supervision Validation Visualization

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## Data Availability Statement

Not applicable.

## Conflicts of Interest

The authors declare no conflicts of interest.

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