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Maternal and pediatric nutrition

Local High-Protein, Plant-Based Ready-to-Use Therapeutic Food Enhances Recovery from Malnutrition in Rats



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A B S T R A C T

Background: Infant or child malnutrition is a major public health issue. With global funding cuts and increasing incidence because of conflicts and climate change, finding cost effective and sustainable solutions is highly needed.

Objectives: We conducted a preclinical study to mimic child acute malnutrition (AM) and evaluate recovery using a novel plant-based ready-to-use-therapeutic food (RUTF) made from locally available ingredients from sub-Saharan Africa.

Methods: Three-week-old rats were assigned to a 6-wk experiment consisting of a 3-wk induction phase, followed by a 3-wk dietary intervention phase. During the induction phase, the rats received either a balanced diet (control) or a protein-deficient diet (to induce malnutrition). For the subsequent intervention phase, both the control and malnourished rats were switched to either a commercial peanut milk (PM) RUTF or a locally produced plant-based chickpea-sorghum-maize-soybean (ChSMS) RUTF, or remained on the same diet as the induction phase.

Results: Compared with the PM formulation, the ChSMS formulation provided a higher protein content (14% compared with 10% of total energy) and greater protein quality (Protein Digestibility-Corrected Amino Acid Score of 87% compared with 69%, respectively). ChSMS was consumed in higher amounts by the rats and resulted in significantly greater body weight and length as compared with PM. In malnourished animals, ChSMS led to catch-up growth, whereas PM did not.

Conclusions: These findings indicate that a locally produced, culturally acceptable, and affordable plant-based RUTF formulated with high protein quality and density may be effective in treating AM in children. Moreover, the observed reversal of stunting and subsequent catch-up growth indicate that this formulation may also be efficacious as a lipid-based supplement in addressing chronic malnutrition.

This trial was registered at the Hebrew University of Jerusalem (HUJI) Authority for Biomedical and Biomedical Models <https://animals.huji.ac.il/>; <https://animals.huji.ac.il/form/request-perform-research-animals-decision-if-specified-research-experiment-animals-defined-law> (ABBMS) as Ethics Number AG-22-16962-3.

Keywords: protein quality, undernutrition, RUTF, alternative protein, catch-up growth, preclinical study

Abbreviations: AIN, American Institute of Nutrition; AM, acute malnutrition; ChSMS, chickpea-sorghum-maize-soybean; CT, control diet; DIAAS, Digestible Indispensable Amino Acid Score; EER, Estimated Energy Requirement; ENP, Equatorial Nuts Processors; HUJI, Hebrew University of Jerusalem; LMIC, low- and middle-income country; MAM, moderate acute malnutrition; MN, micronutrient-deficient diet; PDCAAS, Protein Digestibility-Corrected Amino Acid Score; PER, protein efficiency ratio; PM, peanut milk; RUTF, ready-to-use-therapeutic food; SAA, sulfur-containing amino acid; SAM, severe acute malnutrition; SD, Sprague-Dawley; SMS, sorghum; maize, soybean; UPF, ultraprocessed food.

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Introduction

Approximately 45 million children aged <5 y suffer from acute malnutrition (AM). A third of those cases face the most critical form [1] known as severe AM (SAM) that contributes to nearly 1 million deaths annually [2]. If food shortages persist, AM can become chronic, leading to stunting, a condition affecting 150 million children worldwide [1]. Furthermore, children experiencing a concurrent acute and chronic malnutrition (underweight) face an exceptionally high risk of death [2]. Both acute and chronic malnutrition lead to long-lasting impacts—impairing development, cognition, and immune function, while elevating risk of noncommunicable diseases in later life [2,3]. In poverty-stricken settings, poor hygiene, limited access to clean water, and coexisting diseases can exacerbate malnutrition by causing gut inflammation, affecting gut microflora, reducing nutrient absorption [4], and increasing relapse of AM [5].

Ready-to-use therapeutic food (RUTF) is the standard treatment prescribed by the WHO for children suffering from SAM without medical complications; it can also be used to treat moderate AM (MAM) [6]. The standard RUTF formulation—peanut milk (PM)—is typically a lipid-based paste made with milk powder, peanuts, sugar, and oil, and enriched with vitamins and minerals. RUTF was developed 20 y ago, and its nutritional content equates to the previous in-hospital formulation (F100) (a dried milk powder enriched in vitamins and minerals designed to meet the nutritional requirements of children aged 6 to 59 mo suffering from SAM).

A major constraint in treating SAM is the poor accessibility of RUTF in the most low- and middle-income countries (LMICs) where it is needed. This scarcity exists primarily because a large proportion of RUTF ingredients are produced in high-income countries and current RUTF formulations rely on skimmed milk powder, an expensive ingredient, not readily available in LMICs. Consequently, the current treatment reaches only 30% of children suffering from SAM [7,8]. Furthermore, the recent global funding cuts add pressure on humanitarian aid availability, risking the survival of increasing numbers of children [9].

WHO used to require that a minimum of 50% of the protein in RUTF should come from dairy products. However, with the Codex Guidelines CXG 95-2022 [10], UNICEF and other global institutions have recently waived this requirement. This shift enables the development of locally sourced, affordable, and environmentally sustainable nonmilk formulations, which could also help stimulate local economies [7,11]. One such alternative is a novel plant-based RUTF formulated from African-grown ingredients [soybean, maize, sorghum (SMS)]. This formulation improved iron status [12] and restored circulating amino acids in children with SAM [13]. Children recovered well; however, weight gain was slightly lower than with standard PM-RUTF formulation (i.e., plumpynut or equivalent). This disparity was attributed to the lower protein quality of the SMS [14]; high protein quality is usually harder to reach in nonmilk plant-based formulations such as SMS.

Animal models are used for replicating the complex biological processes associated with conditions such as human malnutrition or disease, providing valuable insight into potential therapeutic interventions and treatments. In the context of evaluating new RUTF treatment, preclinical models provide a cost effective and

ethically advantageous intermediate step before clinical trials. In our study, we used a Sprague–Dawley (SD) rat preclinical model to evaluate the efficacy of chickpea–sorghum–maize–soybean (ChSMS) RUTF, a novel, high-protein, plant-based RUTF. ChSMS is composed of a sorghum–maize–soybean matrix containing chickpea isolate and contains 14% protein over total energy. It is a modification of the SMS formulation previously developed and clinically evaluated by Akomo et al. [12,13]. We compared this novel formulation against standard PM-RUTF that contains 10% protein over total energy. Given the paucity of preclinical research assessing RUTF efficacy, this study addresses a critical gap, generating foundational insights into the potential therapeutic value of plant-based RUTF formulations ahead of future clinical trials.

Methods

In vivo animal (rat) model experiment

An animal model experiment was set up to mimic underweight (wasting and stunting) in children aged 6 to 59 mo and then simulate treatment and possible repletion. A 6-wk experiment was conducted on female SD rats aged 3 to 9 wk, a time-frame chosen to mimic the human growth period from toddlerhood to sexual maturity [15]. Rats were reared under standard environmental conditions ($23^{\circ}\text{C} \pm 1^{\circ}\text{C}$) with a 12-h (8:00–20:00) light and dark cycle in a nonspecific pathogen-free (conventional) animal facility, at the Robert H. Smith Faculty of Agriculture, Food and Environmental Sciences, Hebrew University of Jerusalem (HUJI). All animals were handled according to ethical care and use of laboratory animals, as approved by the HUJI Authority for Biological and Biomedical Models (ethics number AG-22-16962-3).

Forty-eight (48) 3-wk-old recently weaned SD rats were purchased from Harlan Laboratories. On arrival, the rats were weighed and randomly assigned to 12 cages (4 rats per cage; 2 cages per treatment group). Rats in each cage were individually distinguished by ear piercing. Before the experiment began, the rats were given 3 d to acclimate with standard food and water.

The study was divided into two 3-wk phases (Figure 1):

- (1) Induction phase (weeks 1–3): to simulate underweight conditions, rats were fed either a standard control diet (CT) or a protein- and micronutrient-deficient diet (MN).
- (2) Intervention phase (weeks 4–6): rats from both initial diet groups were further subdivided. For the remaining 3 wk, they either received the novel ChSMS-RUTF (CT-ChSMS and MN-ChSMS), the commercial PM-RUTF (CT-PM and MN-PM), or continued the same baseline diets (CT and MN).

Throughout the experiment period, food consumption and body weight were recorded twice a week, whereas body length (from the tip of the nose to the end of the tail) was measured once a week. In addition, rats were monitored for any physical and behavioral changes. The experiment ended with the rats being killed, and tissue and organ samples harvested according to published protocols [16–18]. In brief, the rats were first anesthetized by inhalation, using isoflurane, USP (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) 100%. Final anthropometric measurements—including body weight (g) and length (cm)—were recorded. The animals were dissected, and the right femur bones were harvested. After manual removal of the soft

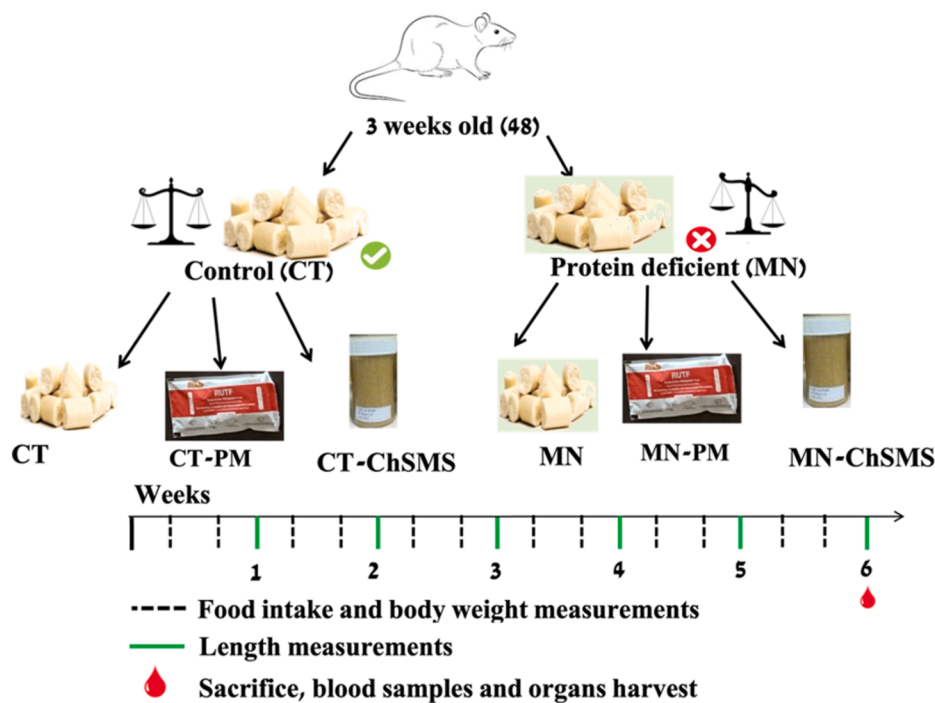


FIGURE 1. Schematic diagram of preclinical experimental setup. CT, standard rodent diet for growth (control group); CT-ChSMS, control diet group switched to chickpea-sorghum-maize-soybean plant-based ready-to-use-therapeutic food; CT-PM, CT group switched to commercially available ready-to-use-therapeutic food; MN, protein-deficient diet inducing malnutrition (malnourished group); MN-ChSMS, MN group switched to chickpea-sorghum-maize-soybean plant-based ready-to-use-therapeutic food; MN-PM, MN group switched to commercially available ready-to-use-therapeutic food.

tissue, right femur length (mm) was measured via micro-computed tomography scanning.

Diet composition and preparation

Four rat diets were used in this experiment:

- 1) Control balanced diet (CT): formulated at HUJI according to the American Institute of Nutrition (AIN-93G) recommendation for the growth phase of rodents. The CT diet contained 16% fat, 63.5% carbohydrates, and 20.5% protein, plus the recommended multimineral and multivitamins (Table 1). To meet Association of Official Analytical Chemists (AOAC) standards for diets, the AIN-93G mineral mix in the CT was adjusted to provide the inorganic sulfate content [$\geq 15\%$ protein (0.964 g/kg diet)]. This ensured sufficient sulfur intake, compensating for the fact that casein alone does not meet a rat's full sulfur requirements.
- 2) Unbalanced protein-deficient diet (MN) formulated at HUJI according to the AIN-93G recommendation for unbalanced diet. The MN diet contained 25% fat, 70% carbohydrates, and 5% protein; and half of the recommended multimineral and multivitamins (Table 1).

Based on AIN-93G guidelines, commercially purchased ingredients were weighed individually and combined in a large plastic tub. Water was added to the mixture to form a firm dough, which was then molded into medium-sized patties.

TABLE 1
Ingredient composition of balanced and unbalanced experimental diets (values are presented as grams per kg dry weight)

Product/ingredient	Control balanced diet (CT)	Unbalanced diet (MN)
Cornstarch	397	438.7
Dextrinized cornstarch	132	145.7
Sucrose	100	110
Fiber	50	50
Soybean oil	70	120
Casein ($\geq 85\%$ protein)	200	50
L-cystine	3	3
Mineral mix (AIN-93G-MX)	35	17.5
Vitamin mix (AIN-93G-VX)	10	5
Choline bitartrate (41.1% choline)	2.5	1.34
Tert-butylhydroquinone	0.014	0.015

Abbreviations: AIN, American Institute of Nutrition; CT, control diet; MN, micronutrient-deficient diet.

These patties were air-dried in an extractor hood chamber for 42 h at ambient temperature. The dried patties were weighed, divided into ~250 g portions, and stored at -20°C until use.

- 1) Chickpea, Sorghum, Maize, Soybeans (ChSMS) RUTF: 6 RUTF formulations were initially developed using linear programming [19] to meet the Codex Guidelines (CXG 95-2022) for children aged 6 to 59 mo. In May 2022 and November 2022, prototypes of each formulation (2.5 kg each) were produced under sanitary laboratory conditions

at Equatorial Nuts Processors (ENP) in Murang'a, Kenya. Amino acid, mineral, and vitamin premixes that were added were formulated to cover the Codex Guideline's requirements, in accordance with previous work [12,13]. Prototype samples were then shipped to Eurofins Laboratories (United Kingdom) for nutritional conformance testing. Based on the results, ChSMS was selected as the most suitable formulation. A larger 20 kg batch of ChSMS was subsequently produced at ENP for the animal study and, after passing aflatoxin and microbiological safety checks at ENP, was shipped to HUJI.

- 2) Peanut butter and milk (PM) standard RUTF: commercially available PM-RUTF (NutriFEEDO) was purchased from Nuflower Foods and Nutrition Private Limited and shipped to HUJI. The purchase consisted of 2 carton boxes, each containing 150 sachets (92 g each) with a shelf life of 24 mo.

Small amounts of ChSMS (from the 20 kg batch) and PM-RUTF products were sent to Eurofins Laboratories (United Kingdom) for full nutritional analysis. Meanwhile, their amino acid profiles and Protein Digestibility-Corrected Amino Acid Scores (PDCAAS) were analyzed at the Nutritional Composition and Digestibility Lab of the University of Nottingham, United Kingdom (Table 2).

Statistical analysis

All data are expressed as mean $\pm$ SD. Statistical differences were analyzed using JMP Pro 17.0.0 Statistical Discovery Software (JMP Statistical Discovery LLC, Cary, USA) via a 1-way analysis of variance or student's *t*-test. Post hoc comparisons between groups were further assessed using a Tukey-Kramer HSD test, with a statistical significance of $P < 0.05$.

Results

Nutritional composition of PM compared with ChSMS

Nutritional composition data of the commercial PM-RUTF and the novel ChSMS-RUTF are detailed in Table 3. Although

TABLE 2

Ingredient composition of ChSMS and PM-RUTFs (values are presented as percentage weight)

Ingredient	PM-RUTF ¹	ChSMS-RUTF
Soybean	0	27.5
Defatted soy	0	8.2
Maize	0	5.3
Sorghum	0	3.4
Palm oil	13.0	23.5
Palm stearin	4.0	4.0
Sugar	28.0	21.0
ChickP (910) ²	0	2.0
Peanut	23.0	0
Milk	30.0	0
Micronutrient and amino acid premix	-	5.0
Stabilizer/emulsifier	2.0	0

Abbreviations: ChSMS, chickpea–sorghum–maize–soybean; PM, peanut milk; RUTF, ready-to-use-therapeutic food.

¹ Nuflower did not provide the formulation. Our approximations are based on previous experiments [14].

² A chickpea protein isolate from ChickP Company, Israel.

both formulations generally aligned with UNICEF/WHO CXG 95-2022 Codex Specifications, which are the reference for children with SAM, several key differences in macronutrients, micronutrients, and protein quality were observed:

- Energy and lipids: both formulations met the energy Codex Specifications. Total lipid content was within the acceptable range for both, although the ChSMS formulation approached the upper limit at 35.8% (specification: $<36\%$).
- Carbohydrates and fiber: PM contained more added sugar than ChSMS (24.9% compared with 21.6%). However, ChSMS slightly exceeded the fiber Codex specification limit with 6.9% (specification: $<5\%$).
- Protein quantity and quality: the protein concentration of PM-RUTF was at the lower limit of the acceptable range (13.4% compared with $>13\%$), whereas ChSMS slightly exceeded the standard upper limit (18.5% compared with $>16\%$). In terms of quality, ChSMS demonstrated a greater PDCAAS (87%) compared with PMs (69%); PM failed to meet the required 90% PDCAAS threshold, whereas ChSMS was borderline.
- Fatty acids: both RUTFs shared similar percentages of omega-3 (n-3) fatty acids relative to total energy (0.9% for PM; 0.8% for ChSMS). ω -6 percentages fell within specification ranges for both, though PM was slightly lower than ChSMS (7.8% compared with 9.8%).
- Micronutrients: all vitamins and minerals met acceptable ranges for both formulations. Notably, ChSMS contained one-third more iodine and more than double the vitamin C content of PM.

Figure 2 uses a radar plot to compare the amino acid balance and overall protein quality of the ChSMS-RUTF and PM-RUTF formulations. To assess protein quality, digestible indispensable amino acid profiles (mg/g protein) of ChSMS-RUTF and PM-RUTF were compared against the UNICEF/WHO CXG 95-2022 Codex Specifications. Digestible amino acid values were sourced from an ileal digestibility database for individual ingredients to calculate the Digestible Indispensable Amino Acid Score (DIAAS). This approach aligns with FAO recommendations by accounting for amino acid-specific digestibility at the terminal ileum, providing a more physiologically relevant assessment than PDCAAS, although both methods yielded similar results.

The evaluation covered the 9 essential amino acids as follows: histidine, isoleucine, leucine, lysine, sulfur-containing amino acids (SAA; i.e., methionine and cysteine), aromatic amino acids (i.e., phenylalanine), threonine, tryptophan, and valine. Although most amino acids in both formulations met or exceeded the reference targets, lysine and SAA were identified as limiting: in the PM-RUTF formulation, with a DIAAS of 69%, lysine fell markedly below the reference pattern, representing the first limiting amino acid, whereas SAA was the second limiting amino acid.

In contrast, ChSMS-RUTF had improved protein quality, with a DIAAS of 87% and SAA as the limiting amino acid. This value approaches the $\geq 90\%$ threshold typically targeted for RUTF formulations.

The effect of the new formulation on growth performance in a rat model for AM and stunting

To assess the impact of these diets on physical growth, we measured body weight (including energy balance), nose-to-tip

TABLE 3
PM-RUTF and ChSMS-RUTF nutritional composition (per 100 g)

Parameter	Unit	UNICEF specifications ¹	PM-RUTF ²	ChSMS-RUTF ³
Ash	g		3.9	4.1
Moisture	%	≤2.5	<2	3.7
Energy	kcal	520–550	535.0	527.3
Carbohydrate	g		51.5	35.9
Protein	g (% total energy)	Spec (3.4): 13–16 (10–12) Spec (4.0): 13–17 (10–12)	13.4 (10.0)	18.5 (14.1)
Lipids	g (% total energy)	Spec (3.4): 26–36 (45–60) Spec (4.0): 26–37 (45–60)	29.3 (49.3)	35.8 (61.0)
n–6 FA	g (% total energy)	Spec (3.4): (3–10) Spec (4.0): 1.7–4.3 (3–7)	4.6 (7.8)	5.9 (9.9)
n–3 FA	mg (% total energy)	Spec (3.4): (0.3–2.5) Spec (4.0): 580–1530 (1–2.5)	542.0 (0.9)	461.7 (0.8)
<i>trans</i> FA	g	≤1.1	0.3	0.3
Fiber	%	≤5	0.8	6.9
Added sugar	g	≤28	24.9	21.6
PDCAAS	—	90–100	69%	87%
Potassium	mg	1100–1600	1240.0	1370.0
Sodium	mg	≤290	136.0	19.8
Calcium	mg	300–785	358.0	339.7
Phosphorus	mg	300–785	295.0	505.3
Magnesium	mg	80–235	78.2	89.2
Iron	mg	10–14.0	11.6	12.4
Zinc	mg	11–14.0	11.3	10.7
Copper	mg	1.4–1.8	1.4	1.2
Selenium	µg	20–40		
Iodine	µg	70–140	87.3	135.0
Vitamin A	mg	0.8–1.6	0.7	1.2
Vitamin B1	mg	>0.5	0.9	0.6
Vitamin B2	mg	>1.6	3.3	2.0
Vitamin B3	mg	>5	8.1	4.7
Vitamin B5	mg	>3	5.1	4.7
Vitamin B6	mg	>0.6	1.6	0.7
Vitamin B7	mg	>60	95.6	65.2
Vitamin B9	µg	>200	480.0	788.3
Vitamin B12	µg	>1.6	2.8	2.4
Vitamin C	mg	>50	79.9	190.3
Vitamin D	µg	15–22	19.3	23.3
Vitamin E	mg	>20	38.8	13.1
Vitamin K	mg	15–30	30.4	24.3

Abbreviations: ChSMS, chickpea–sorghum–maize–soybean; FA, fatty acid; PDCAAS, Protein Digestibility-Corrected Amino Acid Score; PM, peanut milk; RUTF, ready-to-use-therapeutic food.

¹ 2022-UNICEF RUTF Specifications and Codex requirements. Codex Guidelines CXG 95-2022. Applies to both Spec (3.4) and (4.0) if not specified.

² Peanut milk ready-to-use therapeutic food (PM-RUTF) analyzed by a commercial laboratory (Eurofins) as a single sample.

³ Chickpea soybean maize sorghum ready-to-use therapeutic food (ChSMS-RUTF) analyzed by the same commercial laboratory. (Eurofins) in triplicate.

body length, and femoral length as an indicator of longitudinal bone growth throughout the experiment (Figure 3). Significant differences in body weight emerged by day 4 and continued to widen throughout the 21-d first phase. At the end of this induction phase, the mean weights for the CT and MN groups were 167 g and 79 g, respectively (Figure 3A and B). A similar pattern was observed for body length (Figure 3C and D), with significant differences appearing at day 11 and sustained until day 43. By the end of the induction phase (day 22), total body length equalled 35 cm for the CT group and 29 cm for the MN group. These baseline results clearly demonstrate the successful induction of malnutrition and stunting in the MN group before the intervention phase.

After 21 d, the diets were switched to either PM or ChSMS RUTFs to promote rescue and catch-up growth (intervention phase). Surprisingly, the commercial RUTF (PM) did not

manage to increase growth (weight and length) in the malnourished animals (MN-PM) (Figure 3A–D). In contrast, the malnourished rats shifted to the novel RUTF (MN-ChSMS) showed significant weight gain after just 4 d, and length increases from day 11. This upward trend continued until the end of the experiment, with ChSMS-RUTF rats reaching a final weight of 147 g and a length of 34 cm, significantly higher than the unrescued malnourished controls (98 g and 32 cm). Nevertheless, the MN-ChSMS group did not achieve full catch-up growth, falling short of the healthy control group's final metrics (220 g and 38 cm). Meanwhile, the PM-RUTF group showed no significant improvement over the standard deficient diet (MN compared with MN-PM). Within the healthy control group (CT), ChSMS-RUTF had no effect on growth, whereas PM-RUTF actually slowed weight gain without altering body length (Figure 3A–D).

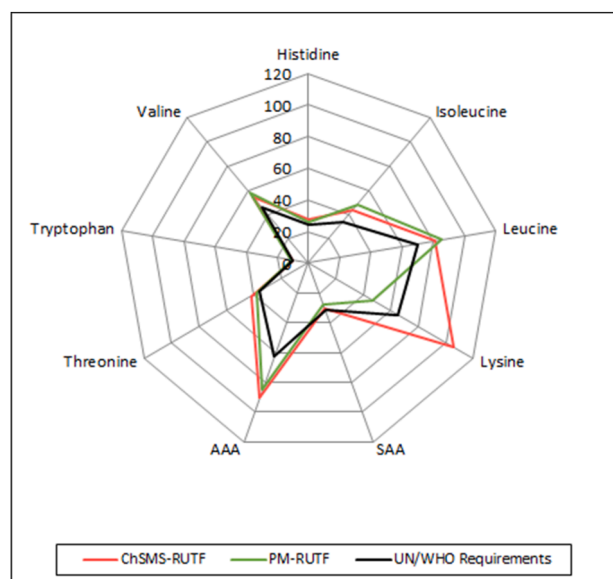


FIGURE 2. Radar plot showing the digestible amino acid profiles (mg/g digestible protein) of ChSMS-RUTF, PM-RUTF relative to the reference (Codex Guidelines CXG 95-2022) pattern for children with severe acute malnutrition (SAM). Reference pattern for children with SAM in mg/g protein (target weight gain 10 g/kg/d, 6 mo to 5 y); histidine (24), isoleucine (34), leucine (70), lysine (65), sulfur amino acids (31), aromatic amino acids (63), threonine (36), tryptophan (10), and valine (46). AAA, aromatic amino acids; ChSMS, chick-pea–sorghum–maize–soybean; RUTF, ready-to-use-therapeutic food; PM, peanut milk; SAA, sulfur-containing amino acid.

At the conclusion of the 6-wk experiment (post-kill), femur length—a proxy for total body length—was measured (Figure 3E). The 3 control groups (CT, CT-PM, CT-ChSMS) maintained the longest mean femur length (31.7 mm) and indicated no significant effects from the RUTF formulations. In contrast, among the malnourished (MN) groups, the untreated MN group had the shortest mean femur length (22.8 mm), followed by the MN-PM group (24.2 mm), whereas the MN-ChSMS group performed the best (25.2 mm) but fell short of complete catch-up growth.

Furthermore, the weight-for-length ratio, calculated from final weight and length data, significantly increased in malnourished animals fed with ChSMS, whereas no change was observed in well-nourished controls (Figure 3F). Together, these results demonstrate that the new ChSMS formulation significantly improves growth (body weight, body and femur lengths) in malnourished rats.

Food consumption of ChSMS and PM formulation in a rat model for AM and stunting

Throughout the experiment, food intake was measured at each time point and converted into energy and macronutrient intake to evaluate the diet's contribution to growth (Figure 4). Total (cumulative) food and macronutrient intake was also calculated (Figure 5). During the induction phase (until day 22), rats consumed significantly more of the CT diet than the MN diet (Figure 4A). Although the MN diet had a slightly higher caloric density than CT (3.5 compared with 3.2 kcal/g, respectively), the MN group still consumed less energy during this initial period (Figure 4B). This trend persisted across the full 6-wk

study, as reflected by the lower total food weight and lower individual and cumulative energy consumption in the MN group (Figure 4A, B; Figure 5A, B). Energy and protein intake in the CT and MN groups directly reflected their growth performance: CT rats increased food consumption and grew significantly (63–220 g; 20–38 cm), whereas MN rats did not increase consumption and showed minimal growth (62–98 g; 20–32 cm). (Figures 3 and 4A, B).

When switched to RUTF (day 22), the rats initially reduced their food intake during a dietary adjustment period before increasing consumption. Figure 4C and D illustrates the superior protein and lipid consumption of the PM and ChSMS RUTFs over the MN diet. In the intervention phase, from weeks 3 (day 22) to 6 (day 39), ChSMS was consumed in amounts similar to the CT and MN diets, but its high caloric density combined with this intake resulted in an overall increase in energy consumption (Figure 4B). Conversely, PM was consumed in lesser amounts (Figure 4A), leaving its overall energy consumption unchanged. This variance is explained by the higher caloric density of both RUTFs (5.3 kcal/g) compared with the standard diets (3.2 kcal/g for CT; 3.5 kcal/g for MN) (Table 3).

When comparing total amount of food and energy intake across the entire study (0–6 wk) to the postswitch period (3–6 wk), the introduction of RUTF clearly drove an increase in consumption (Figure 5A, B, D, E). Specifically, rats maintained on the MN diet for the first 3 wk significantly increased their energy intake during the final 3 wk once switched to either RUTF. Their intake rose from a baseline of 682 kcal on the MN diet to 803 kcal with the PM-RUTF, and peaked at 1102 kcal with the ChSMS-RUTF (Figure 5D). The well-nourished control rats (CT) similarly increased their energy consumption when introduced to the RUTFs (Figure 5E).

The disparity in total protein consumption between rats on the CT diet and rats in the MN group became evident when examining the data from the 6-wk experiment: a rat on the CT diet consumed approximately 5 times more protein than a rat in the MN group. Compared with the CT group, the MN group showed lower protein consumption because of a combination of lower dietary protein density and reduced food intake (Figure 5C). Introducing either RUTF significantly boosted protein consumption in malnourished rats (Figure 5F), reflecting their superior protein profiles (13.4% for PM and 18.5% for ChSMS compared with 5% for the MN diet; Table 2). Compared with the MN baseline, protein intake increased 2.4-fold with PM and 4.3-fold with ChSMS (Figure 5F). This surge in energy and protein intake explains the significant increases in total body weight, length, and femoral growth (Figure 3). Furthermore, ChSMS also drove higher overall protein and fat consumption than PM (Figure 4C, D), whereas carbohydrate consumption was slightly lower (Figure 4E).

ChSMS and PM formulation utilization for growth

To evaluate differences in formulation quality, the energy efficiency ratio (EER; g weight gain per 100 kcal intake) and protein efficiency ratio (PER; g weight gain per g protein intake) were calculated across the entire experimental period (Figure 6). During the induction phase (weeks 0–3), rats fed the malnourished (MN) diet exhibited a significantly lower EER compared with controls (CT) (Figure 6A), indicating reduced energy utilization for growth. In contrast, PER did not differ

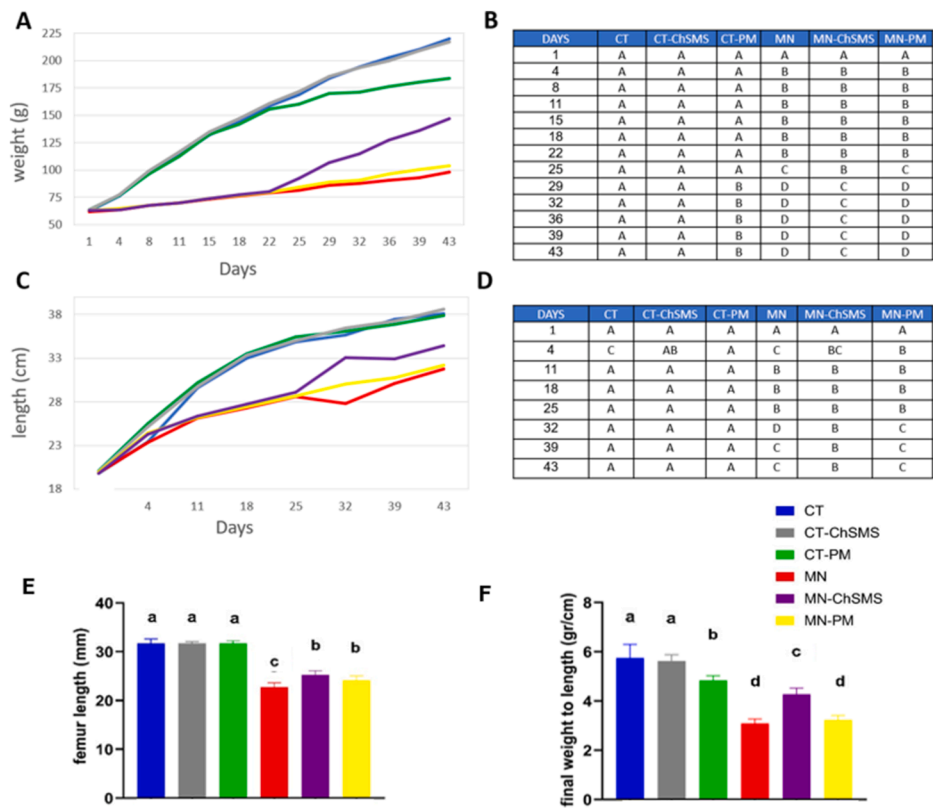


FIGURE 3. Growth pattern of rats (weight and length) throughout the experiment and final femur length (A) body weight (g), (B) body weight statistical analysis, (C) body length (cm), (D) body length statistical analysis, (E) final femur length (mm), and (F) final weight/length (g/cm). Values are expressed as mean $\pm$ SD of $n = 8$ rats/group; different superscript letters are significantly different ($P < 0.05$) by 1-way ANOVA followed by Tukey's test. ANOVA, analysis of variance; CT, standard rodent diet for growth (control group); CT-ChSMS, CT group switched to chickpea-sorghum-maize-soybean plant-based ready-to-use-therapeutic food; CT-PM, CT group switched to commercially available ready-to-use-therapeutic food; MN, protein-deficient diet inducing malnutrition (malnourished group); MN-ChSMS, MN group switched to chickpea-sorghum-maize-soybean plant-based ready-to-use-therapeutic food; MN-PM, MN group switched to commercially available ready-to-use-therapeutic food.

between the groups (Figure 6B), suggesting that protein utilization efficiency was not the primary limiting factor during early growth. In the intervention phase (weeks 3–6), the ChSMS formulation demonstrated superior support for catch-up growth compared with the PM formulation, as reflected by both a higher EER (Figure 6C) and PER (Figure 6D), indicating improved utilization of both energy and protein.

Discussion

Our findings demonstrate that the novel ChSMS formulation significantly outperforms the commercial PM standard in promoting growth. Developed as a plant-based blend from locally sourced African ingredients, including SMS and a small amount of chickpea isolate (ChickP), ChSMS stimulated greater weight and length gains in rats. This recovery was supported by higher overall intake of food, energy, fat, and protein. Notably, the therapeutic advantages of ChSMS were most pronounced in the malnourished group, whereas the PM formulation failed to stimulate recovery. Despite ChSMS facilitating partial catch-up growth rather than full recovery, these results highlight its

potential as an effective intervention for nutritional rehabilitation. A key question remains, however, regarding the direct extrapolation of these animal model findings to humans.

The sensitivity of a rat model to evaluate malnutrition and its recovery

Although animal models cannot fully replicate the clinical and environmental complexity of AM in children, they are needed for mechanistic elucidation that cannot be ethically or practically investigated in young children. Despite their limitations, animal models consistently reproduce core features of AM pathophysiology such as nutritional deficits, gut digestibility, and relevant physiological and developmental processes, offering critical preclinical insight to inform and refine future clinical research [20–22].

We identified only 2 preclinical studies using SD rats that evaluated the effectiveness of plant-based RUTF [19,20], both of which provided limited insights. In the first study, Wamunga and Wamunga [23] fed weanling rats either commercial RUTF (Plumpy'nut) or a plant-based mixture (roasted soybean, peanut, soybean oil, roasted maize flour, sugar, and a mineral mix)

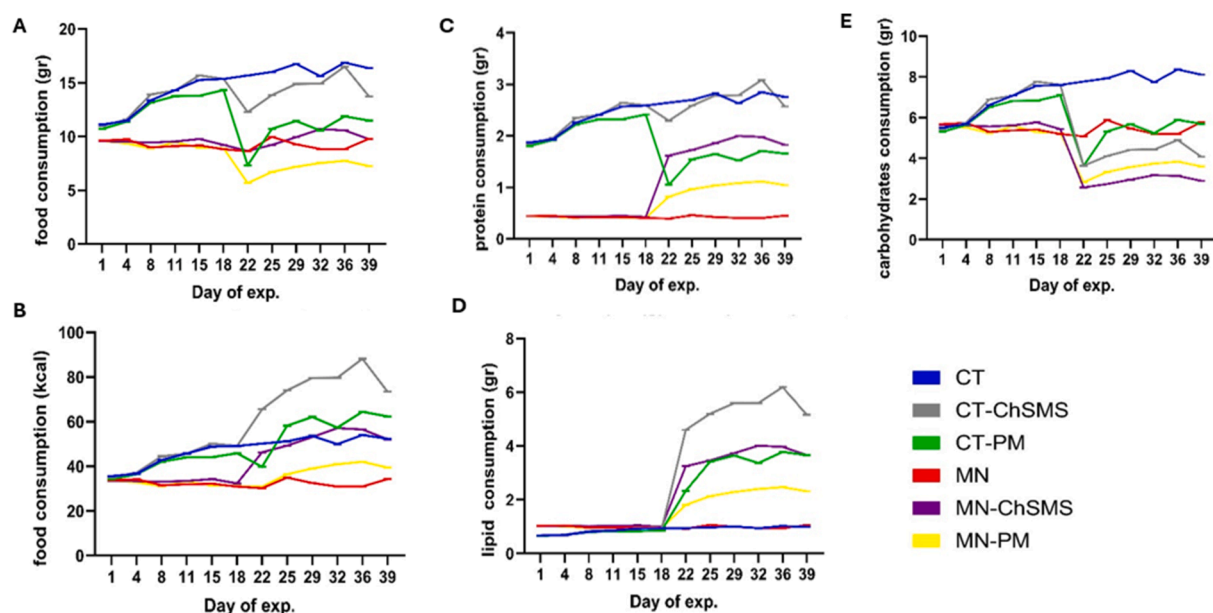


FIGURE 4. Food and macronutrient intake throughout the experiment (A) food consumption (g), (B) energy intake (kcal), (C) protein intake (g), (D) lipid intake (g), and (E) carbohydrate intake (g). Values are expressed as the mean of 8 rats, $n = 2$ cages/group. CT, standard rodent diet for growth (control group); CT-ChSMS, CT group switched to chickpea–sorghum–maize–soybean plant-based ready-to-use-therapeutic food; CT-PM, CT group switched to commercially available ready-to-use-therapeutic food; MN, protein-deficient diet inducing malnutrition (malnourished group); MN-ChSMS, MN group switched to chickpea–sorghum–maize–soybean plant-based ready-to-use-therapeutic food; MN-PM, MN group switched to commercially available ready-to-use-therapeutic food.

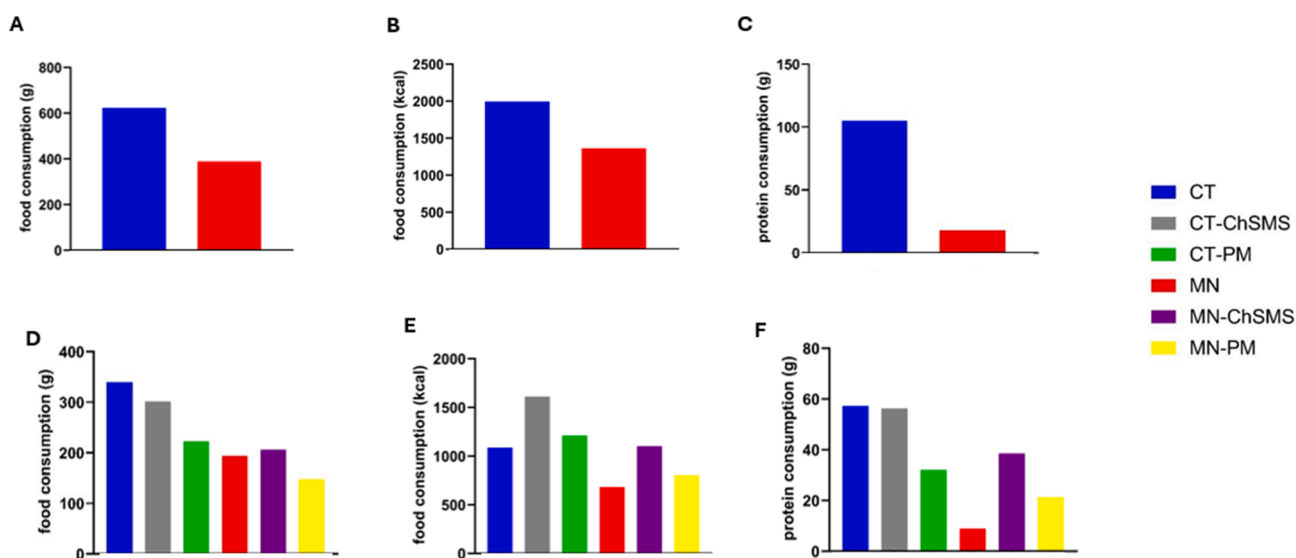


FIGURE 5. Total food and macronutrient intake (A–C) 0–6 wk CT compared with MN (A) food consumption (g), (B) energy consumption (kcal), and (C) protein consumption (g). (D–F) 3–6 wk (D) food consumption (g), (E) energy consumption (kcal), and (F) protein consumption (g). Values are expressed as the mean of 8 rats, $n = 2$ cages/group. CT, standard rodent diet for growth (control group); CT-ChSMS, CT group switched to chickpea–sorghum–maize–soybean plant-based ready-to-use-therapeutic food; CT-PM, CT group switched to commercially available ready-to-use-therapeutic food; MN, protein-deficient diet inducing malnutrition (malnourished group); MN-ChSMS, MN group switched to chickpea–sorghum–maize–soybean plant-based ready-to-use-therapeutic food; MN-PM, MN group switched to commercially available ready-to-use-therapeutic food.

over 30 d. However, the rats showed no growth, remaining at ~ 120 g throughout the treatment. This lack of growth suggests that critical experimental details were omitted from the publication. Ultimately, no significant differences were found between the commercial RUTF and the pulse-cereal mixtures. In

the second study [24], researchers compared the true digestibility and net protein utilization of a standard casein diet, Plumpy'nut, and a laboratory-formulated RUTF made with chickpea and milk (substituting peanut). Although the casein diet performed significantly better, there was no statistical

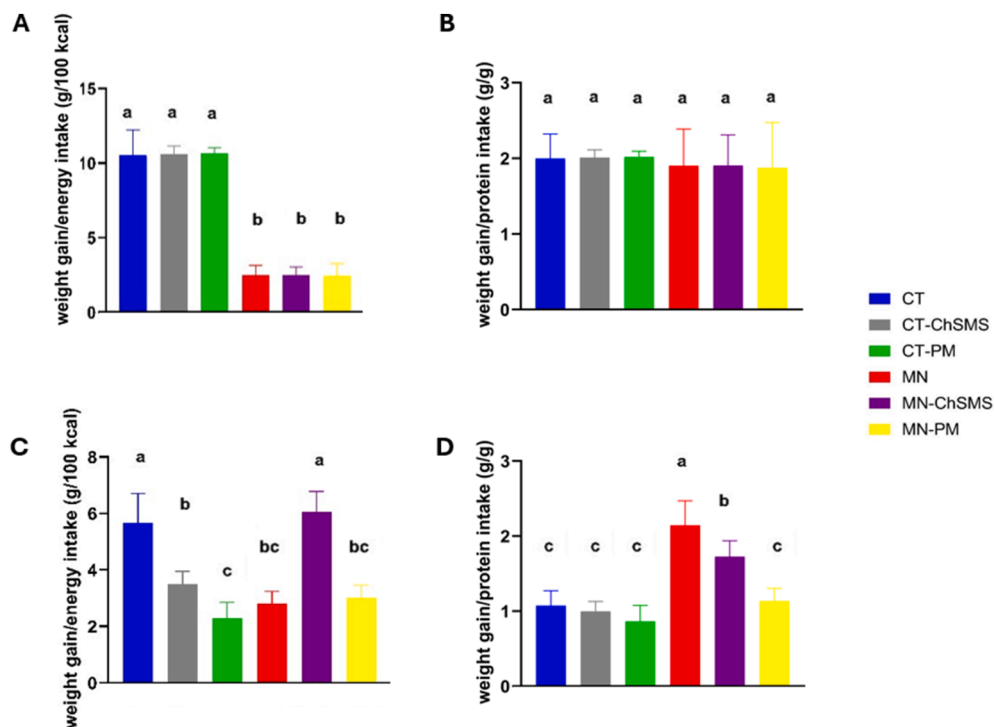


FIGURE 6. EER and PER: (A) 0–3 wk EER (g/100 kcal), (B) 0–3 wk PER (g/g), (C) 3–6 wk EER (g/100 kcal), and (D) 3–6 wk PER (g/g). Values are expressed as the mean $\pm$ SD of $n = 8$ rats/group; different superscript letters are significantly different ($P < 0.05$) by 1-way ANOVA followed by Tukey's test ($P \leq 0.05$). ANOVA, analysis of variance; CT, standard rodent diet for growth (control group); CT-ChSMS, CT group switched to chickpea–sorghum–maize–soybean plant-based ready-to-use-therapeutic food; CT-PM, CT group switched to commercially available ready-to-use-therapeutic food; EER, energy efficiency ratio; MN, protein-deficient diet inducing malnutrition (malnourished group); MN-ChSMS, MN group switched to chickpea–sorghum–maize–soybean plant-based ready-to-use-therapeutic food; MN-PM, MN group switched to commercially available ready-to-use-therapeutic food; PER, protein efficiency ratio.

difference between Plumpy'nut and the chickpea formulation. Unfortunately, this publication also lacked sufficient detail, rendering the results difficult to interpret.

To evaluate how a novel formulation affects juvenile growth and skeletal development, the Monsongo Laboratory used a validated postnatal rat model [25]. The postnatal period is a critical developmental window where nutrition heavily influences both body mass and peak bone density. The rat model was selected due to its high sensitivity to nutritional intake during rapid growth and its metabolic similarities to humans. In addition, the compressed developmental timeline of the rat—progressing from weaning to sexual maturity within 10 wk—allows for rapid, reliable preclinical testing before advancing to human trials [24–26].

Prior research using similar SD rat models indicates that a protein source's impact on growth depends strongly on its concentration. For instance, at a marginal inclusion level of 10%, different protein sources (such as casein, soybean, and chickpea) caused significant variations in weight and length gain, underscoring the role of amino acid composition [18]. However, these differences were largely neutralized when the protein content was increased to 20% [26,27]. This points to a compensatory threshold, suggesting that higher protein quantities can overcome the nutritional limitations of lower-quality protein sources to meet developmental requirements.

Our current results align with this observation: despite containing plant-derived proteins often considered “lower quality” than the milk proteins in the commercial PM formulation, the ChSMS diet promoted significantly better growth outcomes in the malnourished cohort (MN). This suggests that the higher concentration of essential amino acids (protein quantity and quality) and other nutrients provided by the ChSMS formulation allowed it to not only match but exceed the efficacy of the milk-based standard during nutritional rehabilitation. Nevertheless, comparison between human application and the present rat model should be made with a caveat: although this preclinical model effectively mimics malnutrition and growth conditions under controlled environments to assess relative dietary effects, it does not fully replicate the complex physiological and clinical context of childhood malnutrition.

What are the differences in the formulation composition that can explain ChSMS better efficacy?

The ChSMS formulation contained a higher proportion of both fat (61.0% compared with 49.3%) and protein (18.5% compared with 13.4% of total energy) compared with PM. Also, ChSMS exhibited superior protein quality, with a PDCAAS of 87% compared with 69% for PM. This combined increase in nutrient

quantity and quality likely explains why ChSMS could induce better rat growth for the same amount of food consumed. Despite the manufacturer's accreditation, the PM formulation failed to meet the protein quality standards recommended by the UNICEF and Codex Guidelines (CXG 95-2022). Although it remains unclear whether the tested batch was an anomaly, any compromise in protein quality standards is concerning, as it could directly impact the treatment efficacy for children with SAM.

Conversely, our plant-based formulation had a slightly higher protein content than specified by the Codex Guideline. According to its inventor [28], the RUTF formulation has never been fully optimized, and slightly higher protein concentrations—even exceeding the standard 17% upper limit—may benefit growth. High protein quality is essential for the growth and development of young children. In SAM, protein is vital for both weight gain and catch-up growth. For weight maintenance, protein typically accounts for ~3% of total energy intake, whereas for weight gain and catch-up growth, requirements range from 10% to 12% or 13% to 17% of total energy [29]. However, actual protein needs for optimal growth may be higher when accounting for protein quality [30]. Optimizing these targets remains challenging because protein absorption varies based on the food matrix and individual patient needs [31]. Moreover, children with SAM require higher protein intake during infections [32], whereas those presenting with edema may experience reduced protein utilization and decreased plasma amino acid concentrations [33].

A study showed that aromatic amino acids increased protein synthesis in children with SAM [34] and another suggested that milk (casein and whey) proteins were superior to soybean protein [35]. However, other clinical studies did not find differences in MAM children's recovery with different protein qualities [36] or types [37]. It would be advisable to repeat the trial with a higher protein quality in PM (PDCAAS ≥ 0.9) with a similar PDCAAS as ChSMS.

The type of protein could also influence recovery from acute and chronic malnutrition. Although some evidence shows that aromatic amino acids increase protein synthesis in children with SAM [34] and that milk proteins (casein and whey) outperform soybean protein [35], other clinical trials reported no differences in MAM recovery across varying protein qualities [36] or types [37]. To understand these variables, future trials should test a PM formulation with a higher protein quality comparable with that of ChSMS (PDCAAS ≥ 0.9). This would clarify whether the observed differences in malnutrition recovery are driven by protein type or protein quality. Furthermore, future studies should evaluate regional and manufacturer variability in commercially produced PM-RUTFs to determine if protein quality, palatability, and therapeutic performance differ among products manufactured in Europe, North America, and LMICs. Regular auditing should be needed to ensure long-term quality control.

What about rat acceptability of the formulations?

Beyond the compositional differences between ChSMS and PM, the superior growth observed in the ChSMS group may be partly attributable to higher voluntary food intake. Rats consuming the ChSMS formulation ingested significantly greater quantities than those fed PM (Figure 4A). After an initial decline—consistent with adaptation to a novel RUTF—intake of ChSMS recovered to levels comparable to or exceeding those of

the control (CT) diet. To the contrary, PM consumption remained consistently lower throughout the study. This pattern points to reduced palatability or acceptability of the PM formulation, which likely contributed to the impaired recovery observed in this group.

Rats typically exhibit neophobia toward novel foods, resulting in a transient reduction in intake; over time, animals adapt, and if the food is acceptable, food intake returns to normal levels [38]. In this context, the sustained lower intake of PM indicates incomplete adaptation. Palatability is a primary determinant of food intake in rodents [39]. Although the CT and MN diets were provided as dried pellets, both ChSMS and PM were lipid-based, paste-like RUTFs—a novel format that likely triggered an initial neophobic response. Remarkably, ChSMS shares ingredient profiles (cereals and legumes) with the familiar CT and MN diets, whereas PM contains dried milk and peanuts, which may have been less familiar and therefore less acceptable to the rats. Furthermore, the higher fiber content of the ChSMS formulation may have enhanced its acceptability, as more abrasive textures support natural grinding behavior and dental wear (Steven Belmain, rat expert, personal communication). Together, these behavioral and textural factors likely contributed to the higher intake and improved growth outcomes observed with ChSMS. The rat preference for ChSMS as compared with PM may not, however, be translatable to children.

Treatment for both acute and chronic forms of malnutrition

One limitation of using animal models is their short lifespan, which makes it challenging to accurately replicate AM. In our study, rats subjected to the MN treatment gradually reduced their food intake over an extended period (3 wk). Consequently, this model—originally designed to represent AM—also induced stunting and reflected features of chronic malnutrition.

When these stunted rats were subsequently transitioned to the plant-based RUTF, partial catch-up growth was observed, including improvements in linear growth. This suggests that the formulation may have potential not only for treating AM but also for addressing chronic forms.

In children, stunting can be treated using lipid-based supplements, which showed substantial efficacy in recent studies [40]. These supplements, administered in smaller quantities, share similarities with RUTF in their nature (paste-like food) and composition [41]. Moving forward, the development of a unified product that targets both acute and chronic malnutrition could offer a more efficient and cost-effective strategy for tackling this global public health challenge.

The need for sustainable approaches to malnutrition treatment

The current model for treatment AM relies on imported RUTF [41]. Our work shows that locally available African crops—soybean, chickpea, sorghum, and maize—could be formulated into an efficacious RUTF product. Because this formulation is dairy-free, it eliminates the need for expensive imported powdered milk, offering a cost-saving alternative for food industries in sub-Saharan Africa. Furthermore, it utilizes indigenous ingredients and hence could strengthen local economies and fortify agricultural value chains for local smallholder

farmers [11]. Several reviews have highlighted the sustainability benefits of novel RUTFs utilizing locally sourced ingredients [42,43]. One randomized controlled trial in Indonesia [44] found that RUTFs formulated with mungbean, soybean, or peanut achieved comparable recovery rates (measured by weight gain) and had superior acceptability among children with uncomplicated SAM. These findings align with our results and highlight the viability of locally produced therapies. Ultimately, combining plant-based proteins from legumes with nuts, seeds, and cereals offers a more affordable global health and environmental solution, provided the overall amino acid profile and protein quality of the mixture remain high.

However, although plant-based diets offer distinct advantages, the inclusion of ultraprocessed foods (UPFs) could compromise developmental outcomes. Under the NOVA system, traditional RUTFs could be categorized as ultraprocessed industrial formulations due to their high content of fat, sugar, and sometimes additives, such as emulsifiers. Recent preclinical studies using a similar young rat model demonstrated that a UPF-heavy diet (modeled on fast food) significantly hinders growth and skeletal maturation [45]. Despite falling under the industrial formulation category, we argue that our plant-based RUTF avoids these adverse effects: its core ingredients are minimally processed, potentially harmful chemical emulsifiers were replaced by a natural chickpea isolate, and the final product features a high fiber content within a precisely designed, quality-controlled matrix. Finally, nutritional interventions must be carefully designed to prioritize true nutrient density over ultraprocessed alternatives, backed by rigorous clinical monitoring. Beyond immediate health objectives, the development of novel RUTFs should adopt a holistic approach that actively encompasses environmental and socio-economic sustainability.

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Author contributions

The authors' responsibilities were as follows – AB, EM-O, ADT: designed the research; EM-O, ADT: developed the protocol; PA, AB: developed the plant-based formulation; LU, AS, MK, EM-O: conducted the preclinical experiment; MM: conducted protein quality analysis; LU, PA, AB, AS, EM-O, MM: conducted data analysis; AB, EM-O: drafted the manuscript; AB: edited the manuscript to improve its readability; CKN, RR, AW: provided overall advice and guidance to the team; and all authors: reviewed and approved the final version.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Gemini in order to edit the text: AI technologies were used exclusively for editing purposes (grammar and vocabulary), not to generate ideas or concepts. The authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available on request pending (e.g., application and approval, payment, and other).

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