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Effect of Locally Produced Ready-to-Use Therapeutic Food on Children under Five Years with Severe Acute Malnutrition: A Systematic Review

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ABSTRACT

This review assessed the effect of Ready-to-Use Therapeutic Food (RUTF) on children under five years with Severe Acute Malnutrition (SAM). The reviewed studies were obtained from six databases. Using the search strategy, 3,521 studies were selected. After title and abstract screening, 75 studies were obtained for further full article screening. The inclusion criteria were types of study (RCT, quasi-RCT, or crossover), participants (SAM children aged 6−60 months with no complications), interventions (locally produced RUTF and standard RUTF), and outcome measures (recovery rate, mortality rate, weight gain rate, height gain rate, length of stay, weight-for-age z score, height-for-age z score, weight-for-length z score, anemia status, blood iron status, serum albumin, plasma amino acid level, adverse effects and acceptability of RUTF). A total of 33 studies were included in this review. Nine out of twenty-two studies that used standard RUTF had positive effects on recovery outcomes in children with SAM. The alternative RUTF produced from local protein sources showed slightly lower positive effects on SAM treatment than those of standard RUTF. Since the studies used different methods to assess the outcome, no formula could be selected as the best formula and selection should be made based on individual research objectives. In conclusion, both standard and the alternative locally produced RUTF can be applied for treatment of SAM by considering the local preferences, ingredients availability, production sustainability and product safety.

Keywords: CMAM, local protein sources, RUTF, SAM, weight gain

INTRODUCTION

The Basic Health Survey performed by the Indonesian Ministry of Health in 2018 showed that there had been an improvement in the nutritional status of children under five years in Indonesia (Ministry of Health of Republic of Indonesia (MoH RI) 2018). Stunting decreased from 37.2% in 2013 to 30.8% in 2018, while wasting decreased from 12.1% in 2013 to 10.2% in 2018. The wasting prevalence data indicate that severe wasting is still high, where 5.3% and 3.5% of children were severely wasted in 2013 and 2018, respectively. It means that almost one million children under five years of age in Indonesia experience severe acute malnutrition. Even though the number is decreasing, the decline was still deemed insignificant since the World Health Organization (WHO) set the limit of malnourishment prevalence to 20%. Moreover, the reduction of stunting is also one of the targets of Sustainable Development Goals (SDGs), which is in the second goal of “zero hunger." Therefore, along with the United Nations (UN), Indonesia is committed to eradicating any forms of malnourishment, including achieving the world's target regarding stunting and wasting in children by 2025.

Childhood malnutrition may bring long-term effects, i.e. cognitive impairment, delayed motor growth, poor physical performance, low birth weight of future offspring, behavioral

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issues, poor academic performance and low productivity in adulthood (Victoria *et al.* 2008). One of intervention methods that has been used in many countries is the provision of Ready-to-Use Therapeutic Food (RUTF) and Ready-to-Use Supplementary Food (RUSF). Children with severe and acute malnutrition that are managed as inpatients or outpatients can be given RUTF. Many studies have assessed the efficacy and effectiveness of various types of both RUTF and RUSF. Both are lipid-based products fortified with nutrients to treat acute malnutrition in children aged 6−59 months. Their formulations have to comply with WHO specifications. They have to be produced as products that require no cooking so that they can be immediately consumed by the targeted consumers. They are formulated to be high in energy and protein to support the recovery and weight gain of acutely malnourished children by rebuilding their lean tissues and supplementing their dietary nutrient deficiencies (De Pee & Bloem 2009).

Although they seem to be similar, RUSF and RUTF have some differences. RUSF is used to manage Moderately Acute Malnourished (MAM) children aged 6−59 months, while RUTF is used to treat Severely Acute Malnourished (SAM) children of the same age. RUTF can be provided for SAM children admitted in Outpatient Therapeutic Care (OTC) at local health centers with the condition that the children do not have any other medical complications and their appetite and sensory detection skills are not compromised. The dose of RUSF is standardized at 500 kcal/day, while the RUTF dose depends on the children's weight. When there is an improvement in weight gain, the dose should be readjusted. There has been a guideline available for the production of RUTF issued by the joint committee of WHO and FAO in 2019 (Codex Alimentarius Commission 2019).

Few reviews have been published on RUTF (Schoonees *et al.* 2019; Potani *et al.* 2021), however they did not specifically discuss the effectiveness of locally produced alternative RUTFs as compared to the standard RUTF. Therefore, this review was conducted to identify the effect of RUTF on children under five years old children with SAM by including studies that used locally produced alternative RUTFs. Several outcome measures were included as indicators namely anthropometric measurements, biochemical markers, adverse effects and the acceptability test. Findings from this review will provide insights for health practitioners or organizations involved in clinical guidelines development as well as policy makers dealing with SAM.

METHODS

Search strategy

Studies were searched from several databases (The Cochrane Central Register of Controlled Trials, PubMed, Science Direct, Wiley online library, BMJ global health and Oxford Academic). The search strategy did not apply language and date restrictions. The keywords used were "RUTF, SAM", "RUTF and SAM", "ready to use therapeutic food", "ready to use therapeutic food and severe acute malnutrition", "severe acute malnutrition" and "ready to use therapeutic food". The snowball technique was also used to search studies from references listed in related studies. A critical appraisal of the literature screened, selected and included for use in this study adhered to the guidelines as recommended by Young & Solomon (2009).

Studies were selected based on predefined inclusion criteria including types of study (Randomized Controlled Trial (RCT), quasi-RCT or crossover), participants (SAM children aged 6−60 months with no medical complication; weigh-for-height z score under -3 standard deviation; middle upper arm circumference under 115 mm; oedema exist), interventions, and outcome measures (recovery rate, mortality rate, weight gain rate, height gain rate, middle upper arm circumference gain length of stay, weight-for-age z score, height-for-age z score, weight-for-length z score, anemia status, blood iron status, serum albumin, plasma amino acid level, adverse effects and acceptability of RUTF). The exclusion criteria were record duplication, intervention strategy without RUTF, type of study using observational review, subject without SAM, subjects' age other than 6−60 months and outcome measures other than stated in the inclusion criteria.

Data collection and extraction

All records were screened by titles and abstracts obtained from the search and studies that met the predetermined eligibility criteria were selected. In manuscript screening, at least two out of six authors agreed to select a manuscript. When there was a disagreement, then another author would be asked for opinion. The results of the screening steps were presented in Table 1. Once a manuscript was selected, the full text was accessed and information on each of the following aspects: study design, intervention (subject group, dose and duration), outcome and results, were extracted. Result synthesis was made based on the strength of the evidence obtained from the selected studies.

RESULTS AND DISCUSSION

The search strategy performed in this review yielded 3,521 records. From those records, as many as 3,220 studies were excluded based on title and abstract screening, leaving about 301 studies. Next, as many as 226 studies were excluded because they did not include RUTF in their treatment for children with SAM. After that, 43 studies were excluded since they did not fulfill the inclusion criteria. Finally, a total of 33 studies were included in this review. The outcomes observed was taken from a total of 18,668 subjects from all the studies included (Table 1). This shows the strength of the evidence of this review. Figure 1 shows the flow of the systematic review and Table 1 shows the details of the 33 studies.

Recovery rate

Thirteen studies evaluated the effect of RUTF on recovery of children with SAM, with a total of 14,772 children as subjects of the studies. All studies used RCT. Two of them randomized the participants by assigning them to clusters. This finding shows that two updated studies had not been included in the previous review by Schooness *et al.* (2019), which stated that there were eleven studies reporting recovery rate. Studies in this review measured recovery in different ways. Bahwere *et al.* (2014) and Bahwere *et al.* (2017) defined recovery rate as the percentage of children recovered from the study divided by the total number of children who exited the study. Bahwere *et al.* (2016) defined recovery as the absence of bilateral pitting edema and a minimum stay in the program for one month and the case of children admitted with bilateral pitting edema, being clinically well and a MUAC >11.0 cm. Kohlmann *et al.* (2019); Bhandari *et al.* (2017); Jadhav *et al.* (2019); Oakley *et al.* (2010);

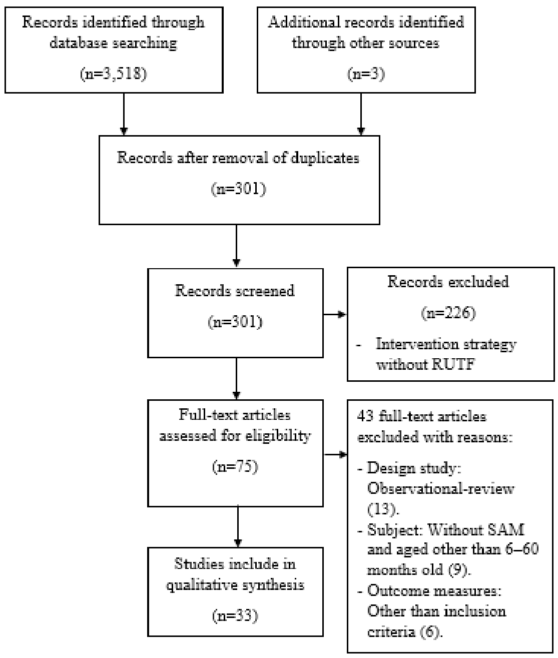

Figure 1. Study flow diagram

Table 1. Studies included in this review

Author (year)	Study design	Number of subjects	Intervention	Outcome measure
Manary *et al.* (2004)	RCT	282	-RUTF -Multivitamin/mineral-fortified RUTF -Maize/soy flour	-Height gain rate -MUAC gain -Weight gain rate
Ciliberto *et al.* (2005)	A controlled, comparative, clinical effectiveness trial	1065	-Home-based therapy with RUTF -Standard therapy	-WHZ -Weight gain rate -Adverse effect
Kerac *et al.* (2009)	RCT	795	-Standard RUTF + synbiotic 2,000 forte -Standard RUTF	-Weight gain rate -Adverse effect
Oakley *et al.* (2010)	RCT (double-blind)	1087	-10% milk RUTF -25% milk RUTF	-Recovery rate -Height gain rate -Weight gain rate
Singh *et al.* (2010)	RCT	112	-Locally produced RUTF -High-calorie cereal milk (HCCM)	-Recovery rate -Blood iron status -Serum albumin -Weight gain rate
Thakur *et al.* (2012)	Quasi trial	98	-L-RUTF: locally made RUTF -F-100	Weight gain rate
Nga *et al.* (2013)	Cross over	67	-Local RUTF (bar) -Plumpy'Nut (paste)	Acceptability
Shewade *et al.* (2013)	RCT	26	-RUTF, supplementary nutrition, feeding counseling, -No-RUTF; only supplementary nutrition and feeding counseling	Weight gain rate
Bahwere *et al.* (2014)	RCT non-inferiority	522	-Milk whey protein-based RUTF -Peanut-based RUTF	Recovery rate
Kaleem *et al.* (2014)	RCT	270	-Imported RUTF -High-Density Diet (HDD) -HDD +micronutrient supplement	-Recovery rate -Weight gain rate
Hsieh *et al.* (2015)	A prospective, randomized, double-blinded, clinical effectiveness trial	141	-Standard RUTF -High oleic acid RUTF	Recovery rate
Irena *et al.* (2015)	RCT (non-blinded)	277	-Peanut-based RUTF -Sorghum-maize-soy RUTF	Weight gain rate

Continue from Table 1

Author (year)	Study design	Number of subjects	Intervention	Outcome measure
Jones *et al.* (2015)	RCT double-blind	61	-Flaxseed oil based-RUTF -Flaxseed oil based-RUTF with addition fish oil capsules -Standard RUTF	Acceptability
Maust *et al.* (2015)	Cluster-RCT	1957	-Integrated management -Standard management	-Recovery rate -Weight gain rate -Adverse effect
Bhandari *et al. (*2016)	Randomized multicenter trial	636	-RUTF-C (centrally produced) -RUTF-L (locally produced) -A-HPF (micronutrient-enriched (augmented) energy-dense home prepared foods)	-Recovery rate -Weight gain rate -Adverse effect
Bahwere *et al.* (2016)	Simple RCT, non-blinded	817	-Dairy-free sorghum-maize-soy RUTF -Peanut-based RUTF	-Recovery rate -Weight gain rate -Mortality rate
Bahwere *et al.* (2017)	A nonblinded, 3-arm, parallel-group simple randomized controlled trial	1075	-Dairy-free, soy, maize and sorghum-based RUTF; -Milk, soy, maize and sorghum-based RUTF -Standard RUTF (peanut and milk–based RUTF)	-Recovery rate -Length of Stay -Weight gain rate -Adverse effect
Ravichandra *et al.* (2017)	RCT	120	-Locally produced RUTF -F-100	-Recovery rate -MUAC gain -Length of stay -Weight-for-length z score -Weight gain rate -Height gain rate
Thapa *et al.* (2017)	RCT	112	-Nutreal RUTF -Defined food	Acceptability
Versloot *et al.* (2017)	RCT (non-blinded)	64	-F100 -F75+RUTF -RUTF	-Length of stay -Adverse effect
Choudhury *et al.* (2018)	A clinical triall with a cross-over design	30	-Rice lentils RUTF -Chickpeas RUTF -Plumpy'Nut	Acceptability
Sato *et al.* (2018)	RCT (non-blinded)	466	-Dairy-free sorghum-maize-soy-RUTF -Milk-sorghum-maize-soy -RUTF -Peanut-milk-RUTF	-Plasma amino acid level -MUAC gain
Sigh *et al.* (2018a)	RCT	75	-NumTrey RUTF -BP100	-Height gain rate -WHZ -HAZ -MUAC gain -Weight gain rate

Continue from Table 1

Author (year)	Study design	Number of subjects	Intervention	Outcome measure
Sigh *et al.* (2018b)	Cross over	52	-NumTrey RUTF -BP100	Acceptability
Akomo *et al.* (2019)	RCT	92	-Dairy-free sorghum-maize-soy RUTF -Milk-sorghum-maize-soy RUTF -Peanut-milk RUTF	-Anemia status -Blood iron status
Kangas *et al.* (2019)	RCT	179	-Reduced RUTF dose -Standard RUTF dose	-Weight gain rate -Height gain rate
Kohlman *et al.* (2019)	RCT, double-blind	1027	-Alternative RUTF -Standard RUTF	-Recovery rate -MUAC gain -Mortality rate -Weight gain rate
Jadhav *et al. (*2019)	An open prospective randomized controlled trial	880	-Indigenous RUTF Medical Nutrition Therapy (MNT) -Standard Nutrition Therapy (SNT)	-Recovery rate -Weight gain rate
Kangas *et al.* (2020)	RCT (non-inferiority study design)	179	-Reduced RUTF dose -Standard RUTF dose	Body composition
Bailey *et al.* (2020)	RCT (cluster) non-inferiority trial	4110	-RUTF treatment with different dose based on MUAC -Standard protocol in each country (RUTF for SAM)	-Recovery rate -Length of stay
Hendrixson *et al.* (2020)	RCT triple blinded	1406	-Oat, peanut and skim milk-based RUTF -Peanut-based RUTF	Weight gain rate
Hossain *et al.* (2020)	Double-blind, randomized non-inferiority trial	120	-Dairy-free soy-based RUTF -Milk-based standard RUTF	-WHZ -MUAC gain -Body composition -Weight gain rate

Bailey *et al.* (2020); Kaleem *et al.* (2014); Singh *et al.* (2010); Maust *et al.* (2015); Hsieh *et al.* (2015); and Ravichandra *et al.* (2017) measured recovery by WLZ >2 SD or MUAC >12.4 cm, WHZ ≥-2 SD and absence of edema, WHZ >-3 SD or MUAC >115 mm, WHZ >-2 SD and no edema, MUAC ≥125 mm and no edema, target weight gain and MUAC ≥11.5 cm, WAZ ≥-2 SD, MUAC >12.4 cm or WHZ ≥-2 SD, had a MUAC >12.4 cm, without edema within 12 weeks of enrollment, attained weight for height Z score of 1 SD below the median of WHO reference and had lost edema for those acute edematous malnutrition, respectively.

Similar to previous reviews (Schooness et *al.* 2019), several studies have compared the effects of giving alternative and standard RUTFs. The others compared the effects of RUTF with F100, energy-dense home-prepared foods, High-Density Diet (HDD) and high-calorie cereal milk (HCCM). The doses of RUTF were 150 kcal/kg/day, 175 kcal/kg/day and 200 kcal/kg/day.

The management of SAM with standard hospital-based protocol proposed by WHO showed that the recovery rates were around 80% (Bhutta *et al.* 2013; Hossain *et al.* 2020; Khanum *et al.* 1998). The highest result found in this review was shown by Ravichandra *et al.* (2017) where 100% of children given Locally-Prepared RUTF (L-RUTF) recovered, even though they did not mention how long the duration of the intervention was. Most studies did not report the duration of the intervention. According to studies that mentioned the intervention duration, the intervention was carried out for two to four months.

These findings indicates that the management of SAM in children without any medical complications by administering RUTF affects recovery positively than standard protocol in a hospital, even the recovery rate exceeds the SPHERE minimum standards of more than 70% (Bahwere *et al.* 2014). It is in line with previous review by Schooness *et al.* (2019), which revealed that RUTF may improve recovery. Furthermore, a more recent study by Kangas *et al.* (2019) found that reduced dose of RUTF successfully supported recovery in children suffering from SAM without any side effects.

Height gain rate

Linear growth is commonly measured in studies with children with MAM where 2.8 mm/week growth rate was expected in healthy 13-month-old children (WHO 2006). The previous review included four studies that measured this outcome (Schooness *et al.* 2019). However, there was another study conducted in 2010 by Oakley *et al.* All these five studies reported height gain in 2,530 children with SAM with provision of RUTF. Kangas *et al.* (2019) measured height gain after sixteen weeks of intervention and they showed that there was height gain by around 0.63 mm/day with a dose of 1−2 sachets of standard RUTF per day.

In another study by Ravichandra *et al.* (2017) who compared the use of their own Local RUTF formula (L-RUTF) with F-100 formula that is commonly used to treat malnutrition, height gain was measured when participants reached a weight-for-height z score 1 SD below the median. They reported that the height gain of the L-RUTF group was better than that of the F-100 group (0.56 mm vs. 0.42 mm). It shows that locally produced RUTF is as potential as standard RUTF in improving height gain of children with SAM.

Weight-for-height z score (WHZ)

Sigh *et al.* (2018a); Ciliberto *et al.* (2005); and Hossain *et al.* (2020), measured and reported WHZ. A newer study by Hossain *et al.* (2020) evaluated WHZ as an endline value of twelve weeks of intervention. Sigh *et al.* (2018a) also measured WHZ as an endline value and they did not mention how long the intervention was. Another study measured WHZ until the subjects (children) attained a WHZ -2 SD. Among the three studies, the best improvement in WHZ was shown by Hossain *et al.* (2020), where the soy-based RUTF group attained 1.22 of WHZ score and milk-standard RUTF group attained 1.22 of WHZ score. The more significant improvement of WHZ in children receiving home-based therapy with RUTF was achieved because of more rapid weight gain and fewer symptoms of infection happened during their recovery period than in children receiving standard therapy (Ciliberto *et al.* 2005). The time point to measure WHZ among these studies was different. This review's findings are in line with the review by Schoonees *et al.* (2019) indicating that both standard RUTF and locally-produced RUTF may improve WHZ in children with SAM.

Height-for age z score (HAZ)

A study by Sigh *et al.* (2018a), which involved 75 children under five years who experienced SAM, evaluated HAZ after providing interventions including fish-based RUTF (NumTrey) and BP-100 (compressed bar RUTF). They showed no statistically significant difference between the standard RUTF (BP-100) and the alternative RUTF (fish-based RUTF or NumTrey) for HAZ in children under five. This finding indicates that formulation of RUTF with other protein sources, such as fish, might bring positive effect as good as standard formulation that uses milk, since the WHO recommends that at least 50 % of protein should come from milk (WHO/WFP/UNSCN/UNICEF 2007). According to Schoones *et al.* (2019), after eight-week of intervention, there was no significant difference in HAZ between standard RUTF and locally-produced alternative RUTF. Meanwhile, other reviews (Bhutta *et al.* 2008; Gera 2010) did not discuss this outcome. As acute malnutrition is linked to an increased risk of stunting, HAZ is also an important parameter to be considered in the management of SAM.

Mid-upper arm circumference (MUAC) gain

Seven studies reported the measurement of MUAC gain in 6,088 children under five years. All of those studies were randomized controlled trials. Hossain *et al.* (2020) and Ravichandra *et al.* (2017) measured MUAC gain after twelve weeks of intervention and children attained WHZ 1 SD below the median, respectively. The other studies did not include data on the duration of intervention. Based on the seven studies, MUAC gain ranged from 0.42 mm/day to 0.9 mm/day. An updated study by Hossain *et al.* (2020) that compared milk-based RUTF (standard RUTF) with soy-based RUTF (dairy-free alternative RUTF) showed an increase in MUAC at the end of the intervention between two groups, namely 0.9±0.7 and 0.9±0.6 cm, respectively. This finding reinforces the findings by Schooness *et al.* (2019), which stated that there was no significant difference between the standard RUTF group and the locally-produced alternative RUTF. Since MUAC has the advantage of being more sensitive in younger children, measuring MUAC is essential for monitoring the condition of children with SAM (Goossens *et al.* 2012).

Body composition

Two studies included in this review listed body composition as one of the outcomes measured. The total subjects included in those studies were 199 children. This type of outcome was not included in the previous reviews (Schooness *et al.* 2019; Bhutta *et al.* 2008; Gera 2010). An updated study by Hossain *et al.* (2020), which compared dairy-free soy-based RUTF to standard milk-based RUTF after twelve weeks of intervention, showed that the average values of final fat-free mass and fat mass in the soy-based RUTF group were higher than those of the milk-based RUTF group (p>0.05). The final total body water was higher in the milk-based RUTF group than in the soy-based RUTF group.

Another study by Kangas *et al.* (2020) compared the effect of providing reduced dose RUTF to standard dose RUTF in children under five years with SAM for sixteen weeks. There was no difference observed in Fat-Free Mass (FFM), Fat Mass (FM) or Fat Mass Index (FMI) between the groups at recovery. Not only depending on the type of diet used, the proportion of different tissue accretion also depends on the nutritional status of the subjects at admission (MacLean & Graham 1980; Radhakrishna *et al.* 2010). Studies that measured body composition indicated that both standard RUTF and locally-produced RUTF may improve body composition of children with SAM without medical complications.

Length of stay (LoS)

Four studies determined length of stay as an outcome measure. Bahwere *et al.* (2017), who compared two alternative RUTFs (Dairy-Free Sorghum-Maize-Soy (F-SMS) RUTF and Milk Sorghum-Maize-Soy (M-SMS) RUTF) to standard RUTF (peanut and milk-based (PM) RUTF), reported that the length of stay of the two alternative RUTFs (FSMS RUTF (n=144); MSMS RUTF (n=144)) was not inferior to the standard RUTF (PM RUTF (n=143)). Ravichandra *et al.* (2017) showed that LoS in children treated with locally-produced RUTF was significantly shorter than that of children treated with F-100 at thirteen and seventeen days, respectively. Versloot *et al.* (2017) reported that there were no differences in the average length of stay among the three feeding strategies (F100, RUTF + F-75, RUTF), which was 7.0 days (SD 3.4). Bailey *et al.* (2020) also revealed that there were no differences in the average length of stay among the two strategies intervention (RUTF treatment with different dose based on MUAC, Standard protocol in each country (RUTF for SAM)) which was 64.5 and 65 days, respectively. WHO's recommended criteria for discharging children from treatment are when they have WHZ or WLZ ≥- 2, or MUAC ≥125 mm and no edema for at least two weeks (WHO 2013). It is similar to the previous review by Schoonees *et al.* (2019), which found no significant differences in terms of length of stay between standard RUTF group and alternative RUTF group. The finding of this review indicates that SAM treatment with locally-produced RUTF was not lower than the standard RUTF in terms of length-of-stay.

Mortality rate

Three studies comparing the alternative RUTF to the standard RUTF, with a total of 3,228 children as subjects, reported mortality rate as one of the outcomes included in their studies. The three studies showed low mortality rate due to treatment of SAM children with RUTF. Bahwere *et al.* (2014), who evaluated the effect of WPC-RUTF (whey protein concentrate-based RUTF) compared to the standard RUTF (peanut-based RUTF), showed that the mortality rate of the WPC-RUTF group (1.9%) was slightly higher than that of the standard RUTF group (0.8%) on both ITT (Intention-to-Treat) analysis and PP (per-protocol) analysis. A similar result was also reported by Bahwere *et al.* (2017), who compared the effect of giving F-SMS RUTF (Dairy-Free Soy, Maize and Sorghum RUTF) and M-SMS RUTF (Milk, Sorghum, Maize and Soy RUTF) to the standard RUTF. Analysis on ITT and PP showed that the F-SMS RUTF group (2.5%) and M-SMS RUTF group (1.7%) had slightly higher mortality rate than the standard RUTF group (1.3 %). In contrast, Kohlman *et al.* (2019) reported 0.5 % mortality rate in their study that used locally-produced RUTF, which was lower than in the standard RUTF (1.5%). A systematic review by Gera (2010) reported that locally-produced alternative RUTF had mortality rate as low as that of the standard RUTF, which was less than 1%. Although there were three studies that measured mortality rate, a meta-analysis by Schoonees *et al.* (2019) concluded that there was very low-quality evidence in terms of mortality rate in studies that used RUTF.

Anemia and iron status

Studies by Singh *et al.* (2010) and Akomo *et al.* (2019) with a total of 504 children as subjects reported the effect of RUTF on anemia and iron status in children with SAM. Singh *et al.* (2010) who compared the administration of locally-produced milk and peanut-based RUTF with High-Calorie Cereal Milk (HCCM) with doses of 5.5 kcal/g and two serving portions, respectively, found that there was an increase of hemoglobin level in both groups (RUTF group had lower result than HCCM). Although the increase of hemoglobin level was reported, but the percentage of iron content in each treatment food was not reported.

Akomo *et al.* (2019) used alternative F-SMS RUTF (Dairy-Free Soy, Maize and Sorghum RUTF) and M-SMS RUTF (9% Milk, Soy, Maize and Sorghum) as compared with the standard (milk and peanut-based) RUTF. The researchers allowed children to eat RUTF ad libitum. However, this study did not state how long the intervention was performed. The results indicated that although the alternative RUTF used cereals, the prevalence of anemia, iron deficiency and iron deficiency anemia in these treatment groups was lower than the standard RUTF group. This might be due to the high content of casein, whey and calcium found in milk that inhibit iron absorption (Cercamondi *et al.* 2013). Moreover, the alternative RUTFs used higher content of iron and vitamin C to achieve the ratio of the optimum phytic acid to iron molar for iron absorption. This study also suggests that the iron content in the current standard RUTF needs to be increased since it is not enough to improve the anemia status in malnourished children. These two studies demonstrated that provisioning locally-produced RUTF is a feasible intervention to improve anemia status in malnourished children.

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Albumin and amino acid level

The amino acid level was one of the outcomes reported by Sato *et al*. (2018) that used alternative RUTF similar to that of Akomo *et al.* (2019). Sato *et al.* (2018) measured amino acids (methionine, leucine, valine, isoleucine, lysine, phenylalanine, tryptophan, threonine, histidine, BCAA (Branched-Chain Amino Acids), EAA (Essential Amino Acids), and cystine) level in children with SAM after administering 200 kcal/kg/day of alternative RUTF and standard RUTF. The results showed that the EAA plasma concentrations in 6−59 months old children with SAM treated with the alternative RUTF were not less than those of children treated with the standard RUTF. SAM children who obtain adequate protein and amino acids from their diet may get improvement in their MUAC as well as the absence of bilateral pitting edema (Sato *et al.* 2018). The positive effect of RUTF on protein synthesis was also shown by Singh *et al*. (2010) who found higher increase of serum albumin in the RUTF group than the HCCM group.

Another study that supplemented Aromatic Amino Acids (AAAs) on SAM children also showed positive effect with faster rate of protein synthesis after supplementation with 330 mg/kg/day of AAAs as compared with isonitrogenous Alaninesupplementation during recovery phase (Hsu *et al.* 2014). The non-inferior results of EAA plasma, including methionine and cysteine, in both alternative RUTF groups (AAAs and Isonitrogenous Alanine Suplementation) suggested that the recovery from malnutrition under alternative RUTF treatment was possibly due to the achievement of the stable supply of

GSH Glutathione) by maintenance of plasma methionine and cysteine levels. With the positive effects shown in recovery rate and weight gain reported in a previous study by Bahwere *et. al* (2017), this review supports the conclusion that the protein source or RUTF does not influence the effectiveness of the product as long as the amino acid composition is well balanced.

Weight gain rates

The total number of subjects involved in the studies that measured weight gain rate was 12,871. From 21 studies that included weight gain as the outcome, only two studies met the SPHERE Standard in weight gain of 5 g/kg/day (Bahwere *et al.* 2017; Irena *et al.* 2015). Several studies compared RUTF with other nutrition management programs. Six studies reported that RUTF had a better outcome in weight gain compared with several other programs, such as High Calories Cereal Meal (HCCM), maize and soy flour-based supplementary food, RUTF with vitamin supplementation and F-100 formula (Bhandari *et al.* 2016; Jadhav *et al*. 2019; Singh *et al.* 2010; Ravichandra *et al.* 2017; Thakur *et al.* 2012; Manary *et al.* 2004; Shewade *et al.* 2013). Two studies that compared alternative RUTF with standard RUTF showed lower weight gain rates (Hossain *et al.* 2020; Oakley *et al.* 2010). Two other studies showed lower weight gain in RUTF treatment than High-Density Diet (HDD) and standard management programs (Kaleem *et al.* 2014; Maust *et al.* 2015). Those studies showed that RUTF treatment had better outcome in weight gain compared to other treatments.

Other studies that used alternative RUTFs (cereal and legume-based RUTF, reduced dose RUTF) and compared the non-inferiority analysis with the standard milk and peanut-based RUTF showed that alternative RUTFs were not inferior to standard RUTF in weight gain rate (Bahwere *et al.* 2014; Bahwere *et al.* 2016; Bahwere *et al.* 2017; Kangas *et al.* 2019). Five studies showed no differences between alternative RUTFs (cereal, legume and fish-based RUTF, RUTF with symbiotic 2,000 Forte , cereal and legume-based RUTF) and standard RUTF (Sigh *et al.* 2018a; Kerac *et al.* 2009; Irena *et al.* 2015). All these studies used alternative protein sources such as legumes, fish and combination of cereals and legumes to reduce dependency on milk or other dairy products. Potani *et al.* (2021) stated in their review that RUTF containing less dairy could be a lower-cost option for treatment of SAM. Those studies showed that locally-produced alternative RUTF did not have significant difference in terms of weight gain as compared to the standard RUTF.

The results of reducing RUTF dose to weight gain rate were varied. Manary *et al.* (2004) found that provisioning of RUTF to fulfill 33% of energy requirement did not result in a better outcome than the standard dose. While Kangas *et al.* (2019) and Kangas *et al.* (2020) stated that the effect of reduced RUTF dose on the tissue accretion of treated children was not different from the standard treatment. The same result was also found in Jones *et al.* (2015), which concluded that reduced RUTF dose in combined treatment was non-inferior to the standard care that used a higher dose of RUTF. Weight gain results shown by these studies ranged from 0.7 to 9.95 g/kg/day for the alternative RUTFs and from 0.6 to 7.3 g/kg/day for the standard RUTF with approximately 90 days of ntervention. Those studies showed that reduced dose of RUTF did not give significantly different result than the normal dose of RUTF.

All those findings indicate that only few studies achieved the recommended >5 g/kg/day of weight gain and that most of the studies were still under the recommended weight gain rate. The lower weight gain rate could be caused by edema, since children with edema tend to lose weight during treatment because they need a higher energy and protein intake to prevent protein depletion (Bahwere *et al.* 2014).

Adverse effects

Seven studies reported adverse effects (diarrhea) during RUTF intervention (Bahwere *et al.* 2014; Bhandari *et al*. 2016; Manary *et al.* 2004; Kerac *et al.* 2009; Versloot *et al.* 2017; Maust *et al.* 2015; Ciliberto *et al.* 2005). Bhandari *et al.* (2016) reported the number of children having diarrhea during the treatment phase. Another study by Ciliberto *et al.* (2005) measured the number of days of diarrhea per group during the first two weeks of the treatment period and found that children who received RUTF had a similar frequency of diarrhea as compared to those receiving the home-based therapy. Those studies had similar RUTF form and composition, which refer to standard peanut and milk-based RUTF, but Bhandari (2016) used locally-based ingredients and peanut paste. In the studies by Versloot *et al.* (2017) and Maust *et al.* (2015), diarrhea was recorded to be higher after the intervention with peanut paste-based standard RUTF.

On the other hand, Bahwere *et al.* (2014); Kerac *et al.* (2009); and Manary *et al.* (2004) measured the proportion of children who had diarrhea. The type of RUTF composition used in those studies was slightly different. Bahwere *et al.* (2014) used standard RUTF (peanut and milk-based) with Whey Protein Concentrate (WPC24), while Kerac *et al.* 2009 used standard RUTF (peanut and milk-based) with symbiotic 2,000 forte and Manary *et al.* (2004) used standard RUTF supplemented with 80% maize and 20% soy.

After the intervention, the highest diarrhea incident was found in the study conducted by Versloot *et al.* (2017), which might be associated to the transition phase. Diarrhea was common in all patients irrespective of the diet group, but it was more prevalent during the transition phase, with an average of 48% at the first day of admission ($p<0.05$). The percentage of children with diarrhea did not decrease during the analysis period.

Acceptability of RUTF

Studies by Choudhury *et al.* (2018); Jones *et al.* (2015); Nga *et al.* (2013); Thapa *et al.* (2017); and Sigh *et al.* (2018b) evaluated the acceptability of RUTF, with a total of 426 children as participants. Choudhury *et al.* (2018) reported that alternative RUTFs (chickpea-based RUTF and rice and lentil-based RUTF) were more acceptable than the standard milk and peanut-based RUTF. A similar result was shown by Thapa *et al.* (2017), where 93% of children participated in the study stated that the alternative RUTF (Nutreal) was acceptable for them. On the other hand, Nga *et al.* (2013) reported that the standard RUTF had a higher palatability score than the local RUTF pressed bar (alternative RUTF). This result was similar to the result shown by Sigh *et al*. (2018b) who reported that Numtrey RUTF (alternative RUTF) that was made from wafer roll filled with fish-based paste was less acceptable than BP-100 in taste trial, even though the acceptability of Numtrey RUTF increased in the intervention trial. Jones *et al.* (2015) also stated that they evaluated the acceptability of their RUTF, but unfortunately no data was found in the report.

Most of the studies included in this review showed that RUTF products in paste form had good acceptability in Africa and South Asia. However, a cross-sectional study carried out in Bangladesh (not included in this review) reported that the standard paste-form RUTF did not have good acceptability according to the children caregivers' perception., with the dissatisfaction came from the taste and consistency of the product (Ali *et al*. 2013). Although the study used caregivers' perception instead of the children, it showed that some aspects need to be considered before development of an alternative RUTF, such as the taste should be less sweet and less salty, the consistency should be less sticky and direct instructions should be provided on the packaging. Nga *et al.* (2013) also suggested that the local preference should always be considered in development of an RUTF product. Other forms of RUTF, such as pressed bar and wafer roll filled with paste, may have good acceptability among children (Nga e*t al.* 2013; Sigh *et al.* 2018b).

Limitation of the studies

The studies included in this review lack monitoring on subjects' compliance and the possibility of sharing the provided RUTF with other family members that could affect the measured outcomes. Moreover, different studies had differences in definition of recovery, cut-off points for each outcome, doses that were used, and duration of interventions that might affect the outcomes. In terms of food safety, majority of the studies did not report any microbiological tests performed or if there were any cases of diarrhea among subjects. Diarrhea is considered one of the important side effects, which may not only happen during transition phase, but it also may recur during rehabilitation phase

CONCLUSION

Standard peanut and milk-based RUTF is used in most of the studies included in this review. Nine out of twenty-two studies showed that standard RUTF had positive effects on recovery rate of SAM children. When alternative RUTF formulas were developed from locally-available ingredients such as fish (whole fish, fish oil), legumes (soy bean, mung bean, chick peas, lentils) and cereals (maize, rice, oats, sorghum), each of them showed variety of strengths in terms of outcomes measured, for example improvement in anemia status from administration of RUTF with combination of cereals and legumes, improvement of blood PUFA status in subjects treated with RUTF added with fish oil, and various other improvements in other RUTF formulas. In general, locally produced RUTF showed positive effects on recovery rate of under five years old children with SAM, with no statistically significant differences with the standard RUTF. It should be noted that compliance to the study protocols must be recorded since it may affect conclusions made.

The studies that were reviewed showed that locally produced RUTF has potentials, providing that the researchers include sensory test as an important criterion to ensure better acceptance from the subjects. Special attention should also be paid when fish is included in the formula, since its flavor is not widely accepted. Furthermore, the form of the product was also found to influence sensory acceptance from the subjects. Therefore, development of alternative RUTFs should always consider local preferences, ingredients availability, production sustainability and product safety (hygiene and sanitation).

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DECLARATION OF INTERESTS

Rimbawan Rimbawan (R R), Zuraidah Nasution (Z N) and Puspo Edi Giriwono (P E G) conceptualized the idea and methodology followed by reviewing and editing. Kharisma Tamimi (K M), Khaerul Fadly (K F) and Astrid Noviana (A N) screened resources and writing original draft. All authors have read and agreed to the published version of the manuscript.

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