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Supplements

Soy Plant-based and Fiber in Children's Gut Health, Growth & Development

Supplementary Paper:

- Benefit of Challenge of Soy Plant-based Formula in Infants and Children
- Perspective of Soy Formula and Fiber Intake among Non-Cow's Milk Drinker Pediatric Patients: A Survey among Indonesian Health Care Practitioners
- The Overview of Food Technology to Process Soy Protein Isolate and Its Application toward Food Industry
- Soy Plant-based Formula with Fiber : From Protein Source to Functional Food
- Soy Isolate Protein Formula : The Usage Beyond Allergic Indication

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SUPPLEMENTARY ARTICLE

Benefit and Challenge of Soy Plant-based Formula in Infants and Children

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Introduction

The first report of soy being administered to an infant is over 100 years old.[1] Since the 1960s the composition of soy formula has been better adapted to the nutritional needs of infants and since 2000 infant formula based on soy fulfils European Directives and legislation for infant feeding.

Soy infant formula contains a soy protein isolate (95% protein), and methionine, carnitine, taurine, iron, calcium phosphor and zinc are added. Heating destroys the anti-protease activity of soy for over 90 %. In 2016, soy infant formula was still 12% of the USA market and 25 % of infants were fed soy infant formula during their first years of life.[2]

In 2006, ESPGHAN published a consensus statement regarding soy infant formula: i) soy protein formula can be used for feeding term infants, but they have no nutritional advantage over cows' milk protein formula and contain high concentrations of phytate, aluminium, and phyto-estrogens (isoflavones), which might have untoward effects; ii) there are no data to support the use of soy protein formulae in preterm infants; iii) indications for soy protein formula include severe persistent lactose intolerance, galactosemia, and ethical considerations (e.g., vegan concepts); iv) soy protein formula have no role in the prevention of allergic diseases and should not be used in infants with food allergy during the first 6 months of life; v) if soy protein formula are considered for therapeutic use in food allergy after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.[3] The cut-off age of 6 months was debated and tended to be followed, although based on weak scientific evidence.

According to a review by Katz et al,[7] based on the information obtained out of 40 studies identified, the established weighted prevalence of soy allergies is 0 to 0.5 % (0.27) for the general population, 0.4 to 3.1 % (1.9) for the referred population, and 0 to 12.9 % (2.7) for allergic children. The prevalence of sensitization after the use of soy infant formula is 8.7 and 8.8 %, depending on the method used.[7] According to this review, there is no difference according to the age of

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6 months. A recently published Mexican consensus paper confirmed the statements of the AAP and concluded that there was no safety issue with soy infant formula.[8] Soy infant formulas have important advantages in terms of cost-benefit, palatability and effects on the intestinal microbiota, compared to other formulas.[8] Although evidence to recommend its use in functional digestive disorders is limited, soy infant formulas have an adequate safety profile and are a valid option for infant feeding.[8]

Infants fed soy infant formula have a normal growth.[9] Lactose-free formula has been recommended in the re-alimentation of an infectious gastroenteritis after failure of lactose-containing re-alimentation.[5] Lactose-free re-alimentation results in a decreased need for hospitalization according to data from Thailand.[10]

Anthropometric patterns of children fed soy infant formula are similar to those of children fed cow's milk formula or human milk.[11] Despite the high levels of phytates and aluminium in soy formula, haemoglobin, serum protein, zinc and calcium concentrations and bone mineral content were found to be similar to those of children fed cow's milk formula or human milk.[11]

Soy formulae used to contain phytates which were blamed for their chelating capacity, preventing the proper absorption of micronutrients.[12] Today, however, phytates are almost totally removed from the soy formulae.[12]

The levels of genistein and daidzein to be higher in children fed soy infant formula; however, no strong evidence for a negative effect on reproductive and endocrine functions was found.[11] Immune measurements and neurocognitive parameters were similar in all the feeding groups.[11] Phyto-estrogens are plant compounds with estrogenic activity. Those contained in soy formula (SF) are of the isoflavone class and include, in order of quantitative and biological importance, genistein, daidzein, and glycitein.[13] All have a molecular structure quite similar to that of the human female hormone 17-β-oestradiol and, consequently, have estrogenic activity, even if 1,000–10,000 times lower.[13] They are present in very large amounts in soy formula, although with differences among commercial preparations. It has been calculated that the mean daily intake of isoflavones by an infant exclusively fed with one of the presently marketed soy formula can be as high as 11 mg/kg body weight, an amount significantly higher than that necessary to exert hormone-like effects in adults.[13,14] According to other data from literature, the isoflavone intake of an infant fed breastmilk or cow milk formula is 0.005–0.01 mg/d, while with soy infant formula amounts of 6–47 mg/day are reached.[15] This intake is similar to the daily intake by an adult with a standard Asian diet (8–50 mg/d) or vegan diet (15–60 mg/day), while vegetarians have a lower intake (3–12 mg/day).[15] A standard Western diet has an isoflavone content of 0.5 – 3.5 mg/day.[15]

A global evaluation of the impact of modern soy formula on human development seems to suggest that their use is not associated with relevant abnormalities.[13] The negative influence of isoflavones, which has been repeatedly demonstrated in developing animals, has not been evidenced with the same relevance in humans. Only children with congenital hypothyroidism can have problems and require re-modulation of thyroid hormone replacement doses. The potential harmful effects of soy isoflavones on child development cannot be definitively excluded.[13] The consumption of soy-based infant formula is not associated with early onset of puberty.[16] Relative to girls fed with cow-milk formula, those fed with soy formula demonstrated tissue and organ-level developmental trajectories consistent with response to exogenous estrogen exposure.[17] However, these effects seem to be transitory as no early infant feeding effects were found on reproductive organs volumes and structural characteristics in children age 5 years.[18]

The other concern to take into consideration is the use of transgenic soy in formulas.[12] The US Department of Agriculture records that up to 93% of soybean crops are transgenic.[12] Adverse effects of transgenic soy were never reported.

The addition of fiber offers an additional benefit in infants and young children with constipation. About 10 % of all infants and young children are constipated.[19] Although all functional gastro-intestinal disorders are considered as separate entities, over 75 % of the infants present with a combination of functional disorders.[20] Fibers lead to an increase of bowel movements and improve stool consistency.[21] Fiber has a significantly improved success rate compared to placebo.[21] Prebiotic oligosaccharides were shown to increase the

defecation frequency and to soften the stools.[22,23] The addition of oligo fructose regulates defecation irregularities associated with low fiber intake.[24] A consistent prebiotic effect along with a decrease in pH and increase in %-bifidobacteria and %-lactobacilli was found in a group administered 0.4 g inulin/100 mL.[25]

Conclusion

Soy infant formula is a valuable alternative for cow milk based infant formula, since nutritional safety and no long-term adverse effects were reported. The supplementation with fiber is effective in the management of constipation.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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SUPPLEMENTARY ARTICLE

Perspective of Soy Formula and Fiber Intake among Non-Cow's Milk Drinker Pediatric Patients: A Survey among Indonesian Health Care Practitioners

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Abstract

Indonesia is one of the highest countries for soy-based product consumption, which the usage also started from early age as breastmilk substitute product, although local regulation and guideline stated that soy-based formula recommended for cow's milk protein allergy. However, evidences showed that soy-based formula supplemented with fiber in non-cow's milk drinker could also have health effect to gastrointestinal system. This online survey aimed to explore the perspective of health care practitioners (HCPs) in recommending soy-based formula for non-cow's milk drinker pediatric patients, as well as identify the required additional ingredient or supplementation, specifically on fiber, in soy-based formula. Majority of respondents (97% of pediatricians ($p<0.001$)), (96% of nurses ($p=0.003$)), (99% of midwives ($p<0.001$)) recommended soy-based formula as nutritional product toward non-cow's milk drinker patients. On the added ingredients required, 43% of respondents mentioned that AA and DHA and 31% mentioned that fibre is the ingredient that need to be added to complete the benefits of soy formula. This study concluded that the overall perspective of HCPs showed that soy-based formula is a nutritional product recommended for non-cow's milk pediatric patients. However, fiber is required to be added to achieve the potential benefits of soy-based formula.

Keywords soy based formula, fiber, children, pediatric patients

Introduction

As one of the highest countries for soy-based product consumption in Asia, Indonesian people has used this food as nutritional source since early age. This includes the use of soy-based formula as the breastmilk substitute product.[1]

Despite the widely used of soy-based formula, Indonesia Pediatric Association (IDAI) specifically recommend this only for infants with Cow's Milk Protein Allergy (CMPA) as well as for several other related medical indications such as post diarrhea lactose intolerance, galactosemia and primary lactase deficiency. Based on the policy and regulation on Indonesia Food and Drugs Association (BPOM) as well as IDAI Guidelines, the management of CMPA consists of diagnosis and

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treatment in children with CMPA. Specifically, for the treatment, the algorithm suggests to eliminates allergen mainly cow's milk protein. For breastfed infant, the infants were suggested to continue breastfeed exclusively and recommended the mother to avoid the consumption of all cow's milk protein and its derivatives. Soy based infant's formula may be consider for availability and affordability concern.[2,3]

Evidences showed that supplementing dietary fiber in children may improve overall diet quality.[4] Dietary fiber intake beneficial in term of physiological effects including reducing postprandial glucose concentrations, improving fecal bulk, promoting laxation, interfering with fat and cholesterol absorption, and altering bacteria populations in the gut microbiome.[5-7] In the gastrointestinal system, soy fiber has been shown to reduce the duration of watery stools during acute diarrhea caused by bacterial and viral pathogens in underdeveloped countries. A study done in middle-class American children showed the efficacy of soy fiber supplemented infant formula, including stool characteristics and weight.[8]

In regards to the fiber content, among plant protein source form legumes, soybeans known as the second lowest fiber source after peanuts (9.3 g/100g versus 8.5 g/100g, respectively) as compared to the highest content found in green peas (25.5 g/100g).[9] However, soybean dietary fiber have a role in antioxidant scavenging activity in plant tissues and maybe also for human.[10]

On the HCPs recommendation pattern toward nutritional product, studies among pediatrician showed that in order for them to utilize probiotic use correctly, it is important to keep updated about new knowledge through various sources and methods, eq. continuous medical education (CME), lectures, workshops, case-based learning, clinical experiences, preceptorships, and even direct information via interaction with representatives from nutrition companies.[11,12] A review showed that education have little impact and knowledge increase observed with multiple learning methods.[13]

This survey aimed to explore the perspective of health care practitioners (HCPs) in recommending soy-based formula for non-cow's milk drinker pediatric patients, as well as identify the required additional ingredient or supplementation, specifically on fiber, in soy-based formula.

Method

An online survey was conducted to 350 Health Care Practitioners (HCPs) in January 2020 for the period of three weeks. The survey was hosted on the Google-form survey platform and distributed through email to all respondents. Several reminders were sent via phone call, email, WhatsApp and text messages, once in every week. Respondents taken from Danone HN HCPs internal database and participants who expressed an interest showed in electronic informed consent in the preview of the survey. The questionnaire adapted from the previous cross-sectional study,[14] and developed in the format of multiple choices, True/False, and Yes/No. At the end of the study, participants were provided with debriefing information and contact details of the research team. A chi-square test was used to analyze cross-tabulated data for bivariate analysis and linear regression model for multivariate analysis, using SPSS version 20, with all outcome variables taken at the 5% significance level ($p<0.05$).

Result

The survey sent to 350 respondents with 277 respondents responded by the end of the survey, which was resulted to 79% response rate. Majority of respondents participated in this survey were pediatricians (n=147), followed by nurses (n=68), and midwives (n=62). As shown in Table 1, most of the pediatricians were consider senior in term of age and length of service, while the average age and length of service of midwives and nurses mostly less than 41 years old and less than 15 years of service, respectively. In term of institution where the respondents work, majority of midwives were affiliated with private hospital and/or private clinics, while the proportions of affiliations among pediatricians and nurses were slightly balanced between private hospital and government hospital. 100% of the respondents confirmed that they were ever consulted with non-cow's milk drinkers' patients in the last month.

Table 1. Demographic characteristic of respondents

Variables	Pediatricians n = 147		Nurses n = 68		Midwives n = 62	
	n	%	n	%	n	%
Age						
<41	46	33	51	37	41	30
≥ 41	101	73	17	12	21	15
Length of Service						
<15 years	34	23	15	23	12	19
≥15 years	113	77	53	77	50	81
Affiliation						
Private hospital	79	54	40	54	50	81
Government hospital	68	46	28	46	12	19
Area						
West	116	79	56	79	48	77
East	31	21	12	21	14	23
Ever Consulted with Non-Cow's Milk Drinkers Pediatric Patients						
Yes	147	100	68	100	62	100
No	0	0	0	0	0	0

Based on respondent' reports during consultation, the reason of why their patients did not drink cow's milk was related to cow's milk protein allergy (59%) and followed by diarrhea (31%). As shown in Figure 1, there were few non-specific medical reasons also mentioned, as well as constipation. When the respondents being asked about the nutritional products recommended for patients whose non-cow's milk drinker, as shown in Figure 2, soy formula was recommended by majority of respondents (61%).

We further analysed the recommendation level on soy formula based on the HCP's characteristic profile. Table 2 shows that 97% of pediatricians ($p < 0.001$), 96% of nurses ($p=0.003$), and 99% of midwives ($p<0.001$) mentioned that soy formula is a recommended nutritional product toward non-cow's milk drinker patients, and the result showed statistically significant across HCP's profile.

This survey also explores the perspective of respondent toward specific ingredients that need to

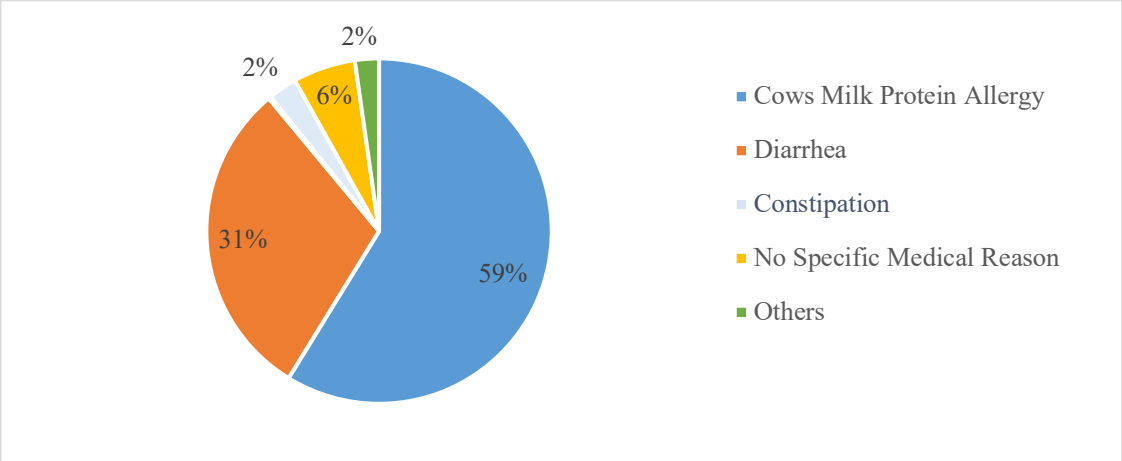

Figure 1. Reason to not consume cow's milk reported from patients during consultation

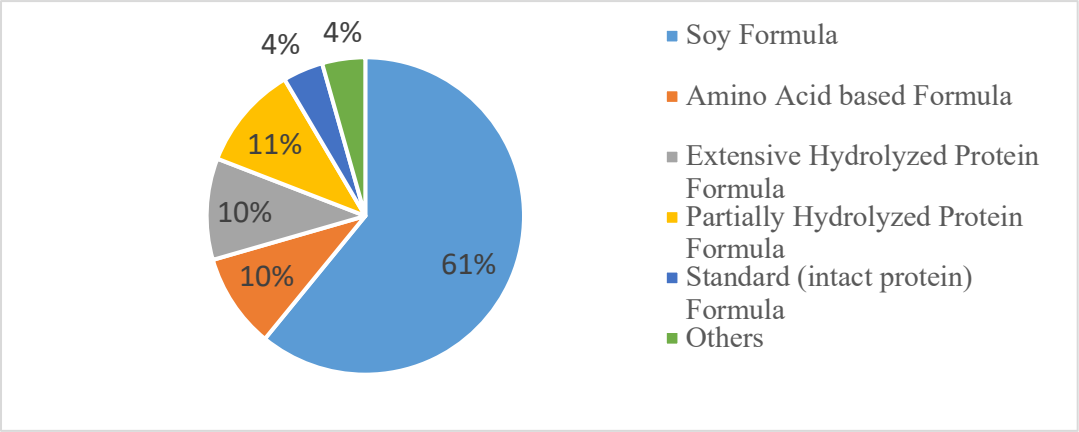

Figure 2. Nutritional products recommended by HCP for non-cow's milk drinkers

Table 2. Cross tabulation of recommendation level of soy formula

Variables	Pediatricians n = 147		p	Nurses n = 68		p	Midwives n = 62		p
	n	%		n	%		n	%	
Soy is a recommended product for non-cow's milk drinker	139	95	<0,001	65	96	0,003	61	99	<0,001
Soy is not a recommended product for non-cow's milk drinker	8	5		3	4		1	1	

be added in the soy formula. Figure 3 showed that 43% of respondents mentioned that AA and DHA need to be added and 31% also mentioned that fibre is the ingredient that need to be added to complete the benefits of soy formula. The respondents were also further asked their perspective toward adequacy level of fibre among non-cow's milk drinker patients, and as shown in Table 3, 31% of pediatricians mentioned that the fibre intake among non-cow's milk drinker patients were inadequate to very inadequate, similar with the perspective of nurses (22%) and midwives (24%), although the result was not statistically significant.

Even though the multivariate analysis in Table 4 showed no statistically significant among demographic characteristic of respondents, however among the midwives and nurses the result showed majority of the respondents (79% of midwives and 56% of nurses) who work in private hospital/clinics recommending soy formula for non-cow's milk drinker compare to those who work in government hospital, and the number showed clinically important.

Discussion

This survey reported that the overall perspective of health care practitioners (HCPs) was in favor with soy formula recommendation to non-cow's milk drinker pediatric patients. This finding is consistent with previous studies and recommendations available in Indonesia as well as global recommendations.[2,15,16] Studies mentioned that the recommendation of soy-based formula in non-cow's milk drinker pediatric patients is higher than regular or standard formula. It is also because the local pediatric association regulates the use of soy formula under certain medical conditions,[2] mainly for cow's milk protein allergy (CMPA) diagnosed patient. Knowing that the symptoms and complaints of CMPA patients could also differ, including gastro intestinal symptoms such as diarrhea and constipation, the findings from this survey that showing the reasons of patients consuming soy formula when they consulted to HCPs also validated.[17] The other study also stated that the most

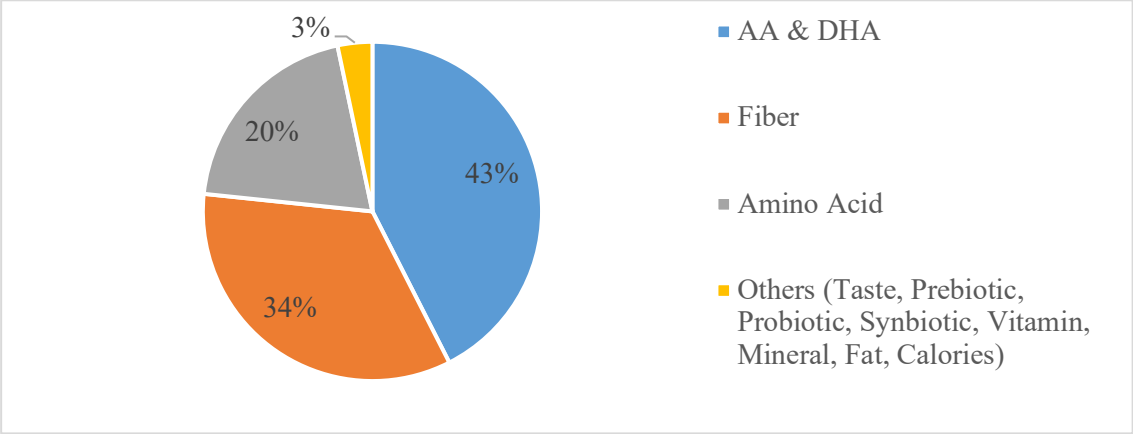

Figure 3. Perspective on specific ingredients that should be added in soy milk

Table 3. Perspective on fibre adequacy in children who couldn't drink cow's milk among healthcare professionals and its relationship

Variables	Pediatricians n = 147		p	Nurses n = 68		p	Midwives n = 62		p
	n	%		n	%		n	%	
Very inadequate	3	2	0.46	2	3	0.68	1	2	0.61
Inadequate	42	29		13	19		14	22	
Adequate	102	69		53	77		47	76	

Table 4. Multivariate analysis of HCP's recommendation level toward soy formula for non-cow's milk drinker based on demographic characteristic

Variables	Pediatricians n=147				p	Nurses n=68				p	Midwifes n=62				P
	Recommend		Do Not Recommend			Recommend		Do Not Recommended			Recommend		Do Not Recommend		
	n	%	n	%		n	%	n	%		n	%	n	%	
Age					1.00					0.56					
<41	44	30	2	1		48	71	3	4		40	65	1	1	1.00
≥ 41	95	65	6	4		17	25	0	0		21	34	0	0	
Length of Service					0.71					1.00					1.00
<15 years	97	66	5	3		44	65	0	0		45	74	1	1	
≥15 years	42	29	3	2		21	31	3	4		16	25	0	0	
Affiliation					0.72					0.54					1.00
Private	74	50	5	3		38	56	1	1		49	79	1	1	
Government	65	45	3	2		27	40	2	3		12	20	0	0	
Area					0.67					0.23					1.00
West	110	75	6	4		53	78	0	0		48	77	0	0	
East	29	20	2	1		12	18	3	4		13	22	1	1	

common reason of recommending soy-based formula by HCPs is to relief of perceived formula intolerance (spitting, vomiting, fussiness) or symptoms of colic since this can be a symptom of CMPA. Other findings of this study also showed that partial hydrolysed formula is not the first choice of HCPs for non-cow's milk drinker patients. This might be positively correlates with the previous

studies and review mentioned that partially hydrolysed formula is more recommended for prevention of CMPA and the benefits of partial hydrolysed formula to gastrointestinal manifestations will be more positive when added with prebiotic, probiotic, palmitic acid, including human milk oligosaccharide.[18]

The recommendation level of soy-based formula across HCPs reported from this study also showed interesting facts. Despite the result showed statistically not significant, however there is higher percentage of HCPs working in government hospitals recommending soy-based formula compare to their colleagues who works in private hospital or clinics. Study in China showed that there is a situation where doctors working in county hospital have more supportive attitude to national essential medicine policy, as they were more accessible to education, training on rational drug use, and better acquisition of medicine knowledge.[19] The assumption of this hypothesis also applied to finding of this study, since the local regulation and recommendation of soy-based formula were established here in Indonesia. Previous study on prescription pattern in Indonesia also confirms this finding.[14] Similar findings have also been seen in the variable of length of service across HCPs. This study showed that despite the statistically not significant result, the HCPs with length of service less than 15 years were more open to recommending soy-based formula.

Other findings from this study is the perspective of HCPs toward fiber intake and ingredient-wise perspective in soy-based formula. Apart of AA and DHA, high number of respondents mentioned that fiber should be added into the soy-based formula to achieve ultimate benefits. Even though majority of respondents also mentioned that fiber intake among non-cow's milk drinker children is adequate, but more than 30% of pediatricians and more than 20% of nurses and midwives still acknowledging that there is still a potential inadequacy of fiber intake among their non-cow's milk drinker patient. Study showed that fiber content of soybeans as the source isolated soy-based formula consider low, even second lowest after peanuts.[9] Study suggested that fiber supplementation especially in the form of oligosaccharide (FOS) and inulin demonstrated positive tolerance in children,[20] and also showed beneficial effect in gastrointestinal health.[21,22] The use of fiber-supplemented soy formula may reduce the duration of diarrheal symptoms in U. S. infants more than 6 months of age with acute diarrhea.[8] Therefore the perspective of respondents of this study toward additional fiber as potential ingredient in soy-based formula is evidence based and consistent with studies and review available.

This survey has major limitation as it is designed as an online survey whereas the subjectivity of respondents potentially interferes the objective of the reports as well as the challenges to identify the factors influencing respondents to recommends the nutritional products.

Conclusion

Overall perspective of HCPs showed that soy-based formula is a nutritional product recommended for non-cow's milk pediatric patients. However, fiber is required to be added to achieve the potential benefits of soy-based formula.

Conflict of Interest

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SUPPLEMENTARY ARTICLE

The Overview of Food Technology to Process Soy Protein Isolate and Its Application toward Food Industry

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Abstract

Soy protein isolate (SPI) is the purest form of protein from soybean with minimum protein content of 90%. Due to its high protein content, SPI is commonly used in food processing for improving the quality of food products, including infant formula. The use of SPI in infant formula is mainly designed for infant who cannot tolerate cow's milk-based formula. This report reviews the benefit of using SPI in soy-based infant formula rather than soymilk from whole soybean itself. It will also review the technology of soy protein isolation which can result SPI for high quality infant formula, including the reducing of unfavourable ingredients which will ensure the safety of soy protein-based infant formula.

Keywords soy protein, soy protein isolate, soy protein based infant formula

Introduction

Soybeans, which are leguminous crops belonging to the family *Fabaceae*, have served as a valuable source of food which contain a nutrient source. This plant product has been widely used in a variety of food products. Applications of soybeans in food products are presented in a variety of forms, including infant formulas, cheese, drinks, miso, tempeh, tofu, salami, and vegetarian meat substitutes.[1]

Commonly, soybean derived products, such as soy protein has received growing an attention due to its chemical composition, functional properties, and multiple applications in food industry. According to Codex Standard,[2] soy protein products are classified based on their dry base protein contents, namely soy flour (40–50% of protein), soy protein concentrates (70 – < 90% of protein), and soy protein isolate (≥90% of protein).

Each type of soy protein has different application in products according to their functional properties (Table 1). Soy protein has a good supply of essential amino acids compared with other plant proteins. Soy protein has high lysine, which is normally lacking in other cereal, but low in cysteine and methionine. Due to its high protein content (~90%), soy protein isolate is considered as one of raw material in producing soy-based infant formula.

Soy Protein Isolate vs Soy Milk

Soy protein isolate (SPI) is the purest form of protein in soybean with minimum protein content of 90% (dry basis), which is obtained by extracting the soluble protein and removing non-protein material

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Table 1. Application of soy protein in food products

Functional properties	Soy forms	Food Application
Fat absorption	F, C, I	Frankfurters, meat burgers, sausage, donuts, bologna
Water absorption	F, C	Confections, breads, cakes
Emulsification	F, C, I	Frankfurters, sausage, bologna, cakes, and breads
Solubility	F, C, I	Beverages
Gelation	C, I	Meat, curd, cheese
Elasticity	I	Baked goods, simulated goods

such as fat and carbohydrates. Because of this process, it has a neutral flavour and cause less flatulence than soy flours.

Soymilk is a milky liquid made from whole soybean or full-fat soy flour. Its composition and nutrient are similar to those of dairy milk.[4] Soymilk processing is including soaking soybean in water, filtering the soybean slurry with gauze, and heating the obtained filtrate by sterilization. According to its processing, it showed that soy milk still contains more non-protein content compared to SPI.

Furthermore, SPI has higher Protein Digestibility Corrected Amino Acid Score (PDCAAS) compared to soymilk, which is 100% and 92.6% respectively.[5] It shows that PDCAAS of SPI is equivalent to animal proteins quality, suggested that SPI is essential as alternative protein source to support growth of infant.

Infant formula is designed to be a supplement to breast milk, and may be also used as a substitute if breastfeeding is feasible, which is made by mixing proteins, fats, carbohydrates, minerals, and vitamin components. The mixture is then blended, pasteurized, homogenized, and condensed, then either spray-dried (powder-base) or sterilized (drink-base).[6]

Soy-based infant formula is designed as a suitable alternative for infant with intolerance to lactose and cow's milk proteins. Lactose intolerance occurs when small intestine fails to produce sufficient amount of lactase enzyme. Lactase enzyme is released in normal infant's digestive system in order to digest milk, including breast milk, whether premature infants sometimes fail to produce enough lactase.[7]

Benefit Use of SPI in Market

Soy protein products, especially SPI have been used as food ingredients in wide category due to their nutritional and functional properties. Moreover, soybean is a low-cost vegetable sources of protein, which cause soy protein products offer more than just obvious economic advantages that vegetable proteins have over animal proteins. Soybean processing into soy protein has resulted in products that can be used for many functions in foods, such as emulsification, binding, and texture.[8] The excellent nutritional value of soy protein has been recognized by Food and Drug Administration (FDA) and the United States Department of Agriculture's (USDA) School Lunch Program.

One of SPI use in the market is as the protein main source in infant formula. Soy-protein based infant formulas in the United States are nearly 25% of the formula market, 13% in New Zealand, 7% in the United Kingdom, 5% in Italy, and 2% in France, which use SPI as their main ingredients.[9,10] In the beginning of their launching into the U.S. market in 1950, soy-based infant formulas were using soy flour as their raw material. The formulas were tan in color and had a nutty odor. Then, in the 1960s, soy-based infant formulas came up with SPI, and within 10 years almost completely replaced soy flour-based infant formula in the U.S. Those formulas are only

darker than milk-based formulas and nearly odourless.[11]

Not only benefit for their appearance, SPI also have lower phytate content because of precipitation method in obtaining protein isolates. The method resulting the increase of absorption and availability of zinc and copper in infant rhesus monkeys and rat pups due to the reduction of the phytate content of soy formula by using SPI.[12]

Food Technology of SPI and Impact on Unfavourable Ingredient

The general methods of soy protein isolation are using aqueous extraction process (isoelectric precipitation principal) and membrane ultrafiltration process. Aqueous extraction technique is based on the solubility of protein at different pHs. Basically, SPI are produced by extracting the soy flakes in alkali condition (pH 8 – 9) with subsequent centrifugation to produce a soy protein extract containing soluble protein, oligosaccharides, and minerals. Acidification of the obtained extract to pH 4.5 (isoelectric point) will precipitate the proteins into a curd. Subsequent washing of the curd will remove soluble non-protein component. The following neutralization at pH 7 and drying finally will result SPI[3].

Whether ultrafiltration membrane is using membrane isolation technique. Different from aqueous extraction, membrane isolation recovers protein directly from soybean flour extracts and thus avoid the generation of whey protein from acid-precipitation, which results higher protein isolate yield, since one-third of soy whey proteins are very hard to recover.[13] According to Codex Standard,[2] maximum water content, ash content, and crude fiber of SPI is 10, 8, and 0.05% respectively, with minimum protein content of 90%.

Soybeans naturally had anti-nutritional factors such as phytic acid, trypsin and other enzyme inhibitors, lectin, and phenolic compounds, which can cause undesirable effects on digestion and absorption of nutrition. Results found that SPI with ultrafiltration process had low phytic acid content, improved digestibility, high water solubility, improved functional properties, and absence of beany flavour with high palatability and nutrition due to the removal of oligosaccharides and minerals which are permeate through the membrane.[14]

Removal of phytic acid in SPI can improve digestibility of minerals such as calcium, therefore manufactures do not need to enrich their soymilk products with calcium carbonate to ensure adequate adsorption. Soybean also contains isoflavones (phytoestrogen) which have been of particular interest due to their effects on sexual development and reproduction. Approximately, 30% of the total isoflavones are lost in the insoluble fraction during SPI production.[15] Another study also showed that soymilk which was made from SPI had lower isoflavones content compared to soymilk from whole soybean due to loss of isoflavones occurs during the separation of isolated protein.[16]

Numerous studies showed that dietary isoflavones in soy-based infant formula do not adversely affect human growth, development, or reproduction.[17] Setchell *et al.*[18] reported that no clinical symptoms, growth, or development adverse effects related to plasma concentration of isoflavones in soy-fed infants. Furthermore, there was also no reported adverse estrogenic effects on sexual development in infants fed soy-based infant formula.

Businco *et al.*[19] also reported that phytoestrogens in soy-based infant formula did not induce hormonal effects in 34 young adults who had been fed soy-based infant formula when they were toddlers. Strom *et al.*[20] also found no statistically significant differences in general health and development between groups who had soy-based infant formula and groups who had milk-based infant formula during their first 4 months, in either females or males. It showed that sexual development and maturation of infants fed soy-based infant formula are normal.

Soymilk has not gained popularity compared to cow's milk due to its off-flavour and only used as a milk substitute by a group of people who cannot tolerate cow's milk. The off-flavour (beany/grassy, bitter, and astringent flavour) of soymilk was from soybean, which was as a result of lipid oxidation, lipoxygenase activity, polar lipids, bitter peptide and lipids[21]. Soybean defatting and protein extraction could have a significant impact on the taste and flavour of SPI and thus on the finished food products

due to the removal of lipids in soy flakes which are the major substrate of lipoxygenase[3].

Besides, the presence of allergenicity in SPI could be removed by using HHP (High Hydrostatic Pressure) processing. HHP treatment could significantly influence the free SH (Sulfhydryl) content and hydrophobicity of SPI, which are closely associated with the allergenicity of SPI. HHP would influence that interaction and interfere with the structure of soy allergen epitopes, thus reducing the allergenicity of SPI. HHP treatment at 300 MPa and 15 min could decrease allergenicity up to 48.6% compared to native SPI.[22]

Food Processing to Ensure High Quality of SPI Formula for Children

Infant formula is designed for use as a substitute for human milk when breastfeeding is unable, then there should be a processing technology to achieve nutrient similarity to human milk. Ingredients added to soy-based infant formula are SPI, which utilize as the main protein source, and supplemented with L-methionine, carnitine, and taurine.

SPI is added to achieve protein content ranging 2.45–2.8 g per 100 kcal. Besides, soy-based infant formula does not contain lactose, it needs addition of corn maltodextrin, corn syrup solids, and sucrose as replacers for carbohydrates then to provide carbohydrate content of 10.26–10.95 g per 100 kcal.[23,9] Furthermore, addition of lipids is also needed, which content ranges from 5.02–5.46 g per 100 kcal, since lipids are predominant source of energy, required for absorption of fat-soluble vitamins, carotenoids, cholesterol, and contribute to flavours and satiety. Fat blends of soy oil and coconut oil with proportions 40% and 60% respectively, which have higher absorption of fat and mineral compared to mixture of palm oil and soy oil.

Soy-based infant formula also needs to be fortified with iron as a way of reducing the prevalence of anemia. Moreover, vitamin such as vitamin D3, vitamin K, vitamin B12 also found in many fortified infant formula.[9,24]

Infant formulas are commonly sold in powdered form. Powdered infant formula is generally manufactured using one of two types of process, namely dry blending process or wet mixing-spray drying. Briefly, dry blending process is process of combining all of the dry ingredients which previously have been prepared individually (heat-treated) to finally dry-blended, whether wet mixing-spray process is using all ingredients in a liquid phase and heat-treating (pasteurization/sterilization) to finally dry-sprayed. Each process has its own advantages and disadvantages.

The advantages of using the dry blending process are using less energy and having the less risk of microbiological contamination because the water is not involved in this process, but the disadvantages are no heat treatment to destroy bacteria in the final product. Furthermore, the different ingredients will segregate during transportation and storage due to their varied densities, resulting in inhomogeneous state for the consumer.[25]

The wet mixing-spray process currently remains the most widely used method of producing powdered infant formula.[23] The advantage of this process is all quality aspects can be more effectively controlled than dry mixing process, resulting improved quality powder including microbiological, physical, and chemical properties, whether its disadvantage is using more energy and time compared to dry mixing process.[25]

Concern of GM and Non-GM Soybean

Genetically-modified (GM) organisms are crop plants that using the latest molecular biology techniques and have been modified to enhance some desired traits. Soybean is one of the examples of GMO results. This kind of soybeans is herbicide Roundup® (glyphosate)-resistant, that will reduce the production cost and limit the dangers of agricultural waste run-off.

In the U.S., the cultivation of GM soybeans was increasing every year. In 1996, approximately 7% of all soybeans cultivated were GMO, up to 42% in 1998, and increased to 54% of all soybeans in 2000.[26] But, GMO still has concerns related to human health risks and long-term effects on human beings. Many people prefer to stay away from GMO because of the transfer of antibiotic resistance, toxicity, and allergenicity possibility due to the presence of transgenes that have been inserted into the crops. Because of these issues, labelling of GM

foods is required by EU legislation, as a tool for the first-time consumer to get well-informed.[27] However, several studies showed no meaningful effects and differences from GM soybeans compared to non-GM soybeans. Netherwood *et al.*[28] reported no gene transfer occur during GM soy fed in seven human volunteers' gut because the transgene did not survive passage through intact gastrointestinal tract.

Another study also found no biologically significant differences occur in the *in vivo* nutritional response of body weight, body weight gain, and food consumption of rats compared to the non-GM soybeans in the diet. That indicate both soybeans were nutritionally equivalent, providing evidence that GM soybeans did not have cause unintended deleterious nutritional changes. Furthermore, no significant differences in MDA (Malondialdehyde) and PC (Protein Carbonyl) levels of rats were found, indicate no differences in lipid peroxidation and protein oxidation levels.[29,30]

Conclusion

Soy protein isolate (SPI) has been widely used due to its chemical composition, functional properties, and multiple applications in food industry, including soy-based infant formula, which is mainly designed for infant who cannot tolerate cow's milk-based formula. The use of SPI can be beneficial for infant formula by resulting better appearance and flavor, lower phytate content, higher protein digestibility, and higher mineral absorption and availability due to protein isolation process with ultrafiltration method, compared to soy-based infant formula using soybean itself. Furthermore, presence of allergenicity in SPI also could be removed by using HHP (High Hydrostatic Pressure) processing. Several studies related to particular interests in soybean such as isoflavone and GMO issues also reported no meaningful adverse effects, which indicate SPI is safe for used as raw material for infant formula production.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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SUPPLEMENTARY ARTICLE

Soy Plant-based Formula with Fiber: from Protein Source to Functional Food

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Abstract

Several factors are fundamental to support child growth and development, including nutrition. Other than energy, protein is the key to balanced dietary macronutrients intake as the building block of child growth. While several micronutrients, i.e. calcium, iron, zinc and vitamins are needed for both optimal growth and development. Among protein-rich foods for young children, cow's milk formula has several limitations, i.e. cow's milk allergy and low fiber content. Although has a low bioavailability for iron absorption, plant-rich protein can be an alternative for young children to be used, i.e. as a soy isolate protein formula. However, due to the fact of low fiber content in soy isolate protein formula, further consideration is needed to have a fiber enrichment. We highlight the fiber content in child formulas to the extent of its benefit for gastrointestinal health in relation to gut movement in preventing constipation, or its role as a functional food with its prebiotics capacity. This article aims to review a suitable type of fiber used for the enrichment for a soy isolate protein formula.

Keywords fiber, functional foods, plant-protein, prebiotics, soy-isolate protein

Important nutrition to support child growth and development

Growth is a typical characteristic of childhood, a sensitive indicator of a child's nutritional status. Deviations in growth are associated with greater risk of disease both in the short and the long run. Monitoring growth is therefore an important tool for assessing the health and well-being of children.[1] Child growth and development is affected by several factors, i.e. nutrition, care, stimulation and health conditions. Considering on nutrition alone, there are nutrition that supports growth.[2] Among others are energy and protein as the fuels and building blocks for rapid linear growth. Energy from dietary intake is needed to build body tissues relative to body weight. Lack of energy intake can delay growth spurts and lead to stunting. Protein, it has to be present in sufficient quantity as well of high quality to be able to get all the nine essential amino acids. The high-quality protein originated from animal

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including dairy products, eggs, meat and poultry, while from plant protein is mostly soy because other plant protein sources, such as peas or nuts, have to be consumed with complementary protein to provide all the nine essential amino acids.[2]

Other than energy and protein, adequate intake of iron is essential as a major component of blood and muscle tissues, especially to form the haemoglobin molecule needed to carry oxygen and myoglobin component for growing muscle. For growing the skeleton, then calcium is the main component of bones while vitamin D assure that calcium will reach the growing bones. We know that numerous metabolic reactions are essential for growth in which zinc is highly required to act as a catalyst for dozens of reactions, especially those metabolic processes related to growth.[2]

Nutrition responsible to support child development, i.e. cognitive and sensory development, is related to neuron growth (including myelin sheath), synthesis of neurotransmitters to relay messages to the brain, and development of the eye. Among others, iodine and zinc are responsible to help regulate brain and nervous system development. Dietary intake of iodine plays a huge role in cognitive development because it is required for synthesis of thyroid hormones. Thyroid hormones is essential for regulating many biochemical processes, in particular are those related to brain development. Zinc also has a role in cognitive development because it is essential for the nervous system growth, i.e. formation of neurons and synapses that allow neurons to communicate to each other. Besides myelin sheath is also important to enable nerve signals to journey rapidly across the neuron, in which iron has a role in developing the myelin. There is also a potential role of omega-3 long chain polyunsaturated fatty acids as a primary component of every cell membrane in the body, including nerve cells. Lots of study still try to confirm the role of DHA, a specific long-chain omega-3 fatty acid to improving learning and memory. As well as of B vitamins (i.e. vitamin B6, vitamin B12, and folate) and choline to cognitive health through their possible roles in nerve cell myelination, neurotransmitter synthesis, and regulation of gene expression in the central nervous system. In developing the senses, vitamin A is essential for the transduction of light into neural signals in the eye. While lutein and zeaxanthin are carotenoids or pro-vitamin A that are found in the retina and in brain tissue to serve as important antioxidant protection and play a role in neural development.[1,2]

Consideration why soy isolate protein formula can be alternative nutrition for young children

We all agree that human milk is the ideal source of nutrition for infant feeding, however some infants are receiving some formula as human milk substitute, cow-milk based, or non-cow-milk based infant formula (i.e. soy-based infant formula). Both human milk substitute should provide a source of nutrition for an extended interval and their nutritional adequacy should be confirmed, especially for the soy protein-based formulas.[3]

Soy protein-based formulas have been provided for almost 100 years since there is a need for a milk substitute for an infant who unable to tolerate a cow milk protein-based formula by changing the formulation to the current soy protein isolate.[3] A systematic review with meta-analysis entitled, “Safety of soya-based infant formulas in children” concluded, “Modern soy-based infant formulas are evidence-based safety options to feed children requiring them. The patterns of growth, bone health and metabolic, reproductive, endocrine, immune and neurological functions are similar to those observed in children fed cow milk formula or human milk” Soy is the only plant protein source containing a complete amino acid profile.[4] Soy-based formulas are well tolerated in infants with CMPA (cow milk protein allergy). Soy formulae used to contain phytates which were blamed for their chelating capacity, preventing the proper absorption of micronutrients. Today, however, phytates are almost totally removed from the soy formula.[5]

Isolated soy proteins are sometimes referred to as the most functional of the soy proteins. These virtually pure, bland-flavored isolates containing a minimum of 90% protein have been designed to function in a given system in the same way as animal proteins. Soy protein supplies all nine essential amino acids and provides many functional benefits to food processors and for a healthy diet. Both isolated and concentrated soy proteins are easily digested by humans and the protein quality is

equal to milk, meat, and eggs. The most refined forms of soybean proteins are the isolates, which contain 90% or more protein. They are prepared by removing the water-insoluble polysaccharides, as well as the oligosaccharides and other low-molecular-weight components that are separated in making protein concentrates. Isolates may contain more than 95% protein but contain 2% to 5% ash and 3% to 4% of minor constituents. Soy concentrates and isolates provide highly concentrated protein sources, high lysine content, bland flavor, and reduction of flatulence factors and reducing sugars, and they may lead to improve overall product quality.[6]

Considering its composition, the isolated soy protein-based formulas provide 67 kcal/dL, iron fortified and meet the vitamin, mineral and electrolyte specification as recommended. The protein is provided from a soy isolate and supplemented with L-methionine, L-carnitine, and taurine. Vegetable oils primarily used for its fat content, include soy, palm, sunflower, olein, safflower, and coconut, in which docosahexaenoic and arachidonic acids are added. Carbohydrate sources are coming from corn maltodextrin, corn syrup solids, and sucrose. The calcium and phosphorous contents are 20% more than cow milk-based formula, and fortified with iron and zinc, because soy phytates and fiber oligosaccharides bind with iron and zinc.[3]

A potential concern for soy protein-based formulas is in relation to phytoestrogens/ isoflavones that consist with the highest amount in soybeans. They have potential negative effects on sexual development and reproduction, neurobehavioral development, immune function and thyroid function. However, up till now there is no conclusive evidence from any animal, human or infant population that dietary soy isoflavones may adversely affect human development, reproduction, or endocrine function.[3] There is also another issue on the relatively high content of aluminium in soy-based formulas that can result in aluminium toxicity in infants and children. Aluminium competes with calcium for absorption, thus increased amount of dietary aluminium from isolated soy protein-based formula may contribute to the reduced skeletal mineralization (osteopenia). However, it is the case for preterm infants and infants with intrauterine growth retardation, and do not seem to be at substantial risk for term infants with normal renal function. Thus, the cow milk protein-based formulas designed for preterm infants are clearly superior to soy protein-based formula for preterm infants.[3]

Consideration to use soy protein-based formula is safe and cost-effective as a dietetic alternatives for infants with galactosemia or primary lactase deficiency or families wishing to avoid feeding their infants formulas containing animal products. However, it is contraindicated in sucrase-isomaltase deficiency and hereditary fructose intolerance. In acute infantile diarrhea, by using soy protein-based formula, it revealed that the duration of diarrhea to be shorter and duration of liquid stools may also shortened. Although the most common reason for use of soy protein-based formula is for relief of perceived formula intolerance (i.e. spitting, vomiting, and fussiness) or symptoms of colic, however there is no significant benefit from soy protein-based formula as compared to cow milk. Also, there is a high frequency of sensitivity to both cow milk and soy antigens in infants, resulting to the need to have a hydrolyzed protein formulas for these infants, and even an extensively hydrolyzed protein formula for infants allergic to cow milk formula.[3]

The nutritional composition of soy isolate protein formula in Indonesia – highlighting low fiber content

In terms as an oil seed, soybean contains several nutrients, i.e. protein, carbohydrate, vitamins and minerals. In dried condition, a dry soybean has 36% protein, 19% oil, 35% carbohydrate of which 17% is dietary fiber, 5% minerals and several other components including vitamins.[7] For its protein quality as protein digestibility corrected amino score, it is found that soybean protein has a biological value of 74, in which 96 for soybeans as a whole and 91 as soybean milk, as compared to 97 for eggs.[6]

Concerning to its fiber content, among plant protein source form legumes, fiber content of soybeans is second lowest after peanuts (9.3 g/100g versus 8.5 g/100g, respectively) as compared to the highest content found in green peas (25.5 g/100g).[8] Although found in a small amount as raffinose and stachyose and other oligosaccharides, however it

cannot be digested in small intestines because the lack of enzyme alpha-galactosidase. Thus, it passes into the colon and serves as an energy substrate for colonic bacteria or so called prebiotics, but also causes flatulence. Furthermore, the soybean dietary fiber are believed having a role in antioxidant scavenging activity in plant tissues and maybe also for human.[9]

The benefit of fiber enrichment in soy protein isolate formula

Considering to the low fiber content and beneficial role of dietary fiber found in soybeans as prebiotics and antioxidants, it is then wise to have fiber enrichment to soybean product such as in soy protein isolate formula. Moreover, the low fiber content will be perturbed during food processing. Further study should be done to find the optimal amount of fiber enrichment needed to have its beneficial effects with a minimal negative effect on gastrointestinal symptoms and absorption of micronutrients, i.e. calcium, iron and zinc. Fiber may role as prebiotics. Prebiotics are non-digestible components of food that in a selective manner trigger the expansion of microbes in the gut with valuable effects for host health. All these demands are completed by non-digestible oligosaccharides that consist of three to ten sugar molecules, and are naturally present in fruits, vegetables, cereals, milk, *etc*., or can be industrially produced.[10]

Majority of clinical studies concerning the effects of supplementation of infant formulas with prebiotics confirmed increase in frequency of defecation and/or softer consistency of stools, similar to that of breast-fed infants. Acidic environment in colon increases solubility of certain minerals. Bioavailability of calcium when consuming prebiotic ingredients has been well-studied. Recent observations show that prebiotic oligosaccharides enhance iron absorption in deficient rats. A meta-analysis that summarized positive context of prebiotics in infant formulas and increased weight gain; Whether this is the result of intensified energy harvests by intestinal bacteria and/or increased absorption by enterocytes is not yet clear.[10]

Prebiotics are being added to infant formula to promote growth and development in infants. However, there is not enough evidence to state that supplementation of term infant formula with prebiotics does result in improved growth or clinical outcomes in term infants. The health benefits include increased mineral absorption. Moreover, food supplements containing prebiotics have beneficial effects on Ca, Mg mineral absorption. Prebiotics also have other positive effects on health, i.e. improving body functions and bone health, decreasing disease risks, reinforcing immune functions, preventing infections and intestinal diseases, and enhancing bioavailability of (calcium and magnesium) minerals.[11]

Prebiotic supplementation of paediatric nutritional products is associated with increased levels of lactic acid bacteria and bifidobacteria, decreased diarrhea, improved allergy symptoms, and decreased rates of infection in infants and children.[12] An increase in bifidobacteria, a decreased stool pH, softer stools and an increase in stool frequency compared to standard infant formula is an almost constant finding.[13] It is widely known that oligosaccharides constitute the third most abundant component in human milk after lactose and lipids. While oligosaccharides are virtually absent from most infant formula, which may account in part for the difference in GI microbiota reported among breast-fed and formula-fed infants.

What will be the suitable fiber/oligosaccharide for soy isolate protein formula that should be plant source, i.e. fructo-oligosaccharides (FOS) and inulin with the right combination? We realize that we could not use gluco-oligo-saccharides (GOS) because it is from lactose/cow's milk, thus not suitable for children who avoiding cow's milk. Study suggested that term infants fed soy-based formulas supplemented with scFOS demonstrated good tolerance and hydration comparable to the control soy-based formula with history of safe use.[14] A beneficial effects of both FOS and inulin enriched in the soy protein-based formula, have to proceed several steps, i.e. preparation of the formula by FOS and inulin enrichment in percentage (%) of total product weight, measurements of active acidity (pH), microbiology and sensory analysis before doing a medical study or clinical trial to assess the different faecal microbiota composition for pathogenic and conditionally pathogenic variety.[15] Based on

Generally Recognized As Safe (GRAS) Notification for fructo-oligosaccharides, the office of food additive safety (HFS-255) from Center for Food Safety and Applied Nutrition Food and Drug Administration USA (January 2017) stated that the typical use levels of FOS in infant formula as starter formula and follow-on formula is 31.5 mg/g powder and 39 mg/g powder, respectively, with the use levels of 400 mg/100mL and 500 mg/100mL, respectively.[16]

Conclusions

Soy isolate protein-based formulas may serve as an alternative for parents to provide foods for their infants and under-five children with sufficient nutrition to support optimal growth and development, as well maintaining gastrointestinal health, especially to those who cannot consume cow-based formula. This is particularly true if the soy isolate protein-based formula has been enriched with dietary fiber, such as FOS and inulin to have a prebiotics role as a functional food.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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SUPPLEMENTARY ARTICLE

Soy Isolate Protein Formula: the Usage beyond Allergy Indication

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Introduction

The usage of soy isolate protein formula for infants was recommended by Indonesian Pediatrics Association (IDAI) through the recommendation of Cow's Milk Protein Allergy (CMPA) management in 2014. Soy Infant Formula (SIF) has been being used for Infants with Cow's Milk Protein Allergy (CMPA) as well as for several other related medical indications such as post diarrhea lactose intolerance, galactosemia and primary lactase deficiency.[1] At early stage of soy formula, it had several deficiencies, infant acceptability, growth, and incomparable with milk-base formula. Current SIF is made from soy protein isolate that contain 2.2– 2.6 g of protein per 100 calories, it is higher than milk-based formula and both showed same growth and development in infants.[2] It contains different fibers, phytate, digestibility, protease inhibitor and proteins. SIF is easily digestible and contain high amino acid content fortified with L-methionine, L-carnitine and taurine. High content of phytate is overcome with zinc and iron fortification as well as increased levels of calcium and phosphor.[3] American Academy of Pediatrics recommends isolated soy protein-based formulas as a safe and effective alternative for providing appropriate nutrition for normal growth and development for term infants whose nutritional needs are not being met from maternal breast milk or cow's milk-based formulas.[3,4]

Soy isolate protein formula is commonly used as management of CMPA besides extensively hydrolyzed formula (eHF) and amino acid formula (AAF). Each formula possesses its own indications, advantages and disadvantages. The AAP (American Academy of Pediatrics) and the ESPGHAN (European Society for Pediatrics Gastroenterology Hepatology and Nutrition) recommended that SIF is a rational option and can be justified in CMPA children.[3,4] Based on the Indonesia Pediatrics Association (IDAI) guidelines, the choice of formula for CMPA is restricted between eHF, AAF or SIF. According to the guideline, SIF is an alternative formula for infant with low to moderate allergy symptoms when there is an issue with affordability or availability of eHF.[2]

Soy isolate protein formula administration is often debated because although it does not contain cow's milk protein, 10–14% children with CMPA

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are also allergic to soy and SIF adverse reaction such as enterocolitis occurred in 30–64% CMPA children.[5,6,7] This condition is a challenge for clinician and may be taken into consideration. Some researchers also debated about its conflicting evidence about the risks and benefits of phyto-estrogens contained in SIF.[8]

The consumption of SIF is a rational option when mature infants are not able to get breastfeeding and intolerance to cow's milk is present. Another indication of SIF is galactosemia, hereditary lactase deficiency and conditions that require vegetarian diet and to reduce colic complaints. However, the benefits of SIF beyond allergies are yet widely known. Therefore, in this review, the Soy Infant Formula safety issues and its benefits beyond allergies are discussed.

Soy infant formula usage in Indonesia

The utilization rates of Soya Infant Formula (SIF) have been repeatedly found to be higher than expected compared to the reported incidence of over mentioned indications for SIF use. It was reported that SIF was used nearly 20 % in Canada (year 2005)[9] and 25% in the USA (year 2008).[6] A recent evaluation of the consumption of different types of feeding among a nationally representative sample of 1,864 infants aged 0–12 months in the USA reported that among 81% of infants who were fed formula or regular milk and 12% consumed SIF.[10] However, SIF is only used for management of Cow's Milk Protein Allergy in Indonesia.[2] This consensus is based on the AAP[6] and the ESPGHAN[4] which stated few indications for the use of SIF in infant. Several studies have shown that presently available SIF can allow for the normal growth and development of full-term infants. Moreover, full-term infants, galactosemia, and hereditary lactase deficiency are the only clinical conditions for which SIF are considered the best solution for feeding infants. Finally, they can be used when a vegan diet is preferred. Other clinical conditions that were initially considered possible indications for SIF use are presently preferentially treated with different nutritional approaches.[11] It is also the consideration for the use of SIF in Indonesia.[2]

According to the Indonesian Pediatrics Association (IDAI) Guidelines, the management of cow's milk protein allergy (CMPA) consists of diagnosis and therapy in children with CMPA. Diagnosis can be performed in children by dietary elimination of cow's milk protein, standardized oral challenge test, IgE specific test, skin test and patch test. Even though the gold standard for diagnosing CMPA is through a standardized oral test, many clinicians still diagnose CMPA based on symptoms. The therapy itself lies within the algorithm of avoiding the allergen which is cow's milk protein. For breastfed infant, it is recommended for the mother to avoid the consumption of all cow's milk protein and its derivatives. In IDAI guidelines, the therapy for CMPA is extensively hydrolyzed protein formula's (eHF) although this formula is more expensive and less palatable than SIF since some cases are also suffer from soy protein allergy. It is stated in the IDAI Guidelines, however, if eHF is not available or too expensive for patients, soy infant formula (SIF) may be used but patients need to be educated with SIF adverse effects.[2]

The World Health Organization (WHO) also mentioned soy infant formula in CODEX STAN 72-1981 of Standard for Infant Formula and Formulas for Special Medical Purposes Intended for Infants. The minimum value of protein for soy infant formula based on soy protein isolate is 2.25 g/100 kcal (0.5 g/100 kJ) based on CODEX. The Indonesian National Food and Drug Agency (*Badan Pengawas Obat dan Makanan*/BPOM) regulates soy infant formula and its minimum value of protein is in line with CODEX, which is 2.25 g/100 kcal and maximum of 3 g/100 kcal. This concludes that soy infant formula has met the standardized minimum for nutrients for infants and is regulated by BPOM though the intended use of SIF is not mentioned in the regulation.[12,13].

Benefits and challenges of soy infant formula

The efficacy of SIF for CMPA management is often debated because although it does not contain cow's milk protein, some children with CMPA are also allergic to soy. Some SIF adverse effects of SIF such as enterocolitis are also a consideration. Despite the low prevalence of soy allergy there is still a possibility of anaphylaxis risk in SIF.[5] The AAP, the EPSGHAN and IDAI recommended SIF as a rational choice and can be justified in CMPA

children.[2,4,6] For breastfed infants, eliminating of all cow's milk protein and other protein sources such as soy is required. For formula-fed infants, current options include specific allergen avoidance and the use of eHF and AAF. Their efficacy for CMPA is approximately 90% compared to other management such as SIF. However, the availability and the taste of the formula might be an issue for compliance, that is why SIF is considered as an alternative.[14]

Medical indication of SIF is actually limited to galactosemia and primary lactase deficiency which are very rare conditions. There is no indication to recommend the use of SIF in the prevention of CMPA, treatment of colic or as a supplement to breastfeeding. Incidence of allergy to soy or cow milk proteins has been reported to be comparable. In addition to the limited medical indications, there is also some economic, religious and philosophical reasons to advice soy although eHF has shown evidence to be more effective. SIF is substantially cheaper than eHF and it is safe and does not financially burden patients. Some eHFs are derived from pork pancreas so religious decision might affect patient decision. In this situation, SIF is a preferable option than other formulas, especially if the patient requests for vegan diet.[15]

The safety of SIF, however, is another debate. Although reports have shown infants with SIF showed normal development and growth, some have concerns with potential adverse effect of phytochemicals in SIF such as phyto-estrogens. SIF showed no significant difference when compared to cow's milk formula and breast milk in parameters such as body length, weight and head circumference.[3,16] Despite SIF's high level of aluminum content, it has been shown that it is not a safety issue since the value is within the limit allowed by WHO and BPOM.[12,13] Disorder of sexual development, hypothyroidism with euthyroid conditions and disorder of immune function have not been proven.[3,6]

SIF administration and its safety issues on sexual development and hormonal disorders are often questioned due to isoflavones content which have active metabolites in blood. Isoflavones are phyto-estrogens that hypothetically may cause disruption of sexual development and disorders of hormonal development in infants. Many studies in animals and mice showed that soy affected sexual development but it turned out that humans have a different metabolism of isoflavones in blood. Isoflavone metabolites are 20–150 times higher in mice than in human. The study concluded that the soy interference with sexual development and hormonal should not be drawn from animal studies.[5] The isoflavone content in soy isolate formula is not significant to cause unfavorable side effect.[6]

The administration of SIF is safe and cost effective for CMPA children if the children cannot tolerate eHF. Many studies showed contradicting results in regards of its safety but all of these were not proven and inconclusive.[3,5,6,15]

SIF beyond allergies

Based on the description above, numerous studies have documented normal growth and development in term neonates fed with SIF. The average energy intake in infants receiving soy protein-based formulas is equivalent to those achieved with cow milk formula. Serum albumin concentration, as a marker of nutritional adequacy is normal in infants with SIF.[6] Mineral content in SIF has been adapted and modern SIF using hydrolyzed phytate does not affect growth and bone mineralization compared to cow's milk formula and does not induce risk of malnutrition.[16]

On the other hand, SIF is not recommended for preterm infants. Serum phosphorus concentrations are lower, and alkaline phosphatase concentrations are higher in preterm infants fed with SIF than they are in preterm infants fed cow milk-based formula. As anticipated from these observations, the degree of osteopenia is increased in infants with low birth weight receiving SIF. The cow milk protein-based formulas designed for preterm infants are clearly superior to soy protein-based formula for preterm infants.[6] The AAP also concluded that the aluminium in SIF is not a safety issue, except in preterm infants and infants with renal failure, because their daily of aluminium intake is lower than 1 mg per day thus SIF contains <0.5 mg/kg/day aluminium in infants consuming SIF 200 mL/kg/day.[2,6,16] Opportunity of using SIF in the recovery of acute infantile diarrhea complicated by secondary or transient lactase deficiency has been addressed in many studies. The duration of diarrhea has been reported to be shorter in infants receiving

SIF and the duration of liquid stools may also be reduced with additional soy polysaccharide fiber compared to human milk and cow-based formula. However, after rehydration, most infants can be managed successfully with continued breastfeeding or standard cow milk or SIF. Because primary or congenital lactase deficiency is rare, very few individuals would require a total restriction of lactose. Lactose intolerance is more likely to be dose dependent. Thus, the use of soy protein-based lactose-free formulas for this indication should be restricted.[6,17]

The most common reason for using SIF by care providers is to relief of perceived formula intolerance (spitting, vomiting, and fussiness) or symptoms of colic since this can be a symptom of CMPA also.[17] Effect of partially hydrolysed formula have not concluded in this particular area. [18] Colicky discomfort is often described by the parents during the first 3 months of age in 10–20% infants. Parents frequently seek relief by changing infant formula, although many factors can cause this behaviour. The benefit of SIF to calm colic is not significant, it might be attributed to sucrose and fiber content. Education and Communication to parents are key in addition to switching to SIF because colic-related behaviour will pass spontaneously between 4 and 6 months of age.[6]

Optimizing growth and development with SIF

Isolated soy protein-based formulas currently on the market are all free of cow milk protein and lactose and provide 67 kcal/dL. All formulas are iron-fortified and meet the vitamin, mineral, and electrolyte specifications addressed in the 2004 guidelines from the AAP for feeding term infants and established by the US Food and Drug Administration. In Indonesia, all SIF are subject to the BPOM regulation[13]. The protein in SIF is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide a protein content of 2.45 to 2.8 g per 100 kcal or 1.65 to 1.9 g/dL. The fat content of soy protein-based formulas is derived primarily from vegetable oils. The quantity of specific fats varies by manufacturer and is usually similar to those in the manufacturer's corresponding cow milk-based formula. The fat content ranges from 5.02 to 5.46 g per 100 kcal or 3.4 to 3.6 g/dL. The oils used include soy, palm, sunflower, olein, safflower, and coconut. Docosahexaenoic and arachidonic acids now are added routinely.[2,6]

In formulas, carbohydrate sources are corn maltodextrin, corn syrup solids, and sucrose, with content ranging from 10.26 to 10.95 g per 100 kcal or 6.9 to 7.4 g/dL. Until 1980, mineral absorption from soy formulas was bad since as mentioned above SIF contains 1.5% phytate and 30% phosphorus is phytate bound. With the current formulations, bone mineralization, serum concentrations of calcium and phosphorus, and alkaline phosphatase concentrations in term infants through 12 months of age are equivalent to those observed in infants fed with cow milk-based formulas. Because soy phytates and fiber oligosaccharides also bind iron and zinc, all soy-based formulas are fortified with iron and zinc.[6,16]

Isoflavones are commonly found in legumes, with the highest amount found in soybeans. Concerns have been raised in relation to phyto-estrogens/isoflavones include their potential negative effects on sexual development and reproduction, neurobehavioral development, immune function, and thyroid function. But as mentioned above, the studies are inconclusive and has not been proven.[3,8]

High content of aluminium in soy-based formulas is debated since the first SIF was established. Although the aluminium content of human milk is 4 to 65 ng/mL, that of soy protein-based formula is 600 to 1300 ng/mL. The toxicity of aluminium is traced to increased deposition in bone and in the central nervous system, particularly in the presence of reduced renal function in preterm infants and children with renal failure. Term infants with normal renal function do not seem to be at substantial risk of developing aluminium toxicity from soy protein-based formulas.[2,3,6]

It is important for pediatricians to know that SIF is adapted to the nutritional needs of infants and SIF fed infants have a normal growth and development. The medical indications for soy are very limited, but the use of SIF is mostly for CMPA in Indonesia. Efforts should be made to increase breastfeeding rate and duration but SIF remains valid option for term born infants if breastfeeding is not possible and cow’s milk formula is not tolerated.

Conclusion

The use of Soy Infant Formula (SIF) are widely known for the treatment and management of Cow's Milk Protein Allergy (CMPA) but other than allergy, SIF has met nutritional needs for term born infants if breastfeeding is not possible and cow's milk formula is not tolerated. The debate about the safety issues on SIF is ranging from sexual development disorder, hypothyroidism and low immune system and its correlation to SIF levels of aluminium, phytate and isoflavone. However, recent studies showed that all of these were not proven and inconclusive. Medical indications of using SIF are limited to CMPA, galactosemia and primary lactase deficiency, but there is room for SIF utilization beyond allergies.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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