23. Soy Protein Diet Improves Nutritional Status of Offspring with Intrauterine Growth Restriction

by Perpustakaan Umsida

Submission date: 30-Mar-2024 02:10PM (UTC+0700)
Submission ID: 2335187648
File name: nal_Status_of_Offspring_with_Intrauterine_Growth_Restriction.pdf (334.67K)
Word count: 7259
Character count: 39795

Journal of Medicine and Health (JMH)
Vol. 5 No. 2 August 2023
e-ISSN: 2442-5257
https://doi.org/10.28932/jmh.v5i2.6175

Review Article

Soy Protein Diet Improves Nutritional Status of Offspring with Intrauterine Growth Restriction: A Scoping Review

Diet Protein Kedelai Meningkatkan Status Gizi Keturunan dengan Pertumbuhan Janin Terhambat: Tinjauan Pelingkupan

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Received: February 3, 2023
Accepted: June 17, 2023

Abstract

The intake of a low-protein diet during pregnancy can lead to alteration of fetal programming with long-term postnatal consequences exposing offspring with malnutrition to metabolic syndrome in adulthood. According a more affordable alternative source of protein, such as soy, is used to improve nutrition. The objective of this study was to examine the advantages and disadvantages of soy as an alternative protein source to improve offspring nutrition with Intrauterine Growth Restriction (IUGR). The method used was a scoping review, and the design was selected to provide coverage on a certain topic with the concepts from available literature**.** Systematic searches were performed in six databases: PubMed, EBSCO, ScienceDirect, SCOPUS, Sage Journals, and Cochrane Library. Data collection included reports published from January 2013 to January 2023. Nine articles meeting the inclusion criteria were obtained and analyzed for review. Protein from a plant source is considered a good alternative in restoring nutrition to malnourished offspring in early life. Furthermore, the dietary deficiency of soy can be corrected with close monitoring. As a conclusion, the quality of life of offspring with IUGR is improved through a well-planned supplementation.

Keywords: low protein diet, fetal programming, soy protein

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How to Cite:
Gunanegara RF, Rosyidah R, Dewanto A, Sunarti. Soy protein diet improves nutritional status of offspring with intrauterine growth restriction: a scoping review. Journal of Medicine and Health. 2023; 5(2): 212-26. DOI: https://doi.org/10.28932/jmh.v5i2.6175

Abstrak

Asupan diet rendah protein selama kehamilan dapat menyebabkan perubahan pemrograman janin dengan konsekuensi pasca-kelahiran jangka panjang. Keadaan ini akan menyebabkan anak dengan malnutrisi saat dalam kandungan mempunyai risiko lebih tinggi untuk mengalami sindrom metabolik di masa dewasa. Sumber protein alternatif yang lebih terjangkau, seperti kedelai, digunakan untuk memperbaiki gizi ibu selama kehamilan. Penelitian ini memiliki tujuan untuk mengkaji tentang kekurangan dan kelebihan kedelai sebagai sumber protein alternatif untuk perbaikan gizi anak dengan Pertumbuhan Janin Terhambat (PJT). Metode yang digunakan adalah scoping review, dan desain dipilih untuk memberikan cakupan pada topik tertentu dengan konsep dari literatur yang tersedia. Pencarian sistematis dilakukan di enam database, yaitu PubMed, EBSCO, ScienceDirect, SCOPUS, Sage Journals, dan Cochrane Library. Pengumpulan data meliputi publikasi yang diterbitkan dari Januari 2013 hingga Januari 2023. Sembilan artikel yang memenuhi kriteria inklusi diperoleh dan dianalisis untuk ditinjau. Protein dari sumber nabati dianggap sebagai alternatif yang baik dalam memulihkan nutrisi anak yang kekurangan gizi di awal kehidupan. Selanjutnya, kekurangan diet kedelai dapat diperbaiki dengan pemantauan ketat. Sebagai simpulan, kualitas hidup anak dengan PJT dapat ditingkatkan melalui pemberian suplementasi yang terencana dengan baik.

Kata kunci: diet rendah protein, pemrograman janin, protein kedelai

Introduction

Both preconception and pregnancy stages have an impact on neonatal growth, which is shaped by the maternal nutritional status. Recognizing the significance of upholding a diverse and nutritious diet prior to and during pregnancy is crucial. Inadequate nourishment during pregnancy continues to be a noteworthy public health issue, especially among disadvantaged and high-risk groups.[1] There is a clear association between the maternal dietary intake in the periconceptional period and the onset of non-communicable diseases in adulthood.[2] Protein deficiency has a negative effect on the growth and development of the fetus. This situation causes the selective distribution of nutrients to maintain brain growth but sacrifices other organs to increase survival in nutrient-limited conditions.[3]

In a study involving mice, the low protein intake by mothers during pregnancy led to permanent changes in gene expression through epigenetic modification.[4] This study resulted in incidence of obesity, impaired glucose tolerance, hypertension, and atherosclerosis even though

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nutrition was improved in subsequent offspring.[5] Also, the adverse effects that arise in mice can reach up to twelve generations.[6] A study on the effects of a low-protein diet during pregnancy on their offspring used mice and rats because they have many similarities with humans. Additionally, they have about 30,000 genes, each of which approximately 95% is shared by all three species.[7]

The offspring of rodents, which in utero experienced growth restriction, improved with a better nutritional intake, but the risk of developing metabolic syndrome as an adult increased.[8] The catch-up growth occurred due to the programming of the fetus, which could not adapt to the improvement of nutritional intake. Children with IUGR experience a significantly greater weight gain, even though they are fed with the same number of calories and protein.[9] Furthermore, the increased risk of metabolic disease in offspring with low birth weight is caused by excess nutrition during the perinatal period.[10] It is also caused by perinatal stress and postnatal overnutrition leading to high weight gain. Therefore, offspring with IUGR require a unique approach to improve their quality of life without increasing metabolic disease risk.

Over the past few years, plant-based proteins have gained traction as viable options in sustainability-focused uses due to their cost-effective origin, positive health effects, contribution to soil fertility, and protein composition ranging from 20% to 40%.[11] There are still limited articles discussing the comparison of protein derived from plants and animals, especially soy protein for treating stunted fetal growth. This scoping review sought to examine the advantages and disadvantages of soy as an alternative protein source to improve offspring nutrition with Intrauterine Growth Restriction (IUGR).

Methods

Design

The method used was a scoping review, and the design was selected to provide coverage on a certain topic with the concepts from available literature. Furthermore, the procedure used the Arksey and O'Malley method, encompassing five sequential stages: 1) identifying research questions, 2) identifying relevant studies, 3) selecting studies, 4) extracting and mapping data, and 5) compiling, summarizing, and reporting results.[12]

Research Questions

The research questions intended to determine the advantages and disadvantages of plant protein over casein.

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Identification of Relevant Studies

Systematic searches were performed across six databases, namely PubMed, EBSCO, ScienceDirect, SCOPUS, Sage Journals, and Cochrane Library. During this process, the Boolean operators, such as "OR" and "AND" truncation, and wildcards were used to broaden the search for various word forms. The keywords used included Mice OR mouse OR rat OR rodent AND "low protein diet" OR "low protein diets" AND soy OR casein AND IUGR.

This review included both primary and quantitative studies of low protein diets containing soy or casein in the offspring of rats or mice undergoing IUGR. The study included articles in the review for the last 10 years, which were articles published from January 2013 to January 2023.

Inclusion and exclusion criteria

All studies on low-protein diets using soy or casein in the offspring of rats or mice were included. The selected articles are studies on experimental animals, have complete text, and are in English. However, the exclusion criteria in the analysis process are opinion articles, posters, editorials, conference abstracts, and textbooks.

Study Selection

to the process of selection adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] First, the data were processed, and the selection process followed the stages of identification, screening, eligibility check, and inclusion. Furthermore, the articles were selected according to Mendeley's assistance. Finally, the findings from the two separate searches were juxtaposed for comparison.

Data Extraction and Mapping

The data extraction was conducted using an Excel spreadsheet and then the data were converted into an extraction table containing the title of the article, author and year of publication, research objectives, design, samples, data collection methods, and the main results.

Compilation, Summarization, and Reporting of the Results

All of the selected articles contain the type of study conducted and the main results of the effect of soy/plant protein on the offspring.

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Results

As many as 201 articles were identified, after which the Mendeley software was employed to select 42 studies with similarities, leaving 159 for initial screening based on their titles and abstracts. The search results were sifted through by examining the titles and abstracts to pinpoint the articles that satisfied the inclusion criteria. Furthermore, 137 articles were considered irrelevant to the title and abstract screening, leaving 22 for full-text review. Accordingly, this study encompassed only 9 articles (Figure 1).

PubMed	Sage Journals	Science Direct	EBSCO	Cochrane Library	Springer Link
14	3	33	80	1	40

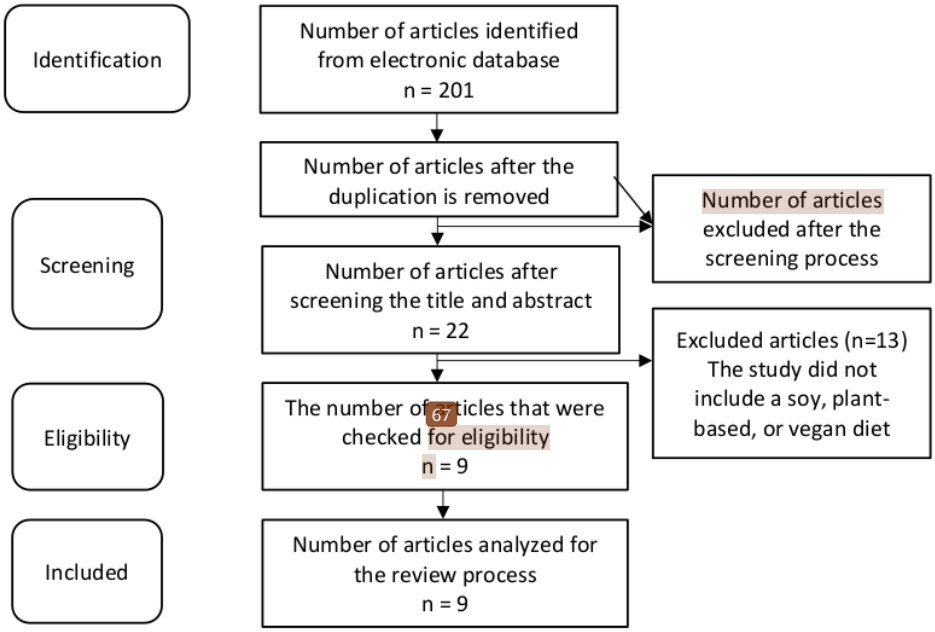

Figure 1. Study identification and inclusion process – Selection reporting items for systematic review and meta-analysis (PRISMA) flowchart[13]

All studies were published in journals between 2013 and 2023. The design used was a systematic analysis of several studies on experimental animals. Further details of each study are described in table 1.

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Table 1. Comparative articles of plant protein and casein protein

No.	Article Title	Author (Year)	Purpose	Methods	Key Findings
1	Beef, Casein, and Soy Proteins Differentially Affect Lipid Metabolism, Triglycerides Accumulation and Gut Microbiota of High-Fat Diet-Fed C57BL/6J Mice	Ijaz et al., 2018[14]	The main focus of this research revolved around the impacts of a diet containing beef, casein, and soy proteins on lipid metabolism, the buildup of triglycerides, and the diversity of microorganisms in the colons of C57BL/6J mice.	A total of 30 seven week-old C57BL/6J male mice were give a low-fat diet (LFD 12% kcal) and the other 30 mice were given a high-fat diet HFD (60% kcal) for 12 weeks. In the context of soy and beef protein diets, the protein powders derived from soy and beef were used to replace casein in both groupsIn the context of soy and beef protein diets, the protein powders derived from soy and beef were used to replace casein in both groups.	The intake of beef protein not only impacts the composition of gut microbiota but also contributes to issues associated with metabolic syndromes such as dyslipidemia, high cholesterol levels, and the buildup of triglycerides in the liver. These factors culminate in systemic inflammation and its linked complications, including impaired glucose metabolism and insulin resistance. The intake of beef protein not only impacts the composition of gut microbiota but also contributes to issues associated with metabolic syndromes such as dyslipidemia, high cholesterol levels, and the buildup of triglycerides in the liver. These factors culminate in systemic inflammation and its linked complications, including impaired glucose metabolism and insulin resistance.
2	Nutritional Recovery with Okara Diet Prevented Hypercholesterolemia, Hepatic Steatosis, and Glucose Intolerance	Lemes, 2014[15]	Assessing the effect of the okara soy diet on mice's hormonal and metabolic profile on a protein-restricted diet during intrauterine life and lactation.	A total of 18 offspring of 23-day-old male rats treated with a low-protein diet during pregnancy were divided into 3 groups, namely the casein diet, okara soy diet, and the diet without protein groups groups. The study duration wawawas 28 days, and it it it used male offspring with a low-protein diet during pregnancy.	The okara soybean diet effectively restored nutrition to male rat offspring whichich were malnourished in early life.

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3	Short- and Long-Term Effects of a Maternal Low-Energy Diet ad Libitum During Gestation and/or Lactation on Physiological Parameters of Mothers and Male Offspring	Alheiros-Lira, 2015[16]	To explore the immediate and prolonged impacts of a brood's low-energy diet during pregnancy and/or lactation on both the brood and her offspring.	A total of 20 offspring of male Wistar rats were distributed into 4 groups based on the brood's diet, namely a control group during pregnancy and lactation, a low-energy diet during pregnancy, a low-energy diet during lactation, and a low-energy diet during pregnancy and lactation. In this study, crude fiber (10% cellulose fiber and pure soluble fiber) was added to a low-energy diet to reduce the total energy value. The study only used male offspring with a normal casein protein and soybean oil diet of 35% calorie reduction.	The negative effects of a brood's low-energy diet during pregnancy on her offspring can be reduced by adding fiber to the diet.
4	Maternal Soy Protein Isolate Diet During Lactation Programmes to Higher Metabolic Risk in Adult Male Offspring	de Almeida Brasiel, 2020[17]	Evaluation of the effect of soy protein isolate diet during lactation on breast milk composition, body composition, glycemic and fat profile as well as thyroid hormone in broods and offspring.	A total of 12 offspring of lactating female Wistar rats were divided into 2 groups, namely the casein diet group and the soybean protein isolate diet group. The study duration was 148 days, and it used a standard protein diet during pregnancy.	Consumption of soy protein isolate during lactation was found to increase the risk of metabolic risk profile in male offspring.
5	The Effects of Whey and Soy Proteins on Growth Performance, Gastrointestinal Digestion, and Selected Physiological Responses in Rats	Wróblewska B, 2018[18]	Evaluation of the impact of soy and whey on the nutrition and physiology of Wistar rats.	A total of 24 male Wistar rats aged 30 days were grouped into three, namely casein group, soy protein group, and whey protein group. The length of the experiment was 28 days, and it used only male offspring with a standard protein diet.	The groups consuming casein and whey proteins exhibited greater body weight and twice the lean body mass compared to the group that consumed soy. Soy and whey proteins lead to a decrease in the protein efficiency ratio, an increase in nitrogen excretion in the urine, and a decline in cecal ammonia levels.

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6	Effects of Voluntary Running and Soy Supplementation on Diet-Induced Metabolic Disturbance and Inflammation in Mice	Yan L, 2013[19]	Knowing the effect of the high-fat diet, physical activity, and protein sources of casein or soy protein isolate, metabolic disorders, and inflammation in rats.	A total of 120 mice were grouped into 8 groups, namely the high-fat diet, the diet with soy protein isolate with physical activity, and no physical activity groups. The trial duration was 14 weeks, and it used only male offspring with a standard protein and a high-fat diet.	The soy protein isolate and physical activity group improved metabolic disorders and diet-induced inflammation in mice.
7	Dietary Soy Protein Isolable Attenuates Intestinal Immunoglobulin and Mucin Expression in Young Mice Compared with Casein	Zeng B, 2020[20]	To compare the impacts of casein and soy proteins on early mouse gut immunity.	A total of 16 mice were grouped into 2 groups: a group with casein diet and a group with soy protein isolate diet. The study period was for 21 days and it only used male offspring with a standard protein diet.	The results showed that the soy protein isolate diet could weaken the gut immunity of mice, as indicated by a decrease in SIgA and mucin production in the intestine.
8	Substitution of Soy Protein for Casein Prevents Oxidative Modification and Inflammatory Response Induced in Rats Fed High Fructose Diet	Sreeja S et al, 2014[21]	The study sought to contrast the impacts of dietary proteins from animal and plant sources on oxidative stress induced by fructose and inflammatory alterations in the liver.	A total of 24 adult male albino Wistar rats with weights ranging from 140 to 160 g were randomly assigned into 4 groups, each consisting of 6 rats. The rats were fed one of the semi-synthetic diets with different sources of carbohydrates and proteins for a duration of 8 weeks.	Replacing casein with soy protein decreased oxidative modifications and inflammatory alterations in rats subjected to a fructose-rich diet. These findings indicate that soy protein, unlike casein, has the potential to prevent the negative effects associated with prolonged fructose consumption.
9	Typical Gut Indigenous Bacteria in ICR Mice Fed a Soy Protein-Based Normal or Low-Protein Diet	Nakamura S et al., 2021[22]	To investigate the impact of a soy-based diet low in protein content on the body and organ weights as well as the composition of the gut microbiome in mice.	A total of 12 mice were divided into two groups: the standard protein (20%) and low protein (5%) diet groups. The study duration was 14 days and it only used male offspring with a low protein diet.	The low-protein group showed lower body and organ weight gain as well as lower microbiome diversity.

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Discussion

Plant Protein as an Alternative Source of Protein

Protein-energy malnutrition is one of the most common nutritional problems in developing countries.[23] This is because of the high price of food obtained from milk protein. However, plant protein is a better alternative to milk as an energy source for infants and adults.[24] Additionally, it is more affordable for low-income individuals.

Soy-based proteins have several advantages over casein. A study showed that it was effective in restoring nutrition in malnourished rats in early life.[15] The administration of soy to the group of recovering rat offspring showed a higher weight gain than that of those fed with a low protein diet. Meanwhile, at the end of the recuperation phase, the rats' body weights and total energy intake from this group remained lower than those of the rats in the control group. The results showed a better metabolic risk profile of offspring undergoing recovery. Additionally, other studies stated that soy reduced hypercholesterolemia[25] and hepatic steatosis and prevented glucose intolerance in offspring prone to diabetes mellitus.[15, 18]

Plant protein has high unsaturated fat, fiber, and antioxidants.[26] Soy has been observed to improve glucose homeostasis, fat profile, and antioxidant reserves.[27] In a study involving pregnant mice with Chronic Kidney Disease (CKD), soy improved kidney function in the offspring. Furthermore, inflammation and cell growth in the kidneys, oxidative stress, and the presence of protein in the urine or proteinuria experienced a decrease.[28] A plant-based, low-protein diet supplemented with amino acids in pregnant women with CKD has a better perinatal outcome. There is a significantly low incidence of Small Gestational Age (SGA) and/or very premature infants (<28 weeks).[29] Proteins derived from plants, which are linked to reduced phosphate absorption[30, 31] are less inclined to cause acidosis[32] and can influence the gut microbiota, resulting in reduced production of uremic toxins.[33, 34] Additionally, the soy isolate diet has the advantage of being relatively high in antioxidant content. The composition of the microbiota and its resulting metabolites is also good.[35] Soy protein is deficient in methionine and cysteine[26], but methionine supplementation can potentially treat hypertriglyceridemia.[25]

The high fiber content in soybeans reduces the adverse effects of a low-calorie diet on offspring during pregnancy.[16] Although this increases satiety by prolonging meal and gastric emptying time, it also enhances chewing, thereby increasing the gastric volume. Accordingly, adding a fiber-rich diet reduces the short-term adverse effects of a low-calorie diet on the offspring.

The offspring of mice administered a protein-sourced diet from soy have lower body weight as well as less fat content in the body and liver when compared with those of mice

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administered casein.[36–38] Soy is rapidly absorbed, causing a lower feeling of satiety and less absorption of amino acids, while it also leads to less protein synthesis.[39] This situation explains the lower body weight in offspring administered soy compared to that of those administered a casein diet. Consequently, the nutrition of offspring with stunted fetal growth is improved with casein[40] in diet in mice.[19]

A well-designed plant-based diet provides adequate nutritional intakes for all stages of life. It is helpful in the therapeutic management of several chronic diseases.[41] However, it does not affect disorders related to pregnancy. For example, preeclampsia and preterm birth incidence remain constant[42–45] while glycemic control in pregnant women with diabetes seems better with a plant-based dietary fiber.[46]

Soybean is the most studied source in dietary protein research. It offers a comprehensive array of amino acids, nearly on par with meat, providing a viable protein substitute.[47] In patients with CKD, it has been shown that a soy-based diet yields beneficial impacts on plasma cholesterol and triglyceride levels[48], serum creatinine and phosphate levels[49], oxidation markers, endothelial function[50,51], glucose metabolism, and proteinuria.[52]

Research has shown that isoflavones, a group of polyphenolic compounds discovered in soybeans, have anti-inflammatory, antioxidant, anticancer, and antimicrobial activities.[53] For example, genistein and daidzein possess a structure resembling estradiol and fall into the category of phytoestrogens because they both have an affinity against the estrogen receptor.[54] Genistein reduces the production of cytokines in vitro through inhibition of tyrosine kinase activity.[28] Furthermore, the isoflavone content had different effects on male mice offspring. There was an increased risk of the metabolic profile when consuming soy protein isolate during lactation. Soy protein isolate diet reduces body protein mass but increases hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, and free T4 levels.[17]

Plant protein contains low vitamin B12, sodium, zinc, calcium, and uremic toxins.[26] Furthermore, it has been shown in several studies that it increases the risk of nutritional deficiencies such as vitamin B12[55,56] and vitamin D[57], iron[58], and zinc during pregnancy, but this can be improved with close monitoring and well-planned supplementation.

Jahan-Mihan found that the offspring of mice receiving soy had higher body weight and blood pressure than those on a casein diet.[39,59] Furthermore, soy protein diets increase body fat, body weight as well as systolic and diastolic blood pressure and decrease insulin sensitivity and hereditary glucose intolerance. This study used the broodstock on a standard protein diet and only examined its effect on male offspring. The results were due to a combination of effects of additional protein and amino acids in the diet and the impact on broodstock offspring during

pregnancy. The study also examined the effect on the offspring of male mice, while the female offspring proved to be different. Metabolic effects in female offspring are less significant than those in the male.[37]

Casein is considered slow protein that gradually releases amino acids and peptides in the duodenum. This process makes the flow of amino acids in the blood slow and stable, ensuring more protein synthesis. Meanwhile, soy is considered fast protein, resulting in increased amino acid degradation and lower protein synthesis. This situation, therefore, contributes to lower body weight.[60]

Based on protein quality ranking, the Protein Digestibility Corrected Amino Acid (PDCAA) value of soy is the same as those of casein and whey, but the efficiency ratio is lower than both.[61] Several studies have stated that the biological value of soy protein is lower than that of casein due to its low synthesis.[62] However, casein has an advantage in protein synthesis for a longer period.[61] Soybean protein which is considered rapid offers short-term benefits. Also, its muscle synthesis is higher than that of casein when examined within 1-2 hours after administration.[63] Meanwhile, the effects of diet on humans depend on the genetic background, as in the case of rodents. Research conducted in Canada indicated that adopting a plant-based diet during pregnancy was linked to a potential likelihood of giving birth to undersized infants among Caucasian mothers, while Asian mothers of South Asian heritage experienced an increase in the weight of the infants they gave birth to.[64]

The results showed that the soy protein isolate diet weakens the gut immunity of mice due to the production of SIgA and mucin in the intestines.[20] Furthermore, it was also found that changes in the metabolic profile of gut microbiota as well as a decrease in bacterial growth were also caused by the antibacterial activity of several components of soy preparations. This situation causes deficiencies related to changes in the composition of the gut microbiome[22] and the ratio of Firmicutes and Bacteroidetes in mice and humans.[65] The comparison of soy protein and casein protein is shown in table 2.

Implications for future study

Soybean is the most studied plant-based protein source in dietary research. Hence, more study is needed on protein sources from other legumes, especially species with high economic potential but have not been widely used in Indonesia. Additionally, further study should emphasize plant and animal protein as supplements, which can complement each other.

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Limitations

This study is a scoping review that covers a large body of literature on a specific topic without thoroughly evaluating the quality of the articles. Therefore, this review does not cover all aspects but only compares plant and animal protein in a limited scope.

Conclusions

A low-protein diet during pregnancy has a negative effect on the health of the offspring, not only in the womb but also in adult life. Furthermore, fetal programming can occur due to the fetus's adaptation process to the influence of the pregnancy environment while in the womb has long-term effects that can be detrimental when not handled properly. Therefore, the quality of life of the offspring experiencing intrauterine growth restriction is improved by good planning, and monitoring of soy supplementation with amino acid content almost equivalent to cow's milk formulas but with a more affordable price.

Table 2. Advantages and disadvantages of soy protein compared to casein protein.

No	Soy protein compared to casein protein
	Advantages
1	Soy protein is fast protein, providing short-term benefits, and muscle protein synthesis from soy protein is higher than that of casein protein when examined within 1-2 hours after administration.[63]
2	The soy protein diet is effective in restoring nutrition to male rat offspring which were malnourished during pregnancy.[15,40]
3	Soy protein has high fiber content, reducing the adverse effects of the brood's low-calorie diet during pregnancy on her offspring.[16,46]
4	Soy protein has high antioxidant content in improving vascular endothelium[50, 51] as well as digestive function[35] and exhibiting anti-inflammatory, anticancer, and antimicrobial activities.[53]
5	Soy protein improves metabolic and inflammatory disorders caused by diet in mice.[19]
6	Soy protein lacks methionine and cysteine[26], but with methionine supplementation, it has the potential to treat hypertriglyceridemia.[25]
	Disadvantages
1	Soy protein diet increases metabolic syndrome characteristics in both the broods[37, 39] and offspring[17], especially in male mice.
2	Soy protein diet increases the risk of nutritional deficiencies such as deficiencies in vitamin B12[55, 56], vitamin D[57], iron[58], and zinc.
3	Mice on a soy protein diet had lower body weight as well as lower body and liver fat content.[18, 36, 38, 39]
4	Dietary soy protein can weaken the gut immunity of mice [20], causing deficiencies associated with changes in the gut microbiome composition[22] as well as changes in the ratio of Firmicutes and Bacteroidetes in the intestines of mice and humans.[65]

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