

Replacing Fetal Bovine Serum with Food Processing Byproducts in Culture Media for Cultured Meat – a Sustainable Development Path

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Abstract. With increasing population and worsening environmental pollution, cultured meat is considered a promising protein source. However, current cultured meat production faces significant challenges, primarily due to the high cost of fetal bovine serum (FBS), a widely used culture medium. In recent years, widely available and abundant food processing byproducts have gained attention, considered as potential alternatives to FBS. This review summarizes three representative food processing byproducts: grain processing byproducts (okara), dairy processing byproducts (whey), and oil processing byproducts (soybean meal). The review first introduces the global annual production and current processing methods of these byproducts. It then discusses the key components in these byproducts that promote cell growth and proliferation. Based on existing experimental data, the application effects of these three food processing byproducts are described. Finally, considering environmental factors, extraction costs, and application effects, the potential of these three types of food processing byproducts as FBS substitutes is comprehensively evaluated, providing a theoretical reference for developing efficient and stable serum alternatives.

Keywords: Fetal bovine serum substitute; food processing byproducts; protein hydrolysate; fermentation extract; sustainable bioprocessing.

1. Introduction

The global food system is facing increasingly severe environmental, ethical and health-related challenges, and cultured meat has become a promising solution in recent years [1]. However, many practical problems have also been found in past studies on cultured meat. Scientists have analyzed the contradiction between the environmental promises of cultured meat and reality and found that some high-purity culture media have an environmental impact that is even greater than that of traditional beef [2]. In addition, fetal bovine serum (FBS) is usually added to the culture medium for making cultured meat because it contains the optimal ratio of nutritional factors and growth factors that can support the growth of different types of cells [3]. However, due to its extremely high cost, there are issues of biosafety and ethics, and many researchers are actively looking for alternatives that can perfectly solve these problems [4].

In recent years, food processing by-products have stood out among many FBS substitutes because of their natural safety as food raw materials, the absence of ethical issues, and the concept of sustainable development [5]. Against this background, more and more researchers have begun to focus on the potential application value of food processing by-products in cell culture. By extracting key components from food processing by-products to replace FBS, serum-free culture media can be prepared, thereby achieving more precise control of the cell culture environment, optimizing cell proliferation and differentiation, and finally improving the quality and yield of cultured meat [4].

This article categorizes potential food processing byproducts that can replace FBS into three main types, selecting those that have been extensively researched and discussed as representatives for analysis and discussion. By reviewing relevant research findings, the application effects and potential advantages of different byproducts in cell culture systems are compared.

2. Analysis of Three Major Food Processing By-products Literature References

This paper mainly classifies food processing by-products that can replace FBS into three categories: grain processing by-products, dairy processing by-products, and oil processing by-products. Among these three categories, okara, whey, and soybean meal, which have received the most discussion, are selected as representatives for discussion.

2.1. Production and Treatment

The huge production volume is an important reason why these three food processing by-products have the potential to replace FBS. According to the consumption of soybean products, about 14 million tons of soybean residue are produced globally each year [6]. However, because fresh okara has poor flavor, rough texture, high water content, and is prone to microbial spoilage, it is often discarded as waste [5]. Then there is whey, which produces about 9 kg of whey for every 1 kg of cheese produced [7]. Currently, about 130 countries and regions around the world produce cheese, with a total global cheese production of 20 million tons [8]. Therefore, the annual production of whey is about 180 million tons. Whey is often regarded as a waste, and if it is discharged directly into the public sewage system without treatment, it will cause serious environmental pollution [7]. Finally, there is soybean meal, which has an annual production of about 122 million tons and contains a large amount of protein [9]. These food processing wastes are not only produced in huge quantities, but are also often treated as waste, causing environmental pollution. If they can be developed and utilized, they can not only reduce resource waste and environmental pollution but also have the potential value of being developed as serum substitutes.

2.2. Key Components

In order to further evaluate the application potential of these food processing by-products in cell culture, it is necessary to analyze the key components that can support cell growth and proliferation. Ultrafiltration-treated fermented okara extract has the potential to be a novel serum substitute [5]. Okara is usually fermented in solid state (SSF), that is, the solid substrate is fermented by microorganisms. The enzymes secreted by the microorganisms hydrolyze the macromolecules in okara into low molecular weight nutrients. For example, proteins are broken down into peptides and amino acids, such as alanine, glycine, valine and leucine, thereby providing a nutrient source for cell culture [5]. Whey protein mainly contains protein components such as β -lactoglobulin and α -lactalbumin. These proteins can be converted into whey protein hydrolysate through hydrolysis [4]. Whey protein hydrolysate mainly contains short-chain peptides and free amino acids. Some of these small peptides can be used as a nutrient source for cell culture, while others can promote cell growth and division [4]. The hydrolysis of proteins in soybean meals can be achieved through enzymatic hydrolysis, which breaks down proteins into smaller peptides and various components essential for animal cell survival and growth, such as amino acids, minerals, vitamins, carbohydrates and lipids [3]. In summary, these food processing byproducts can release nutrients such as peptides and amino acids through fermentation or enzymatic hydrolysis and therefore have important potential in the development of serum substitutes.

2.3. Application Potential

Based on the rich nutrients and bioactive substances in these food processing by-products, a number of studies have explored their application potential in cell culture systems in recent years. For example, fermented okara extract can improve cell survival rate after fractionation and show effects close to serum culture medium under low serum or serum-free conditions, which shows its potential application value as a substitute for animal serum in cultured meat production. Teng et al. used HEK293 and HepG2 cells as models and the cell growth rate reached 70% compared with the positive control group using traditional FBS [5]. Therefore, the experimental results show that soybean residue can replace up to 70% of FBS. In addition, experiments have shown that whey protein hydrolysates

containing α -lactoglobulin and β -lactalbumin can completely replace FBS when lipid mixtures and ITS additives are added. The results show that at concentrations of 0.01% and 0.1%, hydrolysates such as FAB-H, FB-H and TM-H can partially replace up to 50% of FBS in cell culture medium without affecting cell function [4]. Meanwhile, soybean meals were enzymatically hydrolyzed with Alcalase, and the experimental results showed that the hydrolysate could replace up to 50% of FBS porcine muscle stem cells while still maintaining their proliferation and differentiation capabilities [3]. In summary, these protein hydrolysates derived from food processing byproducts have shown good application potential in cell culture and can replace FBS to a certain extent, providing a new research direction for developing low-cost and sustainable serum alternatives.

3. Discussion on the Three Major Food Processing Byproducts

Although the yield and processing methods, key components and application potential of food processing byproducts have been introduced above, there is still a lack of systematic evaluation of the potential of different raw materials as serum substitutes. These three food processing byproducts can solve the ethical and infectious pathogen risks of traditional serum, so the environmental benefits, cost and substitution effect are the key to judging which of these three food processing byproducts has the most potential. According to an analysis by GFI, growth factors account for more than 99% of the total cost of cell culture, so cost is the core indicator. The ideal culture medium formulation should reduce the cost of raw materials without reducing cell yield [10]. Therefore, cost is a very important factor in assessing potential, while there is no data and literature to support the demonstration of environmental and substitution effects. Therefore, I gave the importance of cost 50% and environmental and application effects 25% each for potential assessment.

3.1. Cost

Regarding the cost, specific data on the cost of ultrafiltration of okara to produce fermented soybean residue extract is currently unavailable, so this paper estimates the cost. Currently, solid-state fermentation is the most common fermentation method, which is considered a low-cost biotransformation method in industry. Data is available on the cost of obtaining whey protein hydrolysate through enzymatic hydrolysis. Under these conditions, bioactive whey protein hydrolysate with a sales price of \$20 per kilogram can be produced [11]. Finally, the cost of soybean protein isolate produced by enzymatic hydrolysis of soybean meals is currently around \$3.50 per kilogram [12]. It is known that the protein hydrolysate of okara is obtained through solid-state fermentation, while the protein hydrolysate of whey and soybean meal is obtained through enzymatic hydrolysis. Furthermore, the price of industrial enzyme preparations is relatively high, while the cost of fermentation strains is low. Therefore, the extraction cost of okara is lower. However, due to its high-water content and easy perishability, okara requires additional preservation, which increases the overall cost. Therefore, this paper speculates that the total cost of soybean meals may be lower.

3.2. Environment

The annual global production of the three food processing by-products mentioned in this paper is relatively large, and they are often treated as waste. Therefore, whether their treatment will have an impact on the environment is very important for assessing their potential as food processing by-products to replace FBS. The results show that uncontrolled landfilling of okara will cause the highest environmental burden, mainly due to the emission of methane and ammonia, which will lead to environmental problems such as climate change, acidification, eutrophication and particulate matter formation [13]. Cheese whey is also a wastewater containing a large amount of organic matter and salt before it is used as a by-product with nutritional value. If it is not properly treated, it will have a significant negative environmental impact on the dairy industry. This wastewater usually contains pollutants such as minerals, suspended solids, pH changes, phosphorus and nitrogen [14]. Soybean processing lacks sustainable food processing methods, and a large amount of soybean by-products

are discarded as waste, such as soybean meals, which causes environmental pollution [15]. If these three food processing by-products are not properly treated, they will cause great environmental pollution. There is currently no relevant literature on the degree of pollution of each of them. However, due to the huge annual production of whey, this paper believes that if it is used in an advanced manner, it will be of greatest help to environmental protection.

3.3. Application Effects

The experimental conclusions mentioned above have shown the maximum substitution effect of these three foods for FBS. Okara has the best maximum substitution effect, reaching 70%. In addition to the maximum substitution effect, the function and stability of cells in the culture medium also have a great influence on the application effect. Whey protein hydrolysate showed the best cell culture performance among the three food processing by-products. It can not only significantly promote cell proliferation but also support cell differentiation and exert growth factor-like effects by activating signaling pathways such as PI3K/Akt/mTOR. At the same time, it has good system stability [4]. In contrast, although soybean meal hydrolysate can promote cell growth by providing bioactive peptides and polyamine precursors, its mechanism of action is still not clear, and the system stability is greatly affected by the raw materials and the degree of hydrolysis [3]. Okara extract mainly showed certain metabolic regulation ability, but there was insufficient evidence in terms of cell function, and there were also problems such as inhibitory components and poor stability [5]. Therefore, from the perspective of comprehensive performance, whey has more obvious advantages.

3.4. Most Promising Substitute

Based on the preceding discussion, in terms of cost advantage, soybean meals are superior to okara, which is superior to whey. In terms of environmental advantage, whey is superior to soybean meals, which is superior to okara. In terms of application effectiveness, whey is superior to okara, which is superior to soybean meal. Based on this ranking, each indicator is divided into high, medium, and low levels, and assigned corresponding scores, with five points being the highest and decreasing sequentially. As shown in Table 1, a weighted evaluation model was constructed. This model, through the weighting of the three aspects, identified soybean meals as the most promising food processing byproduct.

Table 1. Scores of three food processing by-products in terms of cost, environment, and application effectiveness.

Food processing byproducts	Cost(50%)	Environment (25%)	Application Effect (25%)
okara	4	2	4
whey	2	5	5
Soybean meal	5	4	2

4. Conclusion

This review, through literature review, investigated the yield and processing methods of three food processing byproducts—okara, whey, and soybean meal—as well as their key components that can replace FBS and their current experimental application effects. A comparative analysis of these three byproducts in terms of cost, environmental impact, and application effects concluded that soybean meals are the most promising, providing a reference for future research. While current research validates the positive trend of food processing byproducts as FBS substitutes, their practical application still faces several challenges. Currently, I believe there are three main challenges: economic, technological, and regulatory. Firstly, there is the economic challenge: the extraction cost of functional components from food processing byproducts remains high. Secondly, there is the technological challenge: the composition of fetal bovine serum (FBS) is highly uncertain, and its

components are not yet fully understood qualitatively and quantitatively, making it difficult for current food processing byproducts to achieve the same effects as traditional serum. Finally, there is the regulatory challenge: these raw materials are usually food industry waste or byproducts, and their application in biomedical or cell culture fields may involve new regulatory requirements.

Based on the above, future research can further enhance the application potential of food processing byproducts as FBS substitutes by focusing on two directions: directed hydrolysis technology and synthetic biology strategies. This will provide new research directions for developing more sustainable and low-cost FBS alternative culture media.

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