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In vitro Cultured Meat: Nutritional Aspects for the Health and Safety of Future Foods

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Abstract

In vitro cultured meat is one of the future foods that might revolutionize meat production by allowing food manufacturers to sidestep traditional animal farming. Despite being in early development, *in vitro* cultured meat faces challenges such as technological limitations and consumer acceptance, hindering its market integration. Beyond being an ethical alternative to conventional meat, it resembles conventionally farmed meat, making it a focus on healthcare and food safety. From a health perspective, it theoretically presents intriguing possibilities in the fields of functional foods, tailored dietary therapy, and public health. In functional foods, its unique composition allows precise nutritional manipulation for specific dietary needs, aligning with personalized nutrition. In dietary therapy, *in vitro* cultured meat might offer customization for individuals with dietary restrictions or health conditions, providing a novel therapeutic avenue. From a public health standpoint, it holds promise in mitigating environmental and health challenges linked to conventional meat production, aligning with sustainability and disease prevention initiatives. However, the potential health risks of *in vitro* cultured meat include concerns about the use of genetically modified starting cells, fetal bovine serum, growth factors, scaffolding materials, and antibiotics during the production process. These additives may have unforeseen long-term health effects if not properly regulated. Additionally, *in vitro* cultured meat may lack some of the natural nutrients found in conventional meat, which could lead to nutritional imbalances. There are also uncertainties about how the texture and bioavailability of nutrients in *in vitro* cultured meat might affect digestion and absorption in the human body. Nevertheless, specific aspects of research in the field of *in vitro* cultured meat demand increased focus from researchers to guarantee the optimal safety standards. An in-depth study on safety-oriented research of *in vitro* cultured meat should be emphasized to ensure benefits for individual and public health.

Keywords: Cellular agriculture, Alternative protein, Nutrients, Future foods, Food safety, Serum replacement

Introduction

Working in the field of future food involves looking at various trends and innovations driven by factors such as population growth, environmental sustainability, technological advancements, and changing consumer preferences. There are several aspects of future food, such as personalized nutrition, insect-based food as well as cellular agriculture [1-4]. Cellular agriculture, also known as cell-based agriculture, is an innovative approach to food production that involves the derivation of animal-based products, such as meat, milk, and eggs, using cell culture techniques rather than traditional livestock farming [3]. An established use of cellular agriculture involves generating *in vitro* cultured meat, to mimic the flavor, consistency, and nutritional composition of traditional meat products, all achieved without the necessity of raising and slaughtering animals.

The initial steps of *in vitro* cultured meat production involve selecting suitable stem cells, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), or muscle stem cells [3,5-10]. Core procedures include extracting cells, reprogramming them, and cultivating them in specialized media. The second step involves cultivating and expanding selected cells in a culture medium, which is commonly animal serum-based, providing essential nutrients. Efforts to develop serum-free media exist due to safety and ethical concerns. The third step focuses on preparing an edible scaffold from biocompatible materials, facilitating cell attachment and growth [11,12]. The cells, once expanded, are seeded onto the scaffold. The cell-seeded scaffold is maintained in a controlled cultural environment, controlling factors like temperature, oxygen, and nutrient supply [13]. Fourthly, cultured cells mature and differentiate into desired components, with tailored cues or conditions. Upon reaching the desired structure, cultured meat is harvested, undergoing additional processing for taste, texture, and nutritional adjustments [6,14,15]. The final steps involve formulating the cultured meat into various products and ensuring the product meets safety, taste, and nutritional standards through quality control measures, including testing for contaminants and sensory evaluations. An illustration of the *in vitro* cultured meat production process is shown in **Figure 1**.

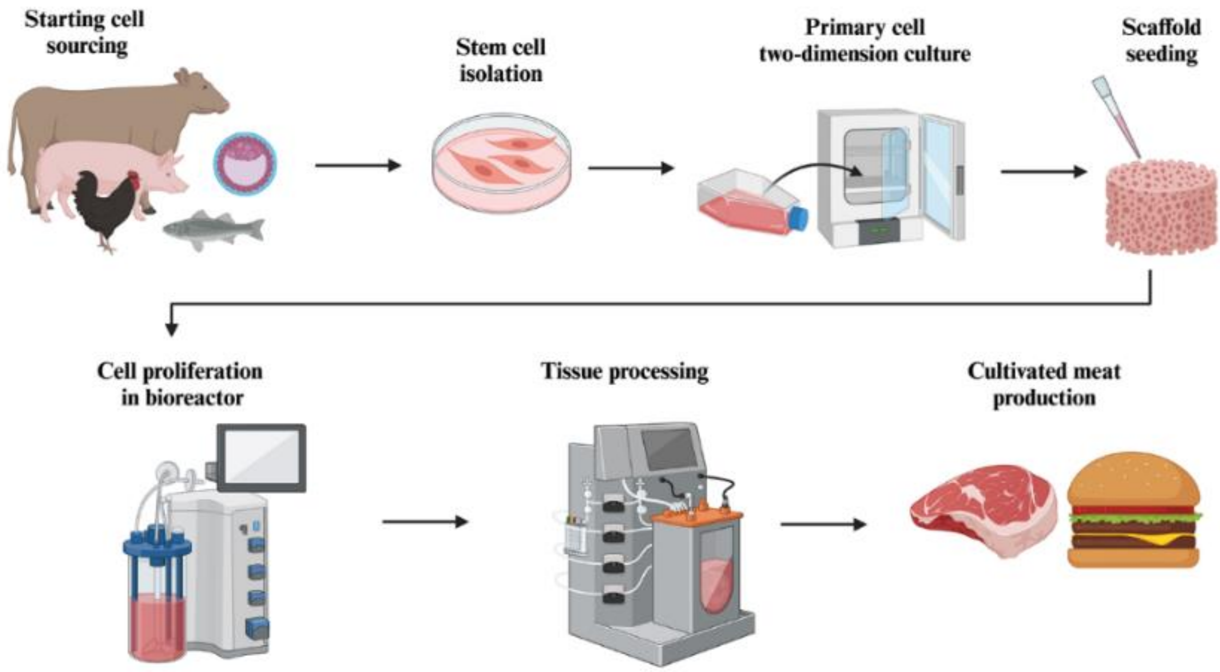

Figure 1 Schematics representation of *in vitro* cultured meat production process. Stem cells are obtained via biopsy, cultured in bioreactors, differentiated, and structured with scaffolds to mimic meat. After maturation for texture and flavor, the cultured meat is harvested and processed into the final product. Created with http://www.biorender.com.

Although the primary focus of *in vitro* cultured meat development lies in providing a sustainable and ethical substitute for traditional meat production, only a limited number of studies have been conducted on the safety, nutritional value, and environmental impact of *in vitro* cultured meat, making it difficult to fully validate the claims made by companies in the industry with complete transparency [16]. However, in theory, *in vitro* cultured meat holds promise in addressing unique solutions to challenges related to functional foods, personalized nutrition, and public health [17].

Additionally, research into the safety and long-term health effects of *in vitro* cultured meat consumption is essential. From a health standpoint, this innovative approach to food production, particularly in the healthcare context, is the focus of this review, which aims to elucidate key nutritional aspects for health and safety considerations related to *in vitro* cultured meat.

Methods

In the present review, we employed a narrative approach to conduct a comprehensive review of *in vitro* cultured meat, with a special emphasis on its benefits and risks for individuals and public health. The relevant keywords, including cultured meat, cellular agriculture, nutrients, and starting cells, were used for information extraction. The objective of this review was to summarize the available data and information. To present the pros and cons of *in vitro* cultured meat, 2 sections were provided: One focusing on its potential health benefits and the other on its potential health risks.

Potential health benefits

In vitro cultured meat as a novel functional food

The categorization of red meat as a potential carcinogen is principally derived from the classification by the International Agency for Research on Cancer (IARC), a subsidiary of the World Health Organization. Red meat is the meat that contains a high concentration of a protein called myoglobin. It is commonly red when raw and dark brown when it is cooked. In 2015, the IARC designated processed meat as Group 1, signifying its carcinogenicity to humans, and red meat as Group 2A, indicating its probable carcinogenicity to humans. This classification stems from observed associations between the consumption of red and processed meats and the onset of specific malignancies, notably colorectal cancer [18,19]. Concerning *in vitro* cultured meat especially beef and pork, it unequivocally falls within the category of red meat owing to its derivation from livestock cells. However, there are differences between how *in vitro* cultured meat is done and traditional farming practices. Myoglobin protein is naturally absent from *in vitro* cultured meat during culturing of the cells. The red color of *in vitro* cultured meat can be manipulated by adding food-grade natural dye [20,21]. Therefore, a notable advantage of *in vitro* cultured meat lies in the precision afforded in controlling its compositional attributes. As posited, it is conceivable that the quality of *in vitro* cultured meat could be modulated by manipulating factors such as fat content, lean muscle mass, and nutritional composition [14,22,23]. This fine-tuning may be achieved through the manipulation of cell culture conditions, directional guidance of cell differentiation, and potential supplementation of the culture medium with substances aimed at achieving desired compositional characteristics, offering health benefits for consumers. However, it is important to note that there is currently limited information on the protein content, amino acid composition, and protein digestibility of cultured meat, as well as the factors influencing these characteristics, underscoring the need for further research. To date, no studies have quantified the protein content of *in vitro* cultured meat. Nonetheless, morphological observations indicate that current culturing techniques result in *in vitro* cultured meat with cytoskeletal protein levels similar to those in conventional meat. Therefore, *in vitro* cultured meat might have significant potential to improve human nutrition as a functional food with notable health applications.

Although *in vitro* cultured meat is still in its early stages, it has the potential to be considered a functional food due to several factors, such as controlled nutrient compositions, health-enhancing additives, reduced harmful components, and customized bioactive compounds. For example, researchers generated tissue resembling meat, characterized by aligned muscle-like and adipose-like layers, and it was synthesized through an iterative stacking process or edible microcarriers and an oleogel-based fat substitute [24,25]. Their method involved the alignment of a myosin-expressing muscle-like layer with an adipose-like layer rich in accumulated fat, resulting in the formation of tissue resembling muscle with fat content. Therefore, these findings shed light on the possibility of controlling the fat composition of *in vitro* cultured meat. In addition to regulating fat content in cultured meat, the capacity to enhance *in vitro* cultured meat with vital nutrients, such as iron and vitamin B12, could effectively mitigate prevalent nutritional deficiencies [22,26,27]. On the other hand, it has been questioned whether some vitamins, minerals, and other nutritionally relevant components present in conventional meat may not be found in cultured meat and if it is possible that this could lead to nutritional distinctions between *in vitro* cultured meat and traditional meat. An *in vitro* study conducted with the C2C12 mouse muscle cell line revealed that supplementing the culture medium with arginine (Arg) enhanced myotube differentiation. Arginine plays a role in shifting skeletal muscle fibers toward slow-twitch types and improves mitochondrial function by upregulating gene expression via the mTOR signaling pathway [28].

Some research findings have illustrated the plausible mechanisms through which the addition of omega-3 fatty acids to cell culture medium could impede skeletal muscle protein degradation, promote muscle protein synthesis, improve insulin sensitivity, and activate satellite cells in skeletal muscle [29,30]. Omega-3 fatty acids, a category of essential polyunsaturated fats, are recognized as vital for the body. The 2 main types of omega-3s found in food are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids have been shown to have a positive impact on heart health; for example, they have been shown to lower blood pressure, reduce triglycerides, decrease the risk of cardiovascular diseases and reduce inflammation [31,32]. Moreover, muscle cells can be modified to have the potential to produce antioxidant compounds like phytoene carotenoids, lycopene, and beta-carotene *in vitro* [33]. These compounds offer various health benefits, such as reducing the risk of prostate cancer, lowering blood pressure, and reducing the oxidation of low-density lipoprotein (LDL) cholesterol, or improving vision as well as skin health [34].

Within the context of mass production of *in vitro* cultured meat, cells in the growth phase can be affixed to scaffold or microcarrier materials, which act as a structural support network for tissue development [35,36]. These 3-dimensional structures are not only designed to interact with and improve the growth and differentiation of starting cells, but they also carry functional ingredients or bioactive compounds within the *in vitro* cultured meat that might be beneficial for health. Edible scaffolds made from different edible polymers can be employed to generate solid structures or coatings that release nutrients or functional compounds gradually during digestion [37-39]. Starch-based structures are suitable for crafting texture-modified foods that imitate traditional products while integrating functional ingredients. Additionally, proteins such as casein or soy proteins can be utilized to create gels or matrices for encapsulating nutrients or enhancing texture [37,38].

In a study conducted by Zheng *et al.* [40], inoculating porcine adipose-derived mesenchymal stem cells (ADSC) on peanut wire-drawing protein (PWP) scaffolds sufficiently preserved several volatile compounds. There were no significant differences in these compounds between *in vitro* cultured fat and porcine subcutaneous adipose tissue (pSAT), indicating that *in vitro* cultured fat and pSAT exhibited certain similarities. Furthermore, it should be noted that certain compounds, such as phenolic compounds derived from sources like olive leaves which enhance the bioavailability of essential minerals in chicken meat production [41], might be useful for the development of the culture medium for *in vitro* cultivation of chicken muscle cells. Additionally, the nutritional composition of *in vitro* cultured meat might be influenced by the components of the growth or differentiation media, as well as the scaffolding materials used to assemble muscle and fat cells. Therefore, it is likely that the nutritional deficiencies of *in vitro* cultured meat could be addressed by adding supplements at the required concentrations during the cell culturing process.

As a result, functional foods can play a role in promoting overall health, reducing the risk of chronic diseases, and improving well-being. *In vitro* cultured meat can be engineered to meet specific dietary needs, making it an invaluable resource for individuals with dietary restrictions, allergies, or conditions like malnutrition. In addition, its ability to provide high-quality protein and essential nutrients might offer a viable solution for patients recovering from surgery or managing chronic illnesses. These advantages of customized *in vitro* cultured meat are properties that position it as a potential future functional food, capable of conferring specific health benefits when integrated into the human diet.

Use of in vitro cultured meat as an additional strategy to reduce the use of antimicrobials and the risk of antimicrobial resistance

Antimicrobial resistance is one of the biggest threats to global health and food security. It can occur naturally; however, it is accelerated by the misuse and overuse of antibiotics [42-44]. The rise in antimicrobial resistance has contributed to a rising incidence of microbial infections that are increasingly challenging to manage, given the diminishing effectiveness of antibiotics. On a broader scale, antimicrobial resistance could hinder the effectiveness of antibiotics in managing outbreaks and treating diseases. On an individual level, the unintended intake of residual antibiotics could lead to drug resistance, allergic reactions, or other adverse effects such as harm to gut microbiota or potential carcinogenic, mutagenic, and teratogenic consequences [45]. This, in turn, has resulted in prolonged hospitalization, elevated medical expenses, and heightened mortality rates [42-44].

While being raised, farm animals can be exposed to pathogens such as Listeria, Salmonella, and protozoa like coccidia; or internal parasites at any age, leading to individual sickness or even a serious disease outbreak [46-48]. Due to the high stocking density, which limits animal movement, intensive animal farming systems often meet only the minimum welfare standards set by regulatory authorities in respective countries. As a result, these conditions are considered sufficient but not optimal for promoting animal health and welfare [49]. This system is frequently associated with the overuse of antibiotics, which are commonly employed to prevent and treat diseases in livestock [50,51]. In the United States, for example, approximately 80 % of all antibiotics sold are intended for use in animal agriculture, and nearly 70 % of these are classified as “medically important” [52]. Consequently, regulatory bodies in many countries have implemented measures to restrict antibiotic use in farm animals [52]. Growing consumer concerns regarding the use of antimicrobials, coupled with issues related to animal welfare, have contributed to an increasing rejection of meat produced from intensive farming systems [53]. In response, the demand for alternatives such as organic farming has been rising. However, it is important to note that antibiotics are still permitted in organic systems for therapeutic purposes when necessary.

For *in vitro* cultured meat, the initial process of cell isolation may involve collecting tissue or cells from live or slaughtered animals in environments that are not sterile. This poses a risk of microbial contamination, making the use of antibiotics potentially necessary to control the growth of bacteria, fungi, or yeast. Therefore, strictly adhering to hygienic control procedures for the collection and transfer of tissue for starting cell isolation is critical, as it minimizes contamination risk and reduces the need for antibiotics. However, in general laboratory practice, cell lines grown *in vitro* are possibly subject to contamination by various microorganisms, such as bacteria, fungi, yeast, and viruses [54,55]. Microbial contaminants, due to their widespread presence in the environment as well as on the skin of personnel, consistently pose a risk to both typical cell culture laboratories and in more complex situations, such as biomanufacturing processes [56]. Consequently, in a typical cell culture laboratory, researchers often introduce antimicrobial substances, such as penicillin, streptomycin, and amphotericin, into the culture medium to prevent the growth of certain microorganisms during the production process.

Regarding bacterial contamination, mycoplasma is a substantial concern in the culture of mammalian cells for research as well as *in vitro* cultured meat production, as it can adversely affect cells by modifying cellular parameters, resulting in unreliable outcomes [57-59]. Mycoplasma is widely acknowledged as a prevalent contaminant in cell cultures, with an estimated infection rate ranging from 5 to 35 % across global cell lines [60]. Due to their minuscule size, mycoplasma bacteria cannot be visually detected using a standard light microscope, potentially allowing them to go unnoticed in cell cultures for extended durations [61]. Apart from contamination with bacteria, viral contamination during mammalian cell culture poses a significant and potentially severe risk. Viruses often pose a greater challenge in terms of detection compared to other types of microbial contaminants [62].

Cultivating animal cells requires a nutrient-rich culture medium; however, this is also a favorable condition for the growth of contaminating microorganisms. With regard to reducing antimicrobial resistance, antimicrobial supplementation should be avoided in the production of *in vitro* cultured meat, making it challenging to keep the cultures free from microbial contamination throughout the production processes. This is probably a chance to achieve the target of reducing antibiotic use in general, thus potentially contributing to the reduction of antibiotic residues as well as antibiotic resistance development.

It has been demonstrated that *in vitro* culture of mammalian cells, such as primary bovine myoblasts and mesenchymal stem cells, without antibiotic supplementation enhances cell proliferation [63]. However, to maintain a contamination-free cell culture environment, it is imperative to take extreme care and be attentive, since microbial contamination can occur at any processing step. Due to the avoidance of using antimicrobial drugs in the production of *in vitro* cultured meat, alternative substances need to be urgently studied. In the last few decades, the antimicrobial effect of edible plants has been intensively investigated, with the aim of using them as natural food preservatives instead of using synthetic substances [64-66]. Plants contain many natural compounds, like tannins, terpenoids, alkaloids, and flavonoids, which *in vitro* studies have revealed to possess antimicrobial properties [67]. Notably, studies have shown that Guava (*Psidium guajava*), Sage (*Salvia officinalis*), Rhamnus (*Ziziphus spina-christi*), Mulberry (*Morus alba* L.), and Olive (*Olea europaea* L.) leaves can inhibit or significantly impede the growth of various pathogens such as *S. aureus*, *E. coli*, *Pasteurella multocida*, *B. cereus*, *Salmonella Enteritidis*, and *M. Gallisepticum* [68]. Extracts from some edible plants exhibit *in vitro* antimicrobial activity in the presence of influencing factors such as NaCl, $NaNO_2$ and lipids, which are commonly used as ingredients in some food types [69-71]. However, the use of plant extracts during the processing of *in vitro* cultured meat to prevent the growth of contaminating microorganisms has not been reported and still requires intensive and comprehensive investigations. As a result, the absence of antimicrobial use in the production of *in vitro* cultured meat ensures a safer product, reducing the risk of antimicrobial resistance in consumers, and reducing the overuse of antimicrobial drugs in the meat industry.

Potential health risks

Due to the fact that producing *in vitro* cultured meat is considered as a new food technology, it raises health and safety concerns for the public. Also, comprehensive long-term studies on its health effects are limited. There are some potential health considerations, and this section will review the potential health risks that should be considered.

Starting cell associated risks

The production of *in vitro* cultured meat typically begins with the isolation of animal-derived cells that have the potential to proliferate and differentiate into muscle, adipose or connective tissues. Muscle stem cells, or satellite cells, are commonly used as they naturally reside in muscle tissue and can differentiate into muscle fibers when cultured under the appropriate conditions. Mesenchymal stem cells (MSCs), which are multipotent and capable of differentiating into various cell types including muscle and fat, are another option, often sourced from bone marrow or adipose tissue. Induced pluripotent stem cells (iPSCs), reprogrammed from adult cells to a pluripotent state, also offer a renewable source of cells with the ability to differentiate into muscle and fat cells. Fibroblasts, cells found in connective tissues, can be reprogrammed to produce muscle or fat cells and are frequently used in *in vitro* cultured meat production due to their ease of culture. Adipocytes, or fat cells, play a crucial role in enhancing the sensory attributes of *in vitro* cultured meat, as they significantly contribute to the organoleptic properties such as flavor, juiciness, and texture, thereby improving the overall sensory experience and consumer acceptance of the final product [8].

Derivation of *in vitro* cultured meat from genetically modified iPSCs or immortal cells is one of the major concerns. Genetic modification can be achieved through traditional methods such as mutagenesis, selective breeding, or more advanced approaches like genetic engineering, including genome editing. Additionally, unintentional genetic alterations may occur, such as spontaneous immortalization after multiple cell passages [7,72,73]. which can become a concern if not properly monitored and controlled. Some technologies used in producing *in vitro* cultured meat and seafood involve genetic engineering, resulting in cells with new or altered trait expressions. When this is the case, it is necessary to evaluate the safety of the genetically engineered (GE) cell lines and their products. For example, cell line immortalization or life extension can be achieved through biotechnological methods that involve oncogenes, although concerns about genomic stability and potential tumorigenicity after genetic modification persist and warrant further research.

The process of generating iPSCs or immortal cells through cell reprogramming involves the manipulation of specific molecular factors to transform differentiated cells into a pluripotent state, allowing them to exhibit greater flexibility and myogenic or adipogenic differentiation potential [7,72,73]. To prevent the integration of viral particles into the host's genome during the reprogramming process, non-integrating methods, such as episomal vectors and Sendai viral vectors, are employed for the generation of iPSCs or immortal cells [7,10,74-76]. Therefore, it is crucial to consider the safety aspects associated with the exogenous genes of *in vitro* cultured meat. The integration of exogenous genes may disrupt normal cellular genes, leading to unintended consequences, such as the activation of oncogenes or the inactivation of tumor suppressor genes, potentially resulting in the development of cancerous cells [77]. Interestingly, a recent study analyzed the relationship between the variation in genetic data in immortal chicken fibroblast cell line and human cancer by using Functional analysis through hidden Markov models (FATHMM) [7]. Their results demonstrated the immortalization events are unassociated with pathogenic transformation. However, cells with integrated exogenous genes may express foreign proteins, triggering an immune response [78,79].

In the context of *in vitro* cultured meat, ensuring the safety of reprogrammed cells is crucial because these cells will be used as a source for producing meat products intended for human consumption. Despite the carcinogenic risk, *in vitro* cultured meat produced from genetically modified starting cells is considered genetically modified food in many countries, including those in the European Union (EU) [80]. Genetically engineered (GE) microorganisms have been utilized for decades in the fermentation processes to produce a wide range of food-grade enzymes and ingredients, including proteins, vitamins, amino acids, organic acids, and flavor compounds [81]. A key distinction between microbial ingredient production and the cultivation of animal cells for meat or seafood is that in microbial fermentation, the microbial cells and their genetic material are typically removed or present at minimal levels in the final product. In contrast, genetically engineered cells in *in vitro* cultured meat and seafood may constitute a significant portion of the final product, as these cells form the primary biological material for consumption. Therefore, in-depth research related to the safety of the development of *in vitro* cultured meat from genetically modified stem cells is an urgent issue in the field.

Allergenic substance

Allergenicity is a critical aspect of food safety assessment, particularly for genetically engineered (GE) foods. Comparative testing has been widely employed to evaluate the allergenic potential of GE foods [82]. For instance, GM plants like soybeans and potatoes have generally shown similar allergenic profiles to their conventional counterparts [83]. A similar expectation exists for *in vitro* cultured meats, which are designed to replicate the properties of conventional products; however, allergenicity in these products has yet to be thoroughly demonstrated. *In vitro* cultured meat, like traditional meat, can potentially cause allergies in individuals, and the risk of allergies primarily arises from several factors, including muscle protein and cell culture components as well as contamination with other allergens. Additionally, there is potential to reduce allergenicity in *in vitro* cultured meat products through targeted modifications, such as the removal of alpha-gal sugars, a strategy successfully implemented in live pigs [84]. Alpha-gal syndrome is a condition in which individuals develop an allergic reaction to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal). This allergy is triggered by the bite of lone star ticks, and individuals with alpha-gal syndrome may experience allergic reactions to the consumption of red meat from mammals, such as beef, pork, and lamb [85,86]. If individuals with alpha-gal syndrome have an allergic reaction to red meat, it is essential to consider the potential implications of *in vitro* cultured meat. Since *in vitro* cultured meat is produced from animal cells, it could still contain the alpha-gal allergen if the source cells are mammalian muscle cells.

In addition to livestock, there have been claims of successful production of *in vitro* cultured shrimp meat [35]. Allergenicity in shrimp meat is primarily associated with the presence of certain proteins that can trigger allergic reactions in individuals who are sensitive or allergic to shrimp. The key allergenic proteins in shrimp include tropomyosin, arginine kinase, and myosin light chain. *In vitro* cultured shrimp meat will contain these proteins if the shrimp cells or tissues used for culturing also contain these allergenic proteins.

Moreover, the process of producing *in vitro* cultured meat involves cell culture, which often requires the use of growth media, cytokines, growth factors and other components, like fetal bovine serum (FBS), to enhance cell growth or production [13,87-89]. Allergenicity related to FBS components, such as growth factors and cytokines, is a critical consideration in the production of *in vitro* cultured meat. Proteins in FBS, including bovine serum albumin (BSA) and insulin-like growth factors (IGFs), could act as potential allergens if they persist in the final product. These proteins may trigger IgE-mediated allergic reactions, where the immune system recognizes them as foreign, leading to histamine release and symptoms like hives, gastrointestinal distress, or anaphylaxis in sensitive individuals [90,91]. BSA is known to cause cross-reactivity in individuals allergic to bovine products like beef or dairy [90]. In addition to IgE-mediated responses, cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) present in FBS could modulate immune activity, potentially exacerbating pre-existing allergic conditions or inducing immune dysregulation [92]. While type III hypersensitivity reactions could occur due to immune complex formation involving residual FBS proteins, delayed hypersensitivity reactions (Type IV) could also arise from foreign cytokines or growth factors acting as haptens, triggering T-cell-mediated responses [93]. To mitigate these risks, many producers are moving toward serum-free media or developing synthetic alternatives to eliminate the presence of bovine-derived components in cultured meat products [94]. These alternatives not only address ethical and safety concerns but also help reduce the risk of allergenicity in the final product, ensuring better safety for consumers, particularly those with known sensitivities to bovine proteins or dairy.

In addition to fetal bovine serum (FBS), scaffolds used to support cell growth during *in vitro* meat production may contain allergenic compounds, particularly when derived from natural sources such as alginate (extracted from seaweed) or chitosan (sourced from shellfish). Individuals with known allergies to shellfish or specific plant-based allergens may be at risk of allergic reactions if residual traces of these materials remain in the final product and are not completely degraded or removed during processing [95]. Furthermore, chemical additives, including antibiotics, antifungal agents, or preservatives used in cell culture media, may persist in trace amounts in the end product and have the potential to elicit allergic or hypersensitivity reactions in susceptible individuals. Incomplete removal of these compounds could pose additional health risks. Additionally, contamination with bacterial endotoxins, such as lipopolysaccharides, during cell culture can induce immune responses, as endotoxins are potent triggers of inflammatory reactions. While endotoxins are not classified as allergens, their presence can exacerbate immune responses and allergic reactions, leading to adverse health outcomes.

Microbial contamination

Microbial contamination in food production is one of the major potential health risks. In general, there might be less microbial contamination during production of *in vitro* cultured meat than during production of traditional meat since the production of *in vitro* cultured meat takes place in a closed system and is conducted under strict hygienic conditions [96]. For traditional meat, microbial contamination can occur throughout the production process, from slaughtering to cutting and packaging. Therefore, fresh meat is probably not free from microbial contamination. However, the microbial loads in meat should not exceed the values allowed by regulatory offices; for example, during its production process, minced meat must contain a total plate count < 6.5 $\log_{10}$ cfu/g and *E. coli* < 2.5 $\log_{10}$, while pathogenic bacteria such as Salmonella should not be detected in this product when sold at retail (European Commission Regulation (EC) No 2073/2005). Therefore, the most critical point regarding the microbial contamination of *in vitro* cultured meat derived from muscle stem cells is the muscle biopsy stage, which is performed on either live or slaughtered animals to procure starting cells for further steps. The procurement of animal tissues must be conducted in a strict hygienic or sterile condition to avoid microbial contamination. It is crucial to maintain stringent contamination control throughout the handling, preparation, and transfer of cells, as well as during thawing and storage, to prevent microbial contamination from equipment or water baths. The use of fully enclosed systems is preferred, as these offer enhanced control and monitoring capabilities to reduce contamination risks. In this regard, bioreactors are expected to provide ideal closed environments that minimize contamination; however, careful design and engineering are essential to fully realize these benefits. Aseptic handling and continuous monitoring of cell cultures for microbial growth and contamination are imperative. Cross-contamination risks can arise from cryopreservation vials leaking in liquid nitrogen during cell banking, and liquid nitrogen itself may carry pathogens capable of contaminating stored cells, even if they are enclosed in freezing vials [97]. During the final stages of food processing, contamination may be introduced from processing methods, additional ingredients, or packaging. Therefore, to reduce the risk, it may be necessary to evaluate whether interventions such as heat treatment, high-pressure processing, or irradiation are required to adequately control microbial contaminants.

An example of a potential risk in animal serum is the presence of a pathogenic and infectious prion (PrPSC), particularly when it is due to potential cross-species and blood-related transmissions. PrPSC is a misfolded prion protein commonly associated with transmissible spongiform encephalopathies, such as scrapie in sheep, chronic wasting disease in deer, bovine spongiform encephalopathy (BSE) in cattle, and variant Creutzfeldt-Jakob disease (vCJD) in humans [98-100]. Therefore, rigorous hygiene protocols within aseptic systems employed in the production of *in vitro* cultured meat substantially enhance its safety profile by mitigating the potential transmission of zoonotic and foodborne pathogens, as well as viruses such as avian influenza and swine flu, or prions associated with encephalopathies [101].

Conclusions

In vitro cultured meat is not only a revolutionary development in sustainable and ethical food production but also holds significant promise as a future food. As research continues to unravel its full potential, *in vitro* cultured meat is poised to play a pivotal role in the future of functional foods, offering consumers a path to improved health and environmental sustainability. From a nutritional aspect of health, the sustainability of *in vitro* cultured meat aligns with health-conscious consumer preferences. *In vitro* cultured meat holds the potential to serve as a highly functional food, as it can be tailored to modify essential amino acid and fat profiles and can be enriched with vitamins, minerals, and bioactive compounds. This adaptability might allow it not only to match the nutritional content of traditional meat but also to surpass it in terms of meeting specific dietary requirements for individuals with various health conditions. The absence of antibiotics contributes to a more sustainable food system that indirectly promotes public health by mitigating environmental and health-related risks. In addition, continuous research and development, especially in-depth studies in safety-oriented research of *in vitro* cultured meat, should be emphasized to address potential health issues and enhance the safety of *in vitro* cultured meat.

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