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Fetal Bovine Serum In Cell Culture: Ethical Concerns & Emerging Non-Animal Alternatives

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Abstract
Fetal bovine serum, or FBS, is known for its rich composition of various factors, including growth factors, proteins, and essential nutrients. It is a supplement used in cell culture and universally applied in biomedical research, biopharmaceuticals and cultured meat production, etc. However, FBS is also intertwined with consequential concerns related to ethics, animal suffering, lack of openness in sourcing and batch-to-batch variability. These complications require an urgent need to find ethical and sustainable alternatives. This literature review examines the biochemical composition of FBS, followed by its functions, limitations and impacts on experimental reproducibility and ethics. Many alternatives sourced from bacteria, algae, plants, etc, are analysed for their capacity to mimic the complex nature and functionality of FBS, which have made advancements in recombinant growth factors, chemically defined media and resourceful and ethical serum compositions. The paper further reviews the applications of both FBS and its substitutes across diverse areas of tissue engineering, regenerative medicine, and cellular agriculture, paving a path of transition from the traditional FBS to ethically responsible alternative and advanced cell culture methods. By evaluating the scientific, ethical, and practical considerations, this review aspires to inform ongoing efforts towards the development and evaluation of animal-free cell culture systems.

Keywords: *fetal bovine serum, cell culture, ethical concerns, serum-free media, vegan alternatives*

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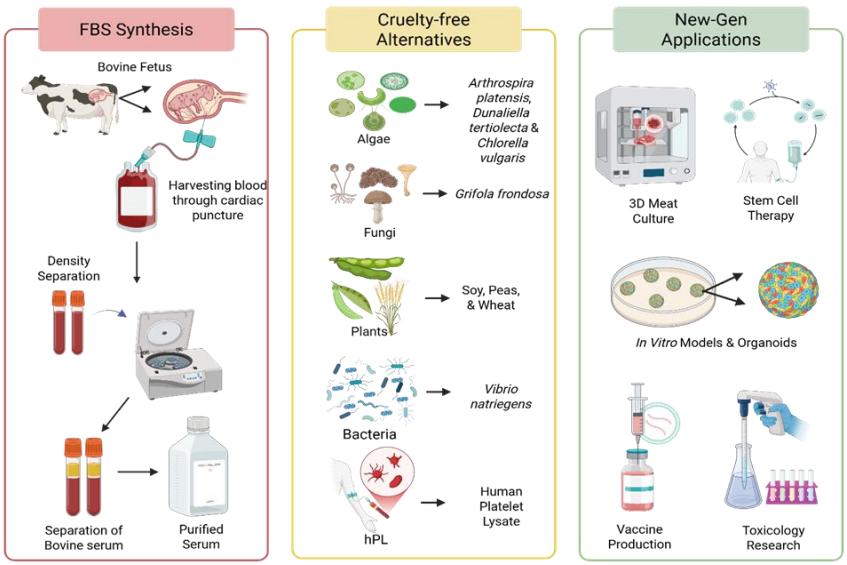

Figure 1.1: Overview of FBS, Cruelty-Free Alternatives & Applications

I. Introduction

FBS is extensively utilised to supplement essential nutrients for the growth, proliferation and survival of a diverse variety of cell cultures used in both research and industry applications (Stival *et al*., 2025). FBS is derived from the blood of the unborn bovine fetuses; therefore, it has a complex nature, as a large part of the mixture is undefined (Liu *et al*., 2023). Despite this, FBS is functionally versatile in nature and is preferred as an additive in the culturing of cell lines, tissues and three-dimensional organs, strengthening the advancements in biotechnology, regenerative medicine, development of cultured meat and pharmaceutical manufacturing (Lee *et al*., 2024; Pilgrim *et al*., 2022). Recent analytical services have discovered that FBS can influence key signals in pathways engaged in cellular responses like cytokine expression and self-proliferation (Liu *et al*., 2023).

In addition, various commercial batches of FBS may influence differences in cellular actions, highlighting the requirement to increase quality control before being used in delicate experimental studies, specifically in immunological and oncological research environments. Regardless of the challenges, FBS remains the most commonly added supplement due to its extraordinary calibre in supporting a broad spectrum of cells by delivering undefined factors that are intricate to replicate in a chemically defined serum-free medium (Lee *et al*., 2022, 2025). The preparatory process for obtaining FBS begins with the cautious collection of blood serum from bovine fetuses obtained from post-slaughter cows, followed by a subsequent purification process to ensure the quality and sterility of the resultant product are maintained. Serum can also be obtained from newborn or adult animals, but FBS is treasured for its low immunoglobulin levels, which reduce the objectionable immune reactions and increase the compatibility with a large variety of cell types (Lee *et al*., 2025).

Through eras of use, FBS has become the benchmark of cell culture media, not only by aiding in proliferation and cell attachment but also being the source for many macromolecular fractions, namely albumin, transferrin and fibronectin, which are important for the sustainability of cellular health (Johnson, 2012; Pilgrim *et al*., 2022). Nonetheless, questions regarding the sourcing of FBS have given rise to scrutiny over quality control, the openness of origin, authentication of batches, and ethical considerations related to the welfare of animals, which decreases the number of incidents related to serum adulteration and mislabelling. This leads to subsequent actions for enhanced traceability and oversight by National and international regulatory bodies (Subbiahanadar Chelladurai *et al*., 2021). From an ethical viewpoint, the method used to derive FBS from the bovine fetus is considered cruel and painful, as it doesn't consider the welfare of the unborn fetuses or their mother, directing interest towards developing chemically defined or vegan media (Lee, Lee, *et al*., 2024; Weber *et al*., 2025). Despite ethical, quality, and regulatory scrutiny on FBS, viable, scalable, food-grade chemically-defined or vegan alternatives remain underdeveloped for reliable cell proliferation and attachment in cultured meat production (Lee *et al*., 2022.,Stout *et al*., 2022; Weber *et al*., 2025).

To completely understand the impact of FBS *in* biology, it is necessary to look into the role and composition in detail, paving the way for subsequent examination of its limitations and to justify the reason behind the development of cruelty-free media (Johnson, 2012; Pilgrim *et al*., 2022).

II. Decoding FBS: Essential Functions, Molecular Composition & The Ethics Behind Its Use

FBS's complexity and nutritional richness come from the blood of bovine fetuses collected and processed after the slaughter of the pregnant cows. It has been playing a major role in the fields of biotechnology, regenerative medicine, pharmaceutical manufacturing, and biomedical research since the 1950s, enabling the smooth *in vitro* culture of animal cells by delivering a comfortable environment that supports robust cell attachment, proliferation, and differentiation. FBS is used to support a variety of cell types ranging from primary cells to immortalised cell lines, helping advancements in complex research required for therapeutic manufacturing, such as vaccine production and monoclonal antibody (Lee *et al*., 2022; Nielsen & Hawkes, n.d.; van der Valk *et al*., 2018). The significance of FBS tracks back to its unparalleled composition with a wide range of bioactive components, which cannot be replicated or found in chemically defined media or adult animal sera, respectively (Lee *et al*., 2025).

Key components that result in the extraordinary efficiency of FBS include a high concentration of serum albumin, which is required for osmotic balance and transport within the cells. Fibronectin is an important component for the adhesion of cell transferrin, which helps with the iron transport. FBS also possesses growth factors, for example, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), insulin-like growth factors (IGFs) and transforming growth factor beta (TGF-β). These growth factors together activate mitosis, cell differentiation and tissue-specific function in a wide variety of cell types (Vultaggio-Poma *et al*., 2024). FBS reduces the immune responses in cell cultures of different species due to its unique property of low immunoglobulin concentration (Lee *et al*., 2022; van der Valk *et al*., 2018). Properties such as proliferation, adhesion, migration and differentiation are essential for both biomedical and cultured meat research. For example, FBS ensures the availability of important factors needed for the eventual differentiation of mammalian muscle satellite cells into multinucleated myotubes (Kim *et al*., 2024; Stout *et al*., 2022). It also establishes cell lines, including hybridoma cells required for monoclonal antibody production, culturing of Chinese hamster ovary cells

for recombinant protein expression and stem cell cultures for tissue engineering and regenerative purposes (Lee *et al*., 2022; Mogilever *et al*., 2025).

Moreover, FBS also reduces the immunological reactivity in xenogeneic animal models, which has proved to be crucial for research and development in animal-derived systems that use human cells (Lee *et al*., 2022; van der Valk *et al*., 2018). Though FBS has some scientific benefits, it also comes with substantial risks and ethical concerns. One of the many well-known ethical disagreements is the practice of collecting blood, which is acquired through a cardiac puncture from the fetuses. This method is criticised as it possibly subjects the fetus to pain and distress before death. The magnitude of the pain experienced by the fetus remains debatable, yet there is consensus that human practice regulations are required to reduce the agony. Certain procedures and protocols recommend euthanasia or extended postmortem intervals before processing the foetus. This decreases the risk of consciousness in the foetus, but the application differs across geographical regions (Jochems *et al*., n.d.).

Beyond ethical principles, there are many practical and scientific disadvantages. The FBS composition is variable in nature based on factors such as the animal's age, diet, geographical region and the batch (Nielsen & Hawkes, n.d., Jochems *et al*., 2002; McCann & Treasure, n.d.). This batch-to-batch variability impacts the experiment's integrity as well as the stability of the cell lines over a period of time (Jochems *et al*., n.d.; Lebedev *et al*., 2025). FBS can also foster biohazardous risks such as mycoplasma bacteria, prions, and endotoxins, which can endanger research and production in a pharmaceutical environment (Lee *et al*., 2022; Weber *et al*., 2025). Based on the discussed risks, the widespread use of FBS is now treated as a scientific and ethical dilemma in the field of life sciences. Therefore, the demand for vegan or non-animal-derived alternatives for FBS is increasing to ensure future advancements in biotechnology and cell culture are ethical, sustainable and scientifically possible (Lee *et al*., 2022; van der Valk *et al*., 2018).

III. Beyond FBS: Rising Ethical And Next-Gen Serum Alternatives

Promising alternatives to fetal bovine serum have acquired value because of the multiple unsolved questions encircling FBS and its use, including increased cost, risk of contamination, ethical dilemmas and batch variability (Lee, Majó, *et al*., 2024; Mogilever *et al*., 2025). These alternatives originate from multiple biological kingdoms, specifically bacteria, fungi, algae, plants, and non-animal sources. Each and every one of these alternatives presents exclusive bioactive substances that have the ability to support animal cell growth. Cooperatively, they provide an opportunity towards culturing systems that are highly reproducible, cost-effective and ethically responsible in nature, by reducing FBS's concentration in culturing media. Full replacement of FBS is an unanswered question.

Table 1.1: FBS Alternatives and Their Benefits

Biological Source	Component/Product	Cell Lines	Key Experiments	Key References
Bacteria	Microbial Lysates (V. natriegens)	Immortalised bovine satellite cells (iBSCs); Mack1 (mackerel)	Short-term proliferation screening (CyQUANT DNA assay, 5 days); long-term adaptation (20+ passages, doubling time ~25h); differentiation into myotubes (Pax7, MHC, desmin staining); outperforms Beefy-9 serum-free media.	(Dolgin *et al*., 2024; Weber *et al*., 2025)
Fungi	Extracts (S. cerevisiae)	Mack1 (mackerel); HeLa; mouse primary fibroblasts	Short-term growth in reduced FBS (L-15 + 2.5% FBS); supports suspension/anchorage-dependent cells; similar growth/viability to FBS in HeLa/mouse fibroblasts (heat-inactivated coelomic fluid context).	(Subbiahanadar Chelladurai *et al*., 2021; Yu *et al*., 2024)
Algae & Cyanobacteria	Extracts (A. platensis/Spirulina, D. tertiolecta); blue spirulina	ZEM2S (zebrafish fibroblasts); QM7 (quail myoblasts)	Viability/proliferation (Alamar Blue, Neutral Red, BrdU, 72h); multi-passage maintenance (up to 6 passages/32 days, Trypan blue); tolerance >10 µg/mL protein; boosts viability.	(Gu *et al*., 2025; Lee, Majó, *et al*., 2024)
Plants	Protein Hydrolysates/Peptones (e.g., rapeseed, soy)	Bovine satellite cells; primary bovine myoblasts	Proliferation in serum-free media supports muscle cell expansion/differentiation (MTT, context from reviews).	(Skrivergaard *et al*., 2023; Warda, n.d.)
Non-Animal	Human Platelet Lysate (HPL)	Vero; Hep-2; hMSCs; hAT-MSCs; primary human macrophages	Proliferation/stability (higher rates than FBS); differentiation without genomic changes; supports stem cell therapies (various assays).	(Gautam *et al*., 2023; Lee *et al*., 2025; van der Valk *et al*., 2018)

Initially, microbial lysates derived from bacteria proved to be a great substitute for FBS (Mogilever *et al*., 2025; Stout *et al*., 2022; Yu *et al*., 2024). Recent studies have shown that *Vibrio natriegens,* a fast-growing marine bacterium, has remarkable potential, and its lysate helps in sustaining the prolonged growth of immortalised bovine satellite cells (iBSCs) with a doubling time almost equal to media consisting of 20 % FBS. The lysate is a complex mix of protein profiles, nucleotides, purines, pyrimidines and aromatic amino acids that strongly support anabolic metabolism in cells (Dolgin *et al*., 2024). Looking at it from an economic standpoint, the *V. natriegens* lysates can cut up to 90% of the costs in contrast to typical serum-based media due to a special feature where both small and large components of the lysate work well together to give an enhanced and combined result. This directly points towards a position where bacterial lysates are a scalable animal-free alternative, especially for applications such as cultured meat and regenerative medicine sectors (Dolgin *et al*., 2024). Beyond lysates, an emerging genetically engineered strain of *V. natriegens*, made capable of producing specific growth factors, also guarantees tailored serum replacements (Lee *et al*., 2022; Weber *et al*., 2025).

Alternatives from fungi also delivered salient contributions; impressively, *Grifola frondosa* extract (GFE) was obtained from an edible mushroom called *Grifola frondosa*. GFE's properties include proliferation, differentiation, myotube formation, and enhancing the growth of bovine muscle satellite cells under reduced serum conditions (Subbiahanadar Chelladurai *et al*., 2021; Yu *et al*., 2024). GFE makes animal cell culture possible as it contains optimal concentrations of polysaccharides, glycopeptide complexes, flavonoids, and other minor bioactive molecules that increase response to gene expression specific to muscles and protein synthesis (Choi & Choi, 2023). Similar to bacterial lysates, GFE reduces the use of FBS by decreasing its concentration and therefore improving cost efficiency in sustainable meat culture (Schenzle *et al*., 2025; Yu *et al*., 2024). Apart from *Grifola frondosa* yeast extract derived from *Saccharomyces cerevisiae* provides nutritional supplements in culturing fish and mammalian cells, highlighting the therapeutic properties of fungal bioactive components, such as supporting anti-apoptotic mechanisms in cells and immunomodulation, which increases their value in serum-free formulations (Amirvaresi & Ovissipour, 2024; Yu *et al*., 2024; Zhang *et al*., 2022).

Another group of extracts with the exemplary potential to replace animal-derived serum in cell culture are algal and cyanobacterium extracts. Studies prove that among 26 species that were screened, extracts from *Arthrospira platensis*, *Dunaliella tertiolecta* and *Chlorella vulgaris* have the most promising effects on cell culture proliferation, survival and expression of protein (Gu *et al*., 2025; Lee, Majó, *et al*., 2024). Algal extracts are a source of not only essential amino acids, peptides and growth factors but also vitamins and antioxidants that support subculturing and regulate cellular functioning in low or serum-free conditions. They can also fix carbon dioxide and recycle nutrients, making algal extracts environmentally friendly. Moreover, proteins extracted from microalgae such as *Galdieria sulphuraria*, native to extremophilic conditions, support the proliferation of mammalian cells and different levels of FBS (Eisenberg *et al*., 2025; Ng *et al*., 2020; Sibinčić *et al*., 2024). New and unconventional methods that boost the bioavailability of proteins and consistency of nutrient composition in every batch drive an increase in curiosity in algae as a calculated source for growth and development of serum-free media.

Plants also offer to be an extensible alternative in the form of protein hydrolysates and peptones prepared from peas, soybeans, wheat, etc (Subbiahanadar Chelladurai *et al*., 2021). These peptones and hydrolysates provide peptides with anti-proliferative properties (Skrivergaard *et al*., 2023; Sundaram *et al*., 2025). In the context of seafood culture and zebrafish embryonic stem cells, it is proven that peptides from peas and mushrooms increase the growth and viability of cells robustly at concentrations as low as 1mg/ml to as high as 10mg/ml, while gradually decreasing the need for animal-derived serum. Moreover, scaffolds and matrices made and infused with vegetable or plant-based protein support tissue formation and strengthen the structure of cells in cultured meat. Plant peptones can also be utilised in regenerative medicine media; for example, wheat-derived peptones have proven to upregulate proliferation and osteogenic differentiation of human stem cells from tooth pulp (Amirvaresi & Ovissipour, 2024; Warda, n.d.). The plant-based peptides also broaden into performing antioxidant and anti-inflammatory functions, which in turn balance long-term viability and environment in cell culture (Subbiahanadar Chelladurai *et al*., 2021).

The only non-vegan alternative to FBS is human platelet lysate, which offers good quality, ethically sourced growth factors which are verified for regenerative therapies. Similar to FBS, human platelet lysate sourcing and processing remain under consideration. It is mainly used in research and therapy, which involves growing human mesenchymal stem cells, which require essential proteins, cytokines and growth factors such as PDGF, TGF-β, and EGF to promote self-proliferation and differentiation. The standardisation for clinical use is still evolving (Gautam *et al*., 2023; van der Valk *et al*., 2018; Warda, n.d.). Authentic formulations such as ClearX9™, an animal component-free media developed by Clear Meat, a foresight biotechnological company that supports the viability and proliferation of a variety of animal cell lines corresponding to the cultures supplementary by FBS (Lee *et al*., 2025). Advancements in recombinant protein engineering validate the study of synthetic growth factor fusions to completely substitute FBS and their constituents by building success in facilitating cell phenotype and probable differentiation over several cell types (Weber *et al*., 2025).

Altogether, the discussed bacterial, fungal, algal plant and non-animal derived alternatives provide crucial bioactive components and corresponding nutrients predominantly accredited to FBS. Current optimisation imposes uniformity with particular cell types, elevating growth differentiation and reproductive ability important for research exploration and commercial application (Lee, Majó, *et al*., 2024; Mogilever *et al*., 2025). The ascending notability and expanding sophistication of FBS's alternative open new doors of possibilities and application across different fields. The upcoming discourse reviews the possible application in vaster detail, indicating have an innovation in animal cell culture media steers transformation in biotechnology (Amirvaresi & Ovissipour, 2024; Dolgin *et al*., 2024; Sibinčić *et al*., 2024; van der Valk *et al*., 2018; Yu *et al*., 2024).

IV. Unlocking Biotechnology: Emerging Applications Of FBS-Free Supplements

The favourable mention of FBS's alternative derived from distinct vegan and non-vegan origins has opened a new perspective in many biotechnological sectors by giving ethically dependable, cost-effective, and replicable culture arrangements that limit issues interconnected with FBS (Gautam *et al*., 2023; Weber *et al*., 2025). The possible applications of the FBS alternatives have been mentioned as follows;

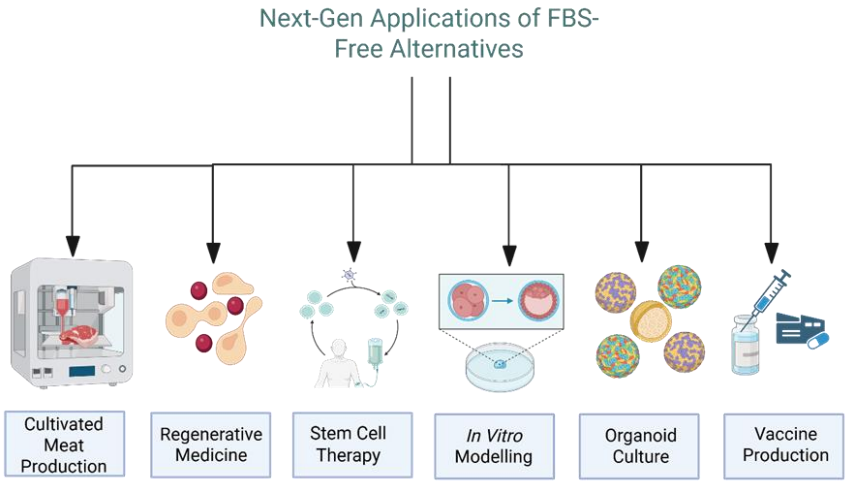

Figure 1.2: Next-Gen Applications of FBS Free Alternatives

Cultivated Meat Production

Lysates harvested from *Vibrio natriegens, Chlorella vulgaris,* and *Arthrospira platensis* have been proven to be successfully blended into muscle satellite cell culture in animals (Dolgin *et al*., 2024; Mojica *et al*., 2024). These lysate supplements have displayed long-term support in both growth and differentiation of immortalized bovine satellite cells, along with myotube formation and maintenance of cellular phenotypes in culture of animal cells. This is because they are composed of both large and small molecular weight components, which are easy to process and do not require any complex fractionation and purification steps. Therefore, the use of bacterial lysate, such as the one derived from *Vibrio natriegens,* aids scalable serum-free production of cultivated meat demanded by consumers as a sustainable and dependable cruelty-free protein source (Dolgin *et al*., 2024; Eisenberg *et al*., 2025; Sibinčić *et al*., 2024). Moreover, ingredients acquired from various algal species furnished the medium with additional nutrients to improve antioxidant capacity and promote recycling of nutrients in media, which results in betterment of the cell culture environment and safety and scalability of culture meat production (Markou *et al*., 2015; Quek *et al*., 2024).

Regenerative Medicine and Stem Cell Therapy

Human platelet lysate is a superior quality serum substitute prepared using clinically sourced human blood. It helps to facilitate the augmentation and differentiation of adipose-derived stromal cells (Subbiahanadar Chelladurai *et al*., 2021). hPL also ensures durable xeno-free habitat for mesenchymal stem cell proliferation, usually out-ranking FBS with respect to doubling time, population levels, and viability of cells, while fostering reliable surface marker expression and multipotency under good manufacturing practices. The above-mentioned merits are partially attributed to hPL due to its high concentration of growth factors, namely PDGF, TGF-β and IGF and offer better batches to batch reliability, in contrast to animal-derived serum (Anerillas *et al*., 2023; Bianchetti *et al*., 2021). Alternatives like fungal polysaccharides or plant-based protein hydrolysate dispense bioactive molecules that support the proliferation of cells and lineage-specific differentiation, important for regenerative tissue engineering applications. For instance, certain polysaccharides acquired from fungi such as yeast and basidiomycetous showcase immunomodulatory and antioxidant properties, which are held estimable

for scaffold initiation and tissue regeneration (Kumla *et al*., 2025). Protein hydrolysate from plants is known to provide mammalian and fish cells with essential amino acids and peptides to stabilise the media and enhance its performance in a serum-free environment (Ho *et al*., 2021). Such additives mitigate the risk of xeno-immunisation and pathogen contamination, which are usually related to animal sera. The lack of animal derivatives reduces major risks while simplifying the supply chain and promoting safe, better reproducible outcomes that meet the recent regulatory expectations for progressive tissue engineering and regenerative medicine applications using stem cells (Su *et al*., 2022).

Complex *In Vitro* Models and Organoids

Complex *in vitro* systems such as organoids, organ-on-a-chip (OoC) platforms and bio-printed tissues are being reproduced with great physiological similarity in the presence of chemically defined serum-free formulation infused with algal and fungal extracts (Zhao *et al*., 2025). Creating such formulations gives complete control over the nutrient and growth factor concentration, which plays a serious role in modelling micro environments for specific tissues and reduces the variability of experiments in stabilising 3D cultures, which can be used to model diseases for regenerative medicine research. Similarly, algal hydrolysates derived from chlorella extract have the properties to improve cell proliferation and extracellular matrix collaborations in 3D hydrogen and organoid systems, validating more substantial and physiologically convincing tissue constructs (Ng *et al*., 2020; Park *et al*., 2024; Usta *et al*., 2014). Scaffolds synthesised with the support of plant-based peptones and hPL can also be used for tissue culturing and proper cellular organisation. Such 3D tissues are necessary for screening drugs and toxicology testing, especially when the scaffolds are strengthened by human platelet lysate, which provides human-derived growth factors which promote mechanical support and angiogenic signalling within 3D organoids and organ-on-a-chip platforms. The systems can accurately mimic human tissue characteristics and can be used for preclinical testing under a controlled serum-free environment. (Burnouf *et al*., 2023; Huang *et al*., 2025; Monteiro *et al*., 2024; Yaja *et al*., 2023., Amirvaresi & Ovissipour, 2024; Yu *et al*., 2024; Weber *et al*., 2025). This transition from FBS to chemically defined animal component-free media may revolutionise the translation reputation of *in vitro* studies for toxicology, pharmacology and individualised medicine (Usta *et al*., 2014).

Biopharmaceutical and Vaccine Production

Bacterial and plant hydrolysates are used as a component in serum-free media to synthesise recombinant antibodies and viral vaccine production, as these hydrolysates support growth in a variety of cell line cultures in suspension media with batch-to-batch consistency (Skrivergaard *et al*., 2023). Studies conducted with soy, wheat, rice, pea and cottonseed-derived hydrolysates prove they can not only sustain prominent animal cell lines such as Chinese Hamster ovarian cells and Vero cells but also increase the production of recombinant protein and viral titers when compared with conventional serum-containing media (Fan *et al*., 2024). The transition towards serum-free media and chemically defined formulations requires an urgent need to increase the regulatory demand to improve the product safety and scalability (Piletz *et al*., 2018; Zhao *et al*., 2025). National and international regulatory guidelines cautiously welcome animal-origin-free and chemically defined media to reduce the prominent issues associated with animal-based serum and encourage scaling up the manufacturing of biopharmaceutical therapeutics and vaccines using the same (Cassotta *et al*., 2022).

Toxicology and Pharmaceutical Research

Serum-free culture of hepatic cell line, such as HepG2, in plant and algal derivatives containing media improves the sensitivity of the assay for cytotoxicity and hepatotoxicity testing and reduces effects that are caused by serum protein-binding test compounds (Pfeifer *et al*., 2024). Adapting the cell from traditional media to defined serum-free media conditions the cell to grow and maintain key hepatic functions and increase response with respect to hepatotoxins in viability and cell death assays. This allows accurate concentrations to respond with relationships to be captured. When the serum protein is absent or present in smaller quantities, the bioavailable fractions of the testing sample can be controlled easily, thereby sharpening the readout for the end point, like mitochondrial dysfunction, oxidative stress and drug-induced liver injury markers. (Canada, n.d.; Helsen *et al*., 2018; Pfeifer *et al*., 2024). This encourages better prediction in toxicological assessment and minimises testing on animals, therefore aligning with the safety and sustainable evolution strategies (Pfeifer *et al*., 2024). Serum-free hepatic models, such as 2D HepG2 cultures and 3D liver spheroids, are recently being used as human-related alternatives, following the 3R principle by reducing and replacing animal usage in regulatory and preclinical toxicity studies. By enhancing standardisation and translatability to human liver responses, these systems support more reliable hazard identification and risk assessment, thereby accelerating the adoption of animal-free approaches in pharmaceutical and chemical safety testing. (Filatova *et al*., 2025; Mickols *et al*., 2025; Ullrich *et al*., n.d.).

V. Conclusion

This review synthesizes the multifaceted role of fetal bovine serum (FBS) in underpinning cellular homeostasis through its proteome of albumins, transferrins, fibronectins, and pleiotropic growth factors, while delineating its intrinsic limitations in inter-batch heterogeneity, xenogeneic immunogenicity, and ethical sourcing deficits. Non-animal alternatives encompassing microbial lysates, fungal polysaccharides, algal hydrolysates, and plant peptones demonstrate commensurate efficacy in recapitulating proliferative kinetics, differentiative cascades, and adhesion dynamics, thereby augmenting metabolic flux and phenotypic stability in xeno-free bioprocessing paradigms.

Key insights affirm that these matrices not only obviate animal-derived contaminants but also potentiate antioxidant buffering and nutrient recycling, fostering reproducible scalability across biotechnological applications. Nonetheless, salient research lacunae endure: the absence of standardized, chemically defined formulations for sustained passaging (>50 generations) of primary progenitors and organotypic assemblies; paucity of omics-integrated (proteomics, metabolomics) delineations of bioactive synergies; and underdeveloped techno-economic analyses for biomass-to-media up conversion amid fluctuating yields.

Future investigations must prioritise high-throughput screening of recombinant fusion proteins and CRISPR-augmented microbial chassis to rectify these voids, catalysing a transition to fully defined, vegan matrices. This paradigm shift aligns cell culture with 3R imperatives (replacement, reduction, refinement) and sustainable biomanufacturing, heralding ethical, reproducible *in vitro* platforms for regenerative therapeutics and cellular agriculture.

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