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Implantable Artificial Liver: A Brief Review

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Abstract: The implantable artificial liver represents a groundbreaking advancement in biomedical engineering, offering a potential lifesaving solution for patients with end-stage liver disease. By integrating bioreactor technology with tissue engineering, these devices aim to replicate key hepatic functions, including detoxification, metabolism, and protein synthesis. Recent developments in biomaterials, microfluidics, and cellular scaffolding have improved biocompatibility and functionality, bringing the concept closer to clinical application. Challenges remain in optimizing long-term stability, immune response management, and efficient vascular integration to ensure sustained performance. As research progresses, the implantable artificial liver has the potential to revolutionize liver transplantation and bridge the gap for patients awaiting donor organs.

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1. Introduction

Biomedical engineering, the application of engineering principles to human biology and medicine, aims to improve patient care through technological innovations. This interdisciplinary field integrates multiple domains, such as physiology, human biology, molecular imaging, and tissue reconstruction. Its primary goal is to develop technologies that facilitate the monitoring of physiological functions and contribute to diagnosis and treatment (Rondón *et al.*,2024). The liver is a very important organ as it is responsible for several essential functions necessary for the homeostasis of the human body. It plays a crucial role in metabolic processes, detoxification, and the production of vital proteins. Any change or impairment in its function can lead to severe and irreversible health complications. Acute and chronic diseases are among the main causes of liver dysfunction and can result in liver failure, a condition characterized by the rapid loss of the liver's vital functions. Currently, the only available treatment for liver failure is transplantation; however, due to the shortage of available donors, this solution is not always feasible. Many patients diagnosed with liver failure die while waiting for a donor.

This issue has sparked the interest of biomedical engineers in developing bioartificial liver devices, either external or implantable, as potential solutions for liver failure. The design of an implantable artificial liver requires both biological and synthetic components to replicate the liver's essential functions. The biological components consist of hepatocytes or stem cells capable of differentiating into hepatocytes, while the synthetic components involve various biomaterials that create a scaffold or matrix for cell adhesion and growth.

Ensuring the viability of liver cells is crucial, requiring a perfusion system to supply nutrients and oxygen while removing waste products. Several implantable artificial liver prototypes have been developed, but none are yet perfect. There is still much to improve, particularly considering the variability among patients. Challenges such as immune system rejection, vascularization, and long-term functionality remain significant obstacles in treating liver failure.

Additionally, ethical and regulatory considerations must be addressed, including FDA approval processes, the use of embryonic stem cells, and the cost and accessibility of advanced biotechnological treatments. Future research on implantable artificial livers will likely focus on stem cell technologies,

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3D bioprinting, and genetic editing. The development of implantable artificial livers represents a breakthrough in biomedical engineering. While significant challenges remain, advancements in biomaterials, cellular technologies, and medical device design suggest that bioartificial organs could soon provide a viable solution to the ongoing organ transplant crisis.

2. Methodology

The methodology used in developing this research will be to conduct a comprehensive review of relevant scientific literature, including research articles, review papers, and textbooks, to gather information on tissue engineering principles, methodologies, recent advancements, and challenges.

a. Search and data compilation: databases will be used, such as Pubmed, Frontiers, UPComing, Wiley Online Library, Royal Society of Chemistry, MDPI, ACS Publications, ScienceDirect, SCOPUS, IEEE, SciELO, RedALyC and GoogleScholar were utilized; key search terms included "Biomaterials," and "Biomedical engineering."
b. Information selection and refinement: With a search period from 2007 to 2025, a comprehensive exploration was conducted. Utilizing Mendeley (Elsevier, 2021) as a bibliography managemen tool, the data was organized based on their relevance to this study.
c. Selection of subtopics: the refined information facilitated the organization of the research structure and clarified the chosen subtopics related to the study.
d. Analysis of results: a critical analysis of the data was conducted, resulting in comprehensive conclusions found in this study (Rondón *et al*.,2023)

3. Results and Discussion

3.1. Functions and Regulation of the Liver

The liver is the largest gland in the human body and one of its most vital organs, playing a central role in nutrient metabolism, detoxification, and waste excretion. Its primary function is to regulate the flow of substances absorbed from the digestive system before distributing them through the circulatory system. The liver's key physiological roles can be categorized into bile secretion, bilirubin metabolism, vascular and hematological functions, nutrient metabolism, metabolic detoxification, and the storage of essential minerals and vitamins.

The liver produces approximately 700 to 1,200 mL of bile per day. Bile is an alkaline, greenish fluid composed of bile salts, cholesterol, bilirubin, electrolytes, and water. Bile salts are essential for the emulsification and absorption of dietary fats, while bilirubin, a byproduct of red blood cell breakdown, serves as a clinical biomarker for liver function assessment.

Beyond its metabolic functions, the liver acts as a blood reservoir, storing a significant volume that can be released into circulation in response to hemorrhage. Kupffer cells, specialized liver macrophages, play a crucial role in immune defense by removing bacteria and other pathogens from the bloodstream, thereby preventing infections. The liver is also a key site for lipid metabolism. It synthesizes various lipids, including triglycerides, phospholipids, and cholesterol. Hepatic triglycerides can be hydrolyzed into glycerol and fatty acids to generate metabolic energy in the form of adenosine triphosphate (ATP). Additionally, the liver releases lipoproteins into the bloodstream, facilitating fat storage in adipose tissue. Cholesterol produced in the liver serves as a precursor for bile salt synthesis, essential for digestion and absorption of dietary fats.

In protein metabolism, the liver synthesizes essential plasma proteins such as albumin and globulin. It also produces amino acids and enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP), which are critical for various biochemical processes.

One of the liver's most vital functions is maintaining blood glucose homeostasis. It regulates glucose levels by releasing glucose into the bloodstream during hypoglycemia and absorbing excess glucose during hyperglycemia, storing it as glycogen or converting it into fat. When glycogen stores

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are depleted, the liver synthesizes glucose through gluconeogenesis, utilizing amino acids and glycerol as precursors.

Metabolic detoxification is another essential liver function. The liver reduces the intestinal and renal tubular reabsorption of potentially harmful substances, promoting their excretion through the intestines and kidneys (Ozougwu, 2017). Additionally, the liver stores crucial vitamins and minerals, including copper and iron. It maintains reserves of vitamin B12 and vitamin D for several months and can store vitamin A for several years. Furthermore, the liver is rich in innate immune cells, including Kupffer cells and natural killer T cells, which contribute to antigen presentation and phagocytosis, ensuring the liver remains free of pathogens. Through its complex regulatory functions, the liver plays a pivotal role in maintaining overall physiological balance and metabolic homeostasis.

3.2. Liver Failure: Causes and Therapeutic Alternatives

Liver failure results from the partial or complete loss of hepatic function and can manifest in either acute or chronic forms. Chronic liver failure typically develops over time due to progressive liver damage. Among the leading causes are liver cirrhosis—often induced by excessive alcohol consumption—chronic viral infections such as hepatitis B and C, and non-alcoholic fatty liver disease, which is closely linked to obesity and insulin resistance (Bernal & Wendon, 2013). If left untreated, these conditions gradually deteriorate hepatic function, ultimately leading to organ failure.

In contrast, acute liver failure occurs suddenly and progresses rapidly, often with severe consequences. One of the most common causes is drug-induced liver injury, particularly acetaminophen overdose, which remains a major contributor to acute hepatic damage worldwide (Tapper & Parikh, 2018). Other triggers include severe viral infections, such as hepatitis A or Epstein-Barr virus, which can cause abrupt and extensive liver inflammation. Autoimmune conditions, such as autoimmune hepatitis—where the immune system mistakenly targets hepatocytes—can also lead to acute hepatic failure. Additionally, rare disorders like Reye's syndrome, primarily affecting children following viral infections, further contribute to the spectrum of acute liver disease (Tiniakos & Burt, 2018).

Regardless of the underlying cause, liver failure leads to a cascade of systemic complications, including toxin accumulation, jaundice (yellowing of the skin and eyes), coagulation disorders, and, in severe cases, multiple organ dysfunction (Asrani & Devarbhavi, 2019). In advanced stages, liver transplantation remains the only curative treatment; however, the limited availability of donor organs poses a critical challenge.

Recent advancements in biomedical engineering offer promising alternatives, particularly the development of bioartificial livers. These technologies aim to provide temporary or even long-term hepatic support, serving as a bridge for patients awaiting transplantation or as a therapeutic option for those ineligibles for a transplant. The continuous evolution of these innovative solutions holds significant potential for improving patient outcomes and addressing the growing demand for effective liver failure treatments.

3.3. Limitations of Liver Transplantation and the Potential of Bioartificial Livers

Due to the shortage of donor organs, many patients die before receiving a transplant. This situation is particularly critical in liver failure, where time is a crucial factor, and the transplant waiting list can be extremely long. Moreover, even when a transplant is successfully performed, patients face associated risks, such as the need for lifelong immunosuppression to prevent organ rejection, leaving them vulnerable to infections and other complications (Fung & Starzl, 2019).

Immunosuppressive medications, while essential for preventing graft rejection, can have significant side effects, including an increased risk of cancer, hypertension, diabetes, and kidney damage. These side effects can severely impact the patient's quality of life and may require additional treatments to manage complications. Surgical risks, such as graft rejection or postoperative complications, further complicate the situation. Postoperative complications may include infections,

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hemorrhages, thrombosis, and biliary problems, which may require additional interventions and prolong the patient's recovery (Selzner & Clavien, 2020). Furthermore, graft rejection can occur at any time, even years after the transplant, necessitating constant monitoring and adjustments in immunosuppressive medication.

Given these limitations, the development of bioartificial liver devices, both external and implantable, has emerged as a promising alternative. These devices could serve as temporary bridges while a patient awaits a transplant or even as a long-term solution in cases where transplantation is not viable. Bioartificial livers combine living liver cells with synthetic materials to mimic key liver functions, potentially providing patients with the necessary time to find a donor or stabilize their health without relying entirely on organ availability.

These devices can be designed to perform critical liver functions, such as blood detoxification and nutrient metabolism regulation, significantly improving patients' quality of life. Additionally, bioartificial livers can be customized to meet the specific needs of each patient, using autologous cells to reduce the risk of immune rejection. Personalization of these devices is crucial, as each patient may have different needs and health conditions that must be considered to maximize treatment effectiveness.

3.4. Design and Challenges of an Implantable Artificial Liver

The design of an implantable bioartificial liver requires a combination of biological and synthetic components to emulate liver functions. This type of organ must perform several essential functions for the body's homeostasis, such as blood detoxification, the production of vital proteins, and nutrient metabolism.

The biological component generally consists of hepatocytes (liver cells) or stem cells capable of differentiating into liver cells. These cells are crucial because they carry out the liver's metabolic and detoxification functions. The viability of these cells is fundamental, and to maintain it, a perfusion system is required to supply nutrients and oxygen while removing waste products. This perfusion system must be able to replicate the liver's natural blood flow, ensuring that all cells receive an adequate supply of oxygen and nutrients while efficiently eliminating waste products. Additionally, it is important for the perfusion system to maintain a sterile environment to prevent infections that could compromise the viability of liver cells.

The synthetic component involves biomaterials that create a scaffold or matrix for the biological cells to adhere to and grow within. This scaffold must be biocompatible and provide a suitable environment for liver cell proliferation and function. The biomaterials used may include biodegradable polymers and other materials that mimic the liver's extracellular matrix. Biodegradable polymers, such as polylactic acid (PLA) and polyglycolic acid (PGA), are particularly useful because they can degrade in a controlled manner within the body, eliminating the need for a second surgery to remove the scaffold. Additionally, these materials can be chemically modified to enhance cell adhesion and biocompatibility. Selecting the appropriate biomaterial is crucial to ensure that liver cells can attach, proliferate, and maintain their functionality in the long term.

Vascularization is one of the biggest challenges in the design of bioartificial organs. A bioartificial liver must have a network of blood vessels to ensure an adequate supply of oxygen and nutrients to liver cells. Poor vascularization can lead to cell necrosis and organ failure. To address this challenge, researchers are exploring various techniques, such as 3D bioprinting of vascular structures and the use of angiogenic growth factors to promote the formation of new blood vessels. 3D bioprinting allows for the creation of complex vascular networks that can integrate with liver tissue, improving perfusion and cell viability. Additionally, angiogenic growth factors, such as vascular endothelial growth factor (VEGF), can be released in a controlled manner to stimulate the formation of new blood vessels within the scaffold (Naruse, Tang & Makuuch, 2007).

Beyond vascularization, ensuring adequate oxygenation is crucial. Liver cells require a continuous supply of oxygen to perform their metabolic functions. Perfusion systems and extracorporeal oxygenation devices can be used to maintain optimal oxygen levels. These systems

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must be designed to provide a steady and controlled oxygen flow, avoiding both hypoxia (oxygen deficiency) and hyperoxia (excess oxygen), which can be harmful to liver cells. Integrating oxygen sensors into the perfusion system can enable real-time monitoring of oxygen levels, ensuring they remain within an optimal range.

The immune response is another critical aspect, which is why the bioartificial liver must be designed to minimize the risk of immune rejection. This can be achieved by using autologous cells (from the patient) or through tissue engineering techniques to reduce immunogenicity. Autologous cells are ideal because they are genetically identical to the patient, significantly reducing the risk of rejection (Stamatoglou & Lodhi, 2021). However, in cases where using autologous cells is not possible, tissue engineering techniques (Rondón *et al*., 2025) can be employed to modify the cells and make them less immunogenic. Additionally, immunomodulatory coatings can be applied to the synthetic scaffold to reduce the immune response. These coatings may include molecules that inhibit immune system activation or promote a tolerant immune response.

3.5. Advances in Bioartificial Livers: Emerging Technologies and Future Challenges

Research in this field is advancing rapidly, with studies exploring the use of induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) to create functional liver tissues. iPSCs are generated by reprogramming adult somatic cells into a pluripotent state, allowing them to differentiate into various cell types, including hepatocytes (Demitriou & Rozga, 2019). This technology provides a potentially unlimited supply of liver cells and avoids the ethical concerns associated with embryonic stem cells. MSCs, derived from tissues such as bone marrow and adipose tissue, can also differentiate into liver cells and possess properties that help reduce the risk of implant rejection.

3D bioprinting and tissue engineering techniques are enabling the creation of three-dimensional scaffolds that mimic the structure of the natural liver, enhancing the viability and functionality of bioartificial devices. 3D bioprinting allows for the precise placement of different cell types in specific locations, replicating the functional zoning of the liver and improving the efficiency of bioartificial devices. Additionally, the integration of perfusion systems in these devices ensures a constant supply of nutrients and oxygen to liver cells, which is crucial for maintaining their long-term viability and function.

As technology continues to progress, bioartificial livers are likely to become a viable and accessible option for many patients, providing an innovative solution to the organ transplant crisis and significantly improving clinical outcomes for those with liver failure. The implementation of these devices in clinical practice will require close collaboration between researchers, physicians, and regulators to ensure their safety and effectiveness.

Furthermore, it is important to consider the ethical and social implications of these advancements, including equitable access to treatments and public education about the benefits and risks of bioartificial livers. Public awareness and education on the importance of organ donation and biotechnology advancements can play a crucial role in supporting these developments. Collaboration among academic institutions, industry, and regulatory agencies is essential to overcoming obstacles and accelerating the implementation of these innovations in clinical practice.

Over time, artificial livers will not only improve a patient's quality of life but also reduce the burden on healthcare systems and offer new hope to those suffering from severe liver diseases. The integration of emerging technologies, such as artificial intelligence and personalized medicine, could also play a significant role in the future of artificial livers, enabling more precise and tailored treatments for individual patients.

Additionally, research in the field of synthetic biology could open new pathways for creating more efficient and functional artificial livers. Synthetic biology enables the engineering of living organisms to perform specific functions, which could be used to design liver cells that are more resistant to adverse conditions and capable of performing liver functions more efficiently (Li & Zhang, 2022). Combining these advanced technologies with traditional tissue engineering approaches could accelerate the development of artificial livers and enhance their clinical feasibility.

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Ultimately, the goal is to create an artificial liver that not only replaces the functions of the natural liver but also improves patients' quality of life and reduces the need for organ transplants. Moreover, implementing public health policies that promote research and development of bioartificial technologies, as well as establishing funding and subsidy programs, could facilitate access to these innovative treatments.

International collaboration may also play a crucial role in advancing this technology, allowing for the exchange of knowledge and resources between different countries and regions. Bioartificial livers represent a promising solution to address the organ transplant crisis and improve clinical outcomes for patients with liver failure, and their continued development is essential for the future of regenerative medicine and biotechnology.

Additionally, large-scale clinical studies must be conducted to assess the safety and efficacy of these devices in different patient populations. These studies should include long-term follow-ups to monitor potential side effects and complications, as well as to evaluate the durability and functionality of bioartificial livers. Collecting robust clinical data will enable researchers and physicians to optimize device designs and improve treatment protocols.

It is also important to consider the psychological and emotional impact on patients receiving bioartificial livers. Adapting to a bioartificial device can be a challenging process, and patients may require psychological support and counseling to manage their expectations and concerns. Proper education and training for patients and their families on the use and maintenance of bioartificial devices are essential for ensuring treatment success.

In the future, the integration of remote monitoring technologies and telemedicine could facilitate continuous follow-up of patients with bioartificial livers, allowing physicians to adjust treatments in real time and respond quickly to any issues. Telemedicine could also improve access to specialized care for patients in rural or underserved areas, ensuring that all patients have the opportunity to benefit from these technological advancements.

The development of bioartificial livers offers significant hope for patients with liver failure, but it also presents complex challenges that must be addressed through research, collaboration, and continuous innovation. The combination of advances in biotechnology, tissue engineering, artificial intelligence, and personalized medicine has the potential to transform the treatment of liver diseases and improve the quality of life for millions of people worldwide. With a comprehensive approach that includes ethical, regulatory, and social considerations, bioartificial livers could become a clinical reality, providing effective and accessible solutions to the organ transplant crisis.

4. Conclusions

The liver is a vital organ with a wide range of essential functions, including detoxification, nutrient metabolism, and the regulation of immune processes. Liver failure, whether chronic or acute, poses a significant threat to millions of people worldwide, highlighting the urgent need for therapeutic alternatives such as an implantable artificial liver.

Developing an implantable artificial liver requires a deep understanding of liver biology and a design that mimics the critical functions of this complex organ. Significant progress has been made in artificial liver design through the integration of cellular sources, innovative biomaterials, and perfusion systems that simulate the blood flow and metabolic exchanges of the human liver. Stem cells and primary liver cells have proven to be promising cellular sources capable of performing vital liver functions, while biocompatible biomaterials provide a structural framework that ensures cell viability and integration into the human body. Perfusion systems are essential for supplying oxygen and nutrients to the cells, enhancing their survival and functionality within the artificial environment.

Artificial liver prototypes developed so far have shown promising results, though they are still in experimental stages. The clinical implementation of these devices also faces significant regulatory and ethical challenges. Regulations regarding the safety and efficacy of bioartificial organs must ensure that patients receive devices that not only replicate liver functions but are also safe and durable. Additionally, ethical concerns surrounding the sourcing of human cells, animal

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experimentation, and human clinical trials remain key topics of debate in bioartificial organ development.

Future research focuses on enhancing artificial liver functionality through advancements in technologies such as liver-on-chip systems and genetic editing of liver cells. These innovations, along with the continuous improvement of biomaterials and perfusion systems, bring the possibility of an implantable artificial liver closer to becoming a viable solution for treating liver failure in the coming years. Collaboration among scientists, engineers, and physicians is essential to overcoming current challenges and creating new opportunities to save lives.

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