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GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

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Abstract.
“Every year, many individuals with tissue or organ problems require urgent care due to medical emergencies, burns, congenital anomalies, and other causes”. Regenerative medicine was created because there aren't enough donors, issues with graft rejection, and insufficient organs or tissues for patients to replace, repair, and regenerate. However, significant tissue defects are difficult to fill with injections alone, making stem cell therapy a crucial component of the area of regenerative medicine. To achieve the intended outcome, the researchers combine stem cells with three-dimensional (3D) printed organs tissue engineering scaffolding. These scaffolds can resemble bone, cartilage, or “extracellular matrix (ECM)” in that they provide structural support and promote adhesion, proliferation, and differentiation, finally resulting in the production of functional tissues or organs. In this study on stem cell regenerative medicine, the therapeutic focused mostly on scaffolding for 3D printed organ tissue engineering. The following applications are demonstrated and compared using various 3D printing processes and starting materials. Then, we go over the benefits of 3D printing over conventional methods, touch on certain issues and restrictions, and make some assumptions about potential applications in the future.

Keywords. Cell, three-dimensional printing, artificial organ tissue, scaffolding materials.

Introduction.
“By delivering artificial bone tissue scaffolds to the site of the lesion and subsequently replacing using new bone tissues and scaffolding inside the body, bone tissue engineering, which combines tries to heal the bone deficiency using scaffolds, seed cells, and cytokines” [1]. Scaffold, also referred to as a short-term artificial ECM, directly impacts cell proliferation and differentiation and can aid in the production of new Bone. The best bone tissue engineering supports should be able to support the formation of blood vessels and nerves. They are suitable for clinical usage because they have the right surface area to porosity ratio, mechanical support, biocompatibility, and surface activity that can encourage cell attachment.

The capacity for multiple differentiation and self-renewal is a property of stem cells. Based on their developmental stage, adult stem cells (ASCs) and embryonic stem cells (ESCs) are two groups of stem cells that can be separated [2]. ESCs, historically the focus of regenerative medicine and tissue engineering healthcare, are produced from the mass of inner cells at the blastocyst phase and possess the capacity for illimitable multiplication and germ layer differentiating. There is extensive use, yet there needs to be more clinical application of ESCs constrained by immunological rejection and other issues.

ASCs have significant potential for tissue damage repair and treatment of diseases in many different types of tissues and are the present focus of regenerative medicine [3]. iPSCs, or regenerative medicine, induced pluripotent stem cells, are intriguing. iPS cell research has greatly advanced the production of organoids, drug discovery, illness mechanism research, and disease treatment.

The field of additive manufacturing (AM), which has seen a remarkable rise in recent years, relies heavily on 3D Printing—the process of making implanted, bioactive devices [4]. ECM, nutrition delivery, and efficient intracellular migration formation for bone tissue regeneration applications require an efficient structure with high accessibility, many connections, and specified pore size and shape. When using traditional procedures like gas foaming, phase separation, or leaching pore-forming agents, the pore shape, dimension distribution, and overall interconnectivity are highly variable. Additionally, clinical applications of 3D Printing indicate improved treatment outcomes and more tailored material qualities. In comparison to solid or hexagonal porous scaffolds, Researchers also discover that square-shaped stands encourage the spread of more hMSCs and chondrogenic differentiation. Because of this, 3D Printing is especially well suited for creating structures for bone tissue healing. It also encourages guided stem cell differentiation and proliferation.

A 3D structure is created by layering unfinished materials or living cells onto preset places in 3D Printing [5]. The target materials are deposited or fixed, which makes 3D Printing the best method for producing clearly defined porosity structures. Additionally, it enables the creation of a tailored implant design for individuals with tissue deficiencies when combined utilizing CT and contours scanning are two examples of 3D computer imaging techniques. Data from CT scans be easily transformed into computer-aided design (CAD) models using the standard tessellation language (STL). By modifying such STL files, We can modify the environment for stem cell development in the modelling program or add the necessary porosity or structural support for medicinal treatments.

Developing scaffolds that facilitate tissue and organ engineering using 3D Printing in stem cell regenerative medicine presents exciting opportunities for overcoming donor scarcity and graft rejection issues. Aiding in the development of functional tissues and organs is the structural support it offers and the attachment, proliferation, and differentiation of stem cells.
The additional divisions of this article are as follows: Part 2 introduces related works, Part 3 discusses the methodology, Part 4 assesses the efficiency of the proposed method, and Part 5 concludes the paper.

**Related works.**

The study [6] evaluated current biomaterials for tissue engineering scaffolds, taking into account qualities like biocompatibility and physical attributes, and suggests novel materials for scaffold construction. The chapter discusses the impact of surface characteristics and mechanical characteristics on cellular contact while analyzing natural and synthetic biomaterials, evaluating biocompatibility, bioactivity, and biodegradation. It also emphasizes the processes used in the manufacture of biomaterials. The chapter presents insights into cutting-edge biomaterial options for scaffolds, taking into account their characteristics and interactions with cells, helping to enhance tactics for tissue engineering. The article [7] Using self-assembled organ-specific, human-derived three-dimensional models, develop more reliable and moral substitutes for animal research. Using self-assembly methods, develop the 3R principles of reduction, refinement, and replacement in research by building organ-specific three-dimensional models without the use of external scaffolds. With its alignment with the 3R principles and promise to lessen the reliance on conventional animal models in scientific research, the self-assembly methodology offers encouraging steps toward the achievement of more relevant and compassionate testing procedures.

The study [8] examined the possibilities for cooperation between human intelligence (HI) and artificial intelligence (AI) in the fields of biomedical engineering and clinical practice, taking into account their complementary uses, advantages, and difficulties. The review focuses on HI integration while analyzing diverse AI applications across the life continuum, including humans and other living things. The review emphasizes that collaboration between AI and HI has the potential to advance healthcare in a number of ways, but it also emphasizes that AI should complement rather than replace human expertise. It also places an emphasis on responsible innovation, addresses societal implications, and takes into account the wider impact of automation and algorithms.

The goal of article [9] examined recent developments in 3-D bioprinting and deposition-based approaches for the creation of novel 3-D scaffolds in regenerative medicine, with a focus on neurodegenerative illnesses. With a focus The essay extensively reviews recent developments in additive manufacturing methods, focusing on three-dimensional printing, laser-based processes, & deposition-based procedures. Additionally, it explores the significance of choosing the right biomaterial, structural attributes, and exact geometrical patterns while fabricating scaffolds. The expanding importance of additive manufacturing in developing customized 3-D scaffolds for neurodegenerative disease modelling and therapy is highlighted in this review.

The study [10] investigated how hydrogels are categorized, what they can be used for, and how to design them for 3D printing, with a particular emphasis on their potential in biomedical and bioengineering applications. The prospectus examines recent developments in 3D bioprinting technology and materials, with a focus on hydrogels. The scenario emphasizes the revolutionary potential of 3D printing hydrogels in industries like bioengineering and medicine. The study [11] in order to give a thorough understanding of the characteristics, manufacturing processes, and tissue engineering applications of smart hydrogels, this review will focus on their potential to operate as supportive matrices for cell development and growth factor delivery. The paper thoroughly covers the characteristics and manufacturing processes of smart hydrogels, discussing their capacity to imitate native tissues, offer mechanical support, and preserve an environment that is favourable for cell life. The crucial part that smart hydrogels play as tissue engineering scaffolds is highlighted by this review.

The article [12] enhanced CD-ECM-based research, this review seeks to present an overview of the techniques for producing cell-derived extracellular matrices (CD-ECMs) and their varied uses in fundamental research and therapeutic approaches. The review talks about CD-ECMs' bioactivity and complexity, their capacity to enhance cellular processes and operate as biomaterials, as well as the difficulties associated with their application. It reviews current approaches and emphasizes the value of developing methods to advance CD-ECM research. To fully utilize CD-ECMs in both scientific and therapeutic contexts, it is crucial to solve present issues and promote interdisciplinary collaboration.

The article [13] examined the most recent developments in tissue engineering (TE), with a focus on scaffold manufacturing methods, particularly electrospinning and 3D printing. It contrasts the widely used methods of 3D printing and electrospinning, comparing their advantages, drawbacks, and adaptability. The research comes to the conclusion that despite great improvements, there are still significant gaps in our understanding of how scaffold construction techniques can be practically applied to preclinical and real-world applications.

The study [14] in order to create natural hydrogels for tissue engineering, new bio fabrication approaches are being investigated and presented in this review. The paper looks at new breakthroughs in bio fabrication techniques for making natural hydrogels, including textile methods and three-dimensional bioprinting. The review was a useful tool for understanding how approaches to tissue engineering and biomaterial creation are changing. The purpose of the article [15] investigated the microenvironmental properties of the intervertebral disc (IVD) in both healthy and degenerative stages, as well as how these elements affect the viability and activity of resident cells and mesenchymal stem cells (MSCs). examines current research projects that aim to improve the efficiency of tissue engineering and cell therapy methods in this setting. Recent research suggests interesting approaches using cell therapies and customized bioscaffolds that aim to enhance the survivability and activity of both resident cells and MSCs, fostering progress in disc regeneration therapies despite difficulties brought on by the hostile microenvironment.

“3D Printing to tissue Engineering.”

When using stem cells, “3D printing” refers to the application of additive manufacturing processes to build specialized
scaffolds and supports stem cells to multiply and differentiate. Making advantage of 3D printing technology to create intricate structures that aid in stem cell development and application in medical treatments.

Various 3D printing technologies

The use of stem cells in fabricating tissue engineering scaffolds using various 3D printing techniques will next be discussed. The operation of these methods and the results of working with cells or raw materials were covered in the following paragraphs.

Fused deposition modeling

Polymers or wax, including polyphenylene sulfonic resins (PPSU), polycarbonate (PC), and acrylonitrile butadiene styrene (ABS), among others, are the main raw materials utilized in the fused deposition modeling (FDM) technique. The filament or linear plastic part gets heated in the nozzle until it melts. The nozzle's shape moves along the planned contour and track of the pieces under computer control, extrudes the hot material, causes it to deposit at the anticipated location, and solidifies. The layers are piled and adhered to the previously produced layers to create a model for the product. Normally, two materials are employed in construction, one of which acts as a support and the other of which is the actual building material. Additionally, we can alter the product's porosity, diameter, and mechanical qualities by adjusting the nozzle's temperature, diameter, movement, extrusion, and building-direction speeds. To create bespoke defect-matching structures for bone healing, FDM technology is used. The scaffolds are modified to increase their biocompatibility and bone conductance and printed out in various porosity and pore sizes to support stem cell proliferation and differentiation. Figure 1 depicts the process of FDM.

Extrusion-3D printing

Extruder depositing with accuracy Low-temperature deposit modelling and 3D bio-plotting are two strategies used in extrusion-based 3D printing.

Precision extrusion deposition

An additive manufacturing process known as precision extrusion deposition (PED) uses accurate material extrusion to construct three-dimensional objects layer by layer. Direct ink writing and robotic deposition are some names for it. Rapid prototyping and 3D Printing both frequently use PED. PED can be used on various materials, including composites, metals, ceramics, and polymers. To enable extrusion and shape retention following deposition, the material is often semi-solid or paste-like. The material's viscosity is frequently changed to guarantee optimum flow and stability during Printing. PED is a useful technology in the additive manufacturing scene because of its adaptability and accuracy.

Low-temperature deposit modeling (LDM)

LDM, or low-temperature deposition modeling, is a technique for additive manufacturing that involves layering materials at relatively low temperatures. Low-temperature spray deposition and cold spray are other names for it. LDM mostly covers or repairs metal surfaces and builds three-dimensional constructions. The versatile additive manufacturing technique known as low-temperature deposition modeling (LDM) enables the deposition of materials at low temperatures, providing benefits regarding material flexibility, process effectiveness, and diminished thermal impacts on the substrate.

3D Bio plotting

The debut of a novel method for producing free-form scaffolds called 3D Bio-plotting allows for the creation of artificial tissue scaffolds containing living cells. The system can cope with biological components sensitive to heat, including cells because no heat is needed.

Stereolithography

In 3D Printing, the Stereolithography (SLA) process is acknowledged as one of the most thoroughly studied and widely used processes. Oligomers, reactive diluents, and initiators are the key components of photosensitive resin materials. A novel ceramic resin featuring fine features, thermal shock resistance, and insulation from heat and electricity was introduced. A directed laser beam creates two-dimensional patterns that aggregate thin layers. The production platform patterns descend over the previous polymerization layer to make the appropriate structure. According to studies, the rich oxygen surfaces of scaffolding were treated with cold atmospheric plasma (CAP). The enhanced surface roughness is advantageous for hMSC proliferation, chondrogenic differentiation, and adhesion. Figure 2 depicts the SLA and Digital light processing (DLP) process.

Digital light processing

An external exposure SLA technology based on a mask. This method exposes a Full layer of the designed shape is applied using a cover on the photosensitive resin's exterior for layer curing. DLP also has improved efficiency and comparatively low cost. It is suitable for creating porous scaffolds with thin walls with complicated characteristic features.

Selective laser sintering

The materials utilized in the Selective laser sintering (SLS) process come in various forms, such as powder, comprising coated wax metal, ceramic, glass, wax, and nylon. Thin layers of the powder are applied to the build platform suppliers of powder and rollers for SLS. A laser beam is used to melt a specific pattern with the powder. After the platform is lowered and the molten
design is covered with new powder, the platform is raised again. The finished product's mechanical properties, pore size, and porosity are all impacted by several specified settings during the complex process of SLS printing. Layer thickness, scan rate, laser output, and other relevant input parameters are important. These variables will impact the final product's quality by affecting the laser beam's energy content in the layer of molten powder. These modifications are employed by scientists to satisfy the requirements of various tissue-engineered scaffolds.

By using indirect SLS printing, it is possible to avoid issues with hydroxyapatite breakdown and wavy deformation at higher operating temperatures. Additionally, it displayed astounding porosity, pore size, distinctiveness, and mechanical durability of osteopenia. Figure 3 depicts the SLS and SLM procedure.

Selective laser melting

It uses a laser to selectively melt a layer of solid particles, followed by solidification, to create pieces. Selective laser melting (SLM), as opposed to SLS, is made by melting and curing off. It is easier to control porosity and shape as a whole, and porous objects with intricate internal systems can be created by using powder rather than applying a binder during the forming process. In addition, Castings are not as strong as SLM-forming components due to instantaneous solidification, fine microstructure, and quick melting of powder using a laser, which gives them notable advantages in forming complex and challenging workpieces. They are also appropriate for processing intricately shaped, irregular supports with excellent quality and a tiny structure.

Systems based on printers.

Printing in three dimensions

A technique for additive manufacturing known as "three-dimensional printing," which also goes by the names "material jetting printing" or "inkjet printing," builds structures by only adhering certain materials together, layer by layer, from a polymer or inorganic powders, 3D designs. Typically, this technology is combined with others like electro-hydro dynamic jetting, stereo lithography, high temperature burning, etc. The next is a business instance of a more popular printing technology combining several different options.

PolyJet

With the help of the 3D printing technology known as PolyJet, real items may be built up layer by layer. It is a proprietary technique created by Stratasys, a renowned 3D printer maker. A UV light source is utilized to cure the photopolymer, instantaneously solidifying it as each layer of droplets is applied. This makes it possible to incorporate many materials into a single print and to create complex geometries. A solid object is created when the layers combine and cure. A popular option for many additive manufacturing applications, PolyJet is a flexible and high-resolution 3D printing method that enables the production of complex, multi-material structures with fine details and smooth surfaces.

Multidisciplinary joint manufacturing

To improve technical benefits or avoid disadvantages, many technologies may be coupled with a single application to jointly develop scaffold materials.
Joint production of various 3D printing technologies

The demands of the 3D printer's instructions might not be met using just one 3D printing technology. For instance, when choosing printing ink, some inks must sufficiently yield strength to satisfy the fundamental printing requirements for 3D bio-printing. The scientists used ultraviolet cross-linking from SLA technology to tackle this issue, which caused the ink to be sheared thin and undergo gelatin-sol transformation for great printability and fidelity.

Manufacturing and conventional technology combined.

Traditional technology is still useful even though the practice of 3D Printing has several advantages over it. For instance, researchers combined casting and FDM technologies with revolutionary bio-inks to develop novel osteochondral tissue constructions. The scaffolds produced had outstanding mechanical qualities and improved hMSC adherence, proliferation, and differentiation.

Manufacturing is both direct and indirect.

Direct Printing's shortcomings, such as its inability to work with low-viscosity materials, have been identified by researchers in the actual use of 3D Printing. Employed indirect Printing was used to address the problem, and useful comparisons were made. By combining approaches for indirect Printing with 3D printers and freeze-drying. To improve control, uniform pore structure, and in vitro bioactivity, a three-dimensional A 3D framework made of silk fibroin and silk fibroin-bioactive glass (SF-BG) with varying levels of bioactivity was developed. Scaffold modification following Printing.

Post-printing conversion is frequently performed to improve or adjust the scaffold performance for the desired outcome. Such changes increase histocompatibility after transplantation, enhancing in vitro stem cell differentiation and proliferation.

Therapeutic applications

With the advancement of the technology for 3D Printing over the last ten years, numerous tissue engineering scaffolds are being created for use in clinical settings using cutting-edge technologies and novel materials. It gives patients and professionals a great deal of hope and inspiration. This technology is widely employed in clinical training, preparatory simulation, perioperative navigation, stomatology, and many other areas, with considerable application potential and market value, in addition to the repair and transplantation of bone defects. However, several issues still need improvement, including inadequate strength, poor biocompatibility, and an unsuitable rate of disintegration. The problems of mechanical stability, biological compatibility, and regulated degradation are best addressed by combining synthetic and natural polymer materials. “The size of the world market for tissue engineering was estimated to be USD 12.76 billion in 2021”, and “it is anticipated to reach USD 31.23 billion by 2030”, “growing at a CAGR of 10.46% from 2022 to 2031”.

Success rates

A growing number of research have produced encouraging findings, significantly improving the success rate of 3D printing in tissue engineering. Applications in regenerative medicine, drug testing, and disease modelling are now possible thanks to this technology's ability to precisely fabricate complex tissue architectures out of living cells and bioinks. While issues like vascularization and the durability of printed tissues remain, ongoing research and innovation are improving the success rate of 3D printing in tissue engineering, bringing us closer to the possibility of realizing functional and transplantable bioengineered tissues.

Conclusions.

In the realm of regenerative medicine, the combination of stem cell therapy and 3D printed organ tissue engineering scaffolds is a promising development. This cutting-edge method offers a workable alternative to repair and regenerate damaged tissues and organs by resolving the problems caused by organ shortages, graft rejection, and tissue abnormalities. The use of multiple 3D printing processes and starting materials exemplifies how adaptable this technology is in creating scaffolds that resemble bone, cartilage, and extracellular matrix and help stem cells attach, proliferate, and differentiate. The benefits of 3D printing, such as exact customizability, reproducibility, and scalability, highlight its advantage over conventional techniques. Although this strategy has a lot of potential, there are some drawbacks, including regulatory obstacles, determining long-term efficacy, and ethical issues. Future developments in this area may result in game-changing applications that completely alter how we treat complicated tissue abnormalities and urgent medical situations with individualized regenerative therapies.

REFERENCES