SAFETY OF CARBON NANOCARRIERS IN BIOMEDICAL APPLICATIONS: BIOCOMPATIBILITY OF GRAPHENE AND ITS DERIVATIVES

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Abstract. The article considers one of the most important factors allowing to determine the possibility of wide and safe use of graphene nanoobjects in modern biomedicine - this is the biocompatibility factor, namely, the interaction of a graphene-containing substance with a given part of the body, which is realized at different scales and at different levels of organization of living matter. Graphene and its derivatives have shown exceptional properties and potential for various applications. While graphene derivatives as graphene-oxide (GO), reduced graphene-oxide (rGO), few-layers graphene (FLG), and multi-layers graphene (MLG) exhibit similar properties to graphene, more research is needed to address scalability and cost-effectiveness for practical applications. In tissue engineering, graphene-based materials have shown promise in scaffolds, biosensors, and drug delivery systems, but optimizing biocompatibility and functionalization strategies are crucial for safe and effective use. This work is a try to better understanding the complex interactions between graphene and biological systems, including cells, tissues, and organs, which is necessary for future research and expanding the use of graphene in biomedical applications.

Key words: *graphene, biocompatibility, functionalization, biomedical applications.*

Introduction. Graphene, a two-dimensional material consisting of a single layer of carbon atoms, has garnered much attention in recent years due to its exceptional mechanical, electrical, and optical properties. As a result, it has been extensively investigated for its potential use in various fields such as electronics, energy, and biomedical applications. The latter is of particular interest due to its unique biocompatibility properties, which make it a promising candidate for developing biosensors, drug delivery systems, and tissue engineering scaffolds.

The biocompatibility of graphene and its derivatives is an active area of research, with numerous studies investigating the material's interactions with biological systems at various scales, ranging from single cells to tissues and organs. Understanding the mechanisms underlying the biocompatibility of graphene is essential for the safe and effective use of this material in biomedical applications.

This article will provide an overview of the current state of knowledge regarding the biocompatibility of graphene and its derivatives. We will discuss the various factors that affect the biocompatibility of graphene, including its physicochemical properties, functionalization strategies, and dosage. Additionally, we will highlight the latest research on the interactions between graphene and different biological systems, including cells, tissues, and organs. Finally, we will discuss the challenges and future prospects of using graphene and its derivatives in biomedical applications.

Graphene and Its Derivatives. Despite its tremendous potential, the practical application of graphene is still limited by the high cost, limited availability, and lack of scalable production methods. Therefore, researchers have explored graphene derivatives, which exhibit properties similar to graphene and can be synthesized at a lower cost [1].

Graphene oxide (GO) is a widely used graphene derivative due to its low cost, ease of synthesis, and functional groups on its surface that enable the functionalization and dispersion of graphene in various solvents and matrices [2]. Reduced graphene oxide (rGO) is obtained by the chemical or thermal reduction of GO, which restores the sp2 hybridization and electronic properties of graphene [3]. Few-layer graphene (FLG) and multilayer graphene (MLG) are graphene derivatives that consist of several layers of graphene sheets stacked together. FLG is characterized by a few (2-5) layers of graphene, while MLG can have more than ten layers [4].

Graphene and its derivatives have a wide range of applications in various fields. In biomedical applications, graphene and its derivatives have been explored for drug delivery, biosensing, and tissue engineering scaffolds due to their biocompatibility and high surface area [5]. Studies have investigated the biocompatibility of graphene with different biological systems, ranging from single cells to tissues and organs. Graphene's high surface area and surface chemistry make it a suitable material for immobilizing biological molecules and detecting biomarkers. Furthermore, graphene-based drug delivery systems have shown promise in delivering therapeutic agents to specific sites in the body.

Applications of Graphene in Tissue Engineering. The unique characteristics of graphene make it an ideal material for a broad range of applications, including tissue engineering. Tissue engineering is the interdisciplinary field of applying engineering principles to develop biological substitutes for damaged or missing tissues. Graphene has been found to have tremendous potential in tissue engineering applications due to its biocompatibility, electrical conductivity, and mechanical properties [2-4].

One of the most promising applications of graphene in tissue engineering is as a scaffold material. Graphene scaffolds have been shown to promote cell adhesion, proliferation, and differentiation [5]. Additionally, graphene's electrical conductivity can stimulate cells' growth and aid in tissue regeneration [6]. Furthermore, graphene's mechanical properties, such as its high tensile strength and flexibility, make it an excellent candidate for developing scaffold materials for various tissues, including bone, cartilage, and skin [7].

Graphene's unique electrical properties also make it a potential candidate for developing biosensors for various biomedical applications. Biosensors developed using graphene-based materials have shown promising results in detecting various biomolecules, such as glucose, cholesterol, and proteins [6]. Graphene's high surface area and its ability to transfer electrons efficiently make it an ideal material for developing biosensors [9]. Additionally, graphene's high biocompatibility makes it a safe material for biomedical applications [10].

Moreover, graphene-based materials can also be used as drug delivery vehicles in tissue engineering. Graphene-based drug delivery systems can enhance drug bioavailability and improve therapeutic efficacy [11]. Graphene's large surface area and high drug-loading capacity make it an excellent candidate for developing drug delivery systems. Furthermore, graphene's biocompatibility and low toxicity make it a safe material for drug delivery applications [12].

Factors Influencing the Biocompatibility of Graphene. The biocompatibility of graphene is influenced by various factors, including size, shape, surface chemistry, concentration, and aggregation state.

The size and shape of graphene can affect its biocompatibility. Smaller graphene sheets can be internalized by cells and potentially cause cytotoxicity, while larger sheets may be more biocompatible. Additionally, graphene oxide sheets with rounded edges have been found to be less toxic than sheets with sharp edges [7].

Surface chemistry is another important factor that influences the biocompatibility of graphene. The presence of functional groups on graphene's surface can affect its interaction with biological systems. For example, the presence of carboxylic groups can enhance the solubility and biocompatibility of graphene, while the presence of amino groups can increase its toxicity [8].

The concentration of graphene also plays a role in its biocompatibility. High concentrations of graphene can cause cell death and induce inflammation, while lower concentrations may be more biocompatible. Additionally, the aggregation state of graphene can affect its biocompatibility. Aggregated graphene can induce inflammation and oxidative stress, while dispersed graphene may be more biocompatible.

Other factors that may influence the biocompatibility of graphene include its purity, crystallinity, and surface charge. Purer and more crystalline graphene may be less toxic, while the surface charge can affect its interaction with biological systems.

Functionalization Strategies for Enhancing Graphene's Biocompatibility. Functionalization strategies have been developed to tailor graphene's physicochemical properties to specific biomedical applications. Functionalization of graphene can be achieved by attaching various molecules and atoms to its surface, such as peptides, proteins, polymers, and nanoparticles. Additionally, functionalization with polymers can increase the stability and solubility of graphene in biological fluids and enhance its biocompatibility.

Functionalization of graphene can be achieved by attaching various molecules and atoms to its surface, such as peptides, proteins, polymers, and nanoparticles. One of the most common methods for functionalizing graphene is covalent functionalization, where molecules are attached to the surface through covalent bonds. This method ensures strong binding between the functional molecules and graphene, but it may also alter graphene's physicochemical properties [9].

Non-covalent functionalization is another strategy for functionalizing graphene, where molecules are attached to the surface through non-covalent interactions such as electrostatic forces, hydrogen bonding, and van der Waals forces. Non-covalent functionalization can preserve the intrinsic properties of graphene and enhance its biocompatibility [10].

Functionalization strategies can also be used to tailor the surface charge of graphene, which is a critical factor affecting its interaction with biological systems. The surface charge of graphene can be controlled by functionalizing it with charged molecules such as polymers or nanoparticles [11].

Functionalization of graphene can also enhance its solubility in biological fluids, which is necessary for its effective use in biomedical applications. The functionalization of graphene with polymers or surfactants can increase its solubility and stability in aqueous solutions [12].

Dosage-Dependent Effects of Graphene on Biological Systems. The dosage of graphene is an important factor that influences its effects on biological systems. Several studies have shown that graphene exhibits a dosage-dependent effect on biological systems. At low doses, graphene has been reported to enhance cell proliferation and differentiation, promote wound healing, and have anti-bacterial and anti-inflammatory effects. For instance, Luo et al. demonstrated that low concentrations of graphene oxide enhanced the proliferation and differentiation of human mesenchymal stem cells [13]. Additionally, Shanmugam et al. reported that low concentrations of graphene oxide could promote wound healing in mice [14].

However, at high doses, graphene can be cytotoxic and induce inflammation and oxidative stress in cells. The cytotoxicity of graphene has been found to be influenced by various factors such as size, shape, surface chemistry, and concentration. For example, smaller graphene sheets may be more cytotoxic due to their increased cellular uptake [15]. Moreover, graphene oxide with high oxygen content has been found to induce greater oxidative stress than reduced graphene oxide with low oxygen content [6].

The dosage-dependent effects of graphene on biological systems have been observed in both in vitro and in vivo studies. For instance, Jasim et al. reported that high doses of graphene oxide could induce liver toxicity in mice [16]. Similarly, Wu et al. found that high doses of graphene could induce inflammation in human lung cells [17].

Interactions between Graphene and Cells. Understanding the interactions between graphene and cells is crucial for the safe and effective use of graphene in biomedical applications.

Several studies have investigated the interactions between graphene and cells. Graphene has been found to interact with cells in different ways, depending on factors such as size, shape, surface chemistry, and concentration. For example,

small graphene sheets with high surface area have been found to be more cytotoxic than larger sheets [18]. Additionally, graphene oxide with carboxyl or hydroxyl groups on its surface has been found to be more biocompatible than graphene oxide without these functional groups [19].

The interaction between graphene and cells can also affect cell behavior and functions. For instance, Qi et al. found that graphene oxide could promote the differentiation of human neural stem cells into neurons [20]. Moreover, Devi G.V et al. reported that graphene could induce osteogenic differentiation of human mesenchymal stem cells [21]. On the other hand, several studies have reported that graphene can induce cytotoxicity, inflammation, and oxidative stress in cells [22].

The interaction between graphene and cells is also influenced by the protein corona that forms around graphene upon its contact with biological fluids. The protein corona can affect the biocompatibility and toxicity of graphene by altering its interactions with cells. For example, the protein corona formed around graphene oxide can reduce its cytotoxicity by shielding its surface groups that can induce cytotoxicity [23].

Interactions between Graphene and Tissues. Various factors, such as size, shape, surface chemistry, and concentration, determine the way graphene interacts with tissues. Depending on these factors, graphene can interact with tissues in different ways. For instance, larger graphene sheets with more layers are less harmful to cells than smaller ones [24]. The interaction between graphene and tissues can also affect tissue functions and responses. For example, Liu et al. reported that graphene could enhance the osteogenic differentiation of bone marrow mesenchymal stem cells [25]. Moreover, graphene oxide has been found to induce angiogenesis in vitro and in vivo, which can be potentially useful for tissue regeneration [26]. However, graphene can also induce inflammation and oxidative stress in tissues, leading to tissue damage [15].

The interactions between graphene and tissues are also influenced by the protein corona that forms around graphene upon its contact with biological fluids. The protein corona can affect the biocompatibility and toxicity of graphene by altering its interactions with tissues [27]. For example, the protein corona formed around graphene oxide can reduce its cytotoxicity by shielding its surface groups that can induce cytotoxicity [28].

Interactions between Graphene and Organs. Several studies have investigated the interactions between graphene and organs. For example, graphene has been shown to accumulate in the liver, spleen, and lungs of mice after intravenous injection, indicating its potential toxicity to these organs [24]. In contrast, graphene oxide has been found to accumulate primarily in the spleen and to a lesser extent in the liver and lungs [29]. Furthermore, graphene has been shown to interact with the brain and induce changes in its functions, although the underlying mechanisms are not fully understood [30].

The interactions between graphene and organs can also affect the organ functions and responses. For example, graphene oxide has been shown to induce apoptosis and impair the functions of immune cells in the spleen [31]. Moreover, graphene has been found to enhance the functions of pancreatic β cells, which could be potentially useful for the treatment of diabetes [32]. However, graphene can also induce inflammation and impair the functions of heart cells, leading to cardiac dysfunction [33].

The interactions between graphene and organs are also influenced by several factors, including the size, shape, surface chemistry, and concentration of graphene. The protein corona that forms around graphene upon its contact with biological fluids can also affect its interactions with organs [23]. Therefore, it is important to carefully control these factors to minimize the potential toxicity of graphene to organs.

Challenges and Future Prospects for the Use of Graphene in Biomedical Applications. Despite the potential benefits, several challenges exist in the development and application of graphene-based biomedical technologies. One of the major challenges is the potential toxicity of graphene and its derivatives. Studies have shown that the size, shape, and surface functionalization of graphene can influence its biocompatibility [34],[24]. Thus, careful consideration must be given to the design and preparation of graphene-based materials to ensure their safety and efficacy in vivo.

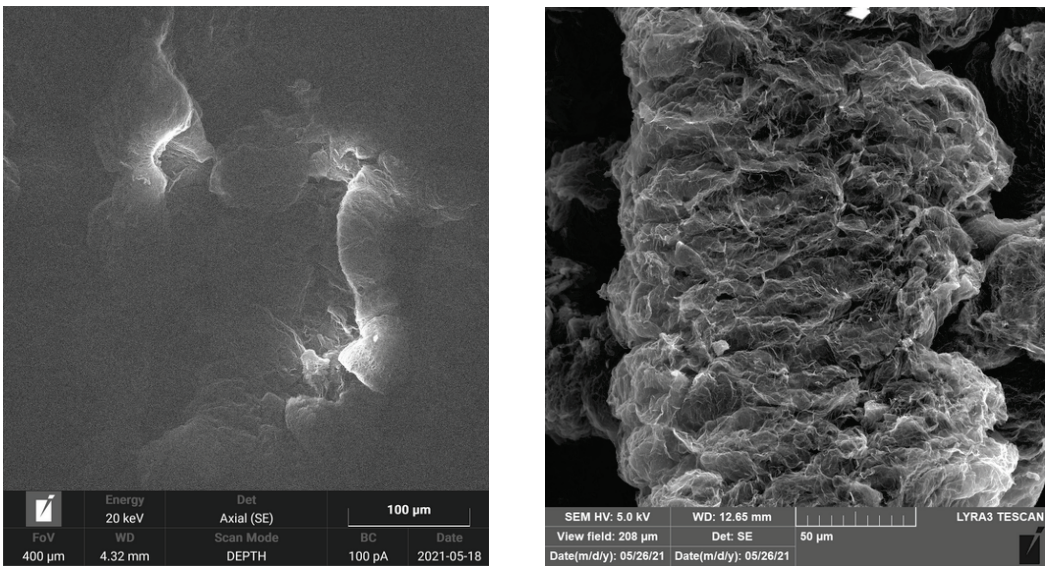
Another challenge is the difficulty in achieving scalable production and processing of graphene-based materials [35]. The synthesis of high-quality graphene is still a complex and expensive process, limiting its widespread use in biomedical applications. Furthermore, the lack of standardization in the characterization of graphene materials can hinder the reproducibility and comparability of results [36].

Despite these challenges, graphene-based technologies show great potential in biomedical applications. Graphene-based nanomaterials have been investigated for their potential use as drug delivery systems [37]. The large surface area and high drug-loading capacity of graphene oxide make it an attractive candidate for drug delivery applications [38]. Moreover, graphene oxide has been shown to enhance the therapeutic efficacy of anticancer drugs by promoting their uptake by cancer cells [39].

In addition to drug delivery, graphene-based biosensors have also been developed for the detection of various biomolecules, including proteins and DNA [40]. The high sensitivity and specificity of graphene-based biosensors make them promising for early disease diagnosis and monitoring. Graphene-based materials have also been investigated for their potential use in tissue engineering [41]. The high conductivity of graphene and its derivatives make them attractive for neural tissue engineering applications, while the high mechanical strength of graphene has been utilized in the development of scaffolds for bone tissue engineering.

Interaction between PolyGraphene and Intestine. In this part, we will give, as a good example, the result of designing an effective tool and choosing a method for safe use in medical practice of graphene-containing carbon material PolyGraphene (PG). The rationale for the prospects of this development was the results of studying the interaction of such a graphene-like carbon product as PolyGraphene with tissues and internal walls of the intestine.

In fact, a carbon nanocomposite of PolyGraphene (PG) obtained as expanded graphite after hydro-termic treatment



(а) **(б)**

Figure 1. Image (a) of a PolyGraphene (PG) obtained using a Transmission Electron Microscope (TEM) - JEOL JEM-2100; Image (b) of a PolyGraphene (PG) obtained using a Scanning Electron Microscope (SEM) - TESCAN LYRA

of modified graphite became to be able to interact as sorbent PG with wide range of organic pollutants. To date, it was studied the sorption properties of carbon material as an example of PolyGraphene (PG) concerning of organic pollutants. PG - version of ultrafine carbon sorbent, which was developed on the basis of the modified oxygen-containing expanded graphite (OCEG). Materials like PG have a very high absorption capacity, especially with respect to hydrophobic compounds (1:30 - 1: 100). For this reason, such materials are effectively used for the purification of aqueous solutions and suspensions from a wide range of organic pollutants (from benzene to oils). Since the envelopes of bacteria and viruses, as well as many toxins, are hydrophobic, forms of graphite obtained by thermal decomposition can effectively sorb and retain toxins, antibiotics, virus particles, pathogenic microorganisms, and many xenobiotics (for example, diclofenac). These facts indicate possible biomedical and biotechnological applications of PG.

Electron microscopy of various samples of PG showed that this material is a stack of graphene sheets with a multiplicity of 1-10-100, depending on the preparation technology (Figure 1). Repeated chemical modification and thermo-activation allows to obtain a material with stacks of lesser frequency, up to single sheets of graphene. Various technological options for producing PG were investigated and the best option was determined in terms of the ratio of functional characteristics and the cost of the resulting sorbent.

During experiments it was studied a new form of an oxygen-containing expanded graphite, which after repeated thermal activation and chemical modification with using ultrasound results in a material with stacks of carbon layers with higher multiplicity (10-40), but containing both single sheets of graphene. It is possible to include this material in classification of nanocomposite sorbents and the graphene-containing carbon forms. The authors introduce a new classification of this type of material and see it as an Oxidized PolyGraphene (OPG).

Enterosorption - the method based on linkng and removal from the digestive tract (DT) with the medical or preventive purpose of endogenous or exogenous substances, metabolites, various products of a microbic origin.

The last achievements in the field of physiology and pathology of digestion allow to consider enterosorption mechanisms from mass exchange positions between the internal and enteral medium. In this regard, enterosorbents can be estimated not only as effective remedies of a detoxication of an organism, but also as a factor, in itself having essential impact on activity of the digestive and transport conveyor and an exchange of the main nutrients.

Though materials and manufacturing techniques of sorbents significantly differ, the main medical requirements to enterosorbents remain rather constant: 1) convenient pharmaceutical form and lack of unpleasant organoleptic properties of a preparation; 2) not toxicity - preparations in the course of passing up through a gastrointestinal tract shouldn't collapse to fragments which can be soaked up and make negative impact on bodies and systems; 3) prepa-rations shouldn't injure the mucous; 4) there has to be a good evacuation warning a sorbent congestion in an intestines gleam; 5) high sorption ability to the deleted components; 6) at not selective sorbents possibility of sorption of useful nutrients has to be minimum; 7) lack of a desorption in process of advance through a gastrointestinal tract, lack of dependence from pH of medium.

Objective. The study of the interaction of OPG with the structure of the mucous of small intestine to determine possibility of using the OPG for detoxification general and selective action.

Conditions of experiments. Histologic research of a small intestine. For 20 rats through a probe was entered PolyGraphen's suspension into initial department of a duodenum. After 2.5 hours for receiving samples of biomaterial to rats was done euthanasia according to the European bio-ethical standards of manipulations with laboratory animals.

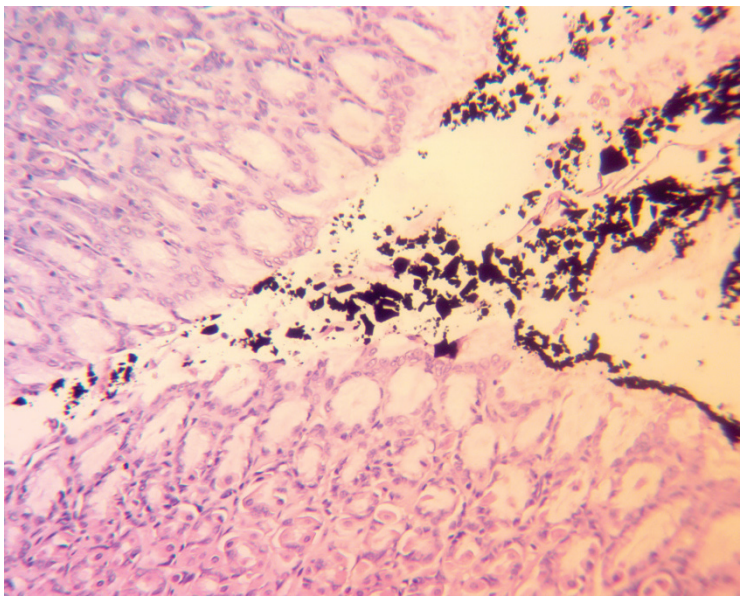


Figure 2. Oxidized PolyGraphene remains as a part of a himus and in the field of near wall of a mucous membrane of intestine. OPG does not enter the intercellular space in the epithelium, does not penetrate into the cells and doesn't get directly to a surface of cages of an epithelium

Further was opened an abdominal cavity of rats, was cuted sites of medial department of a duodenum, initial department of lean gut and distal department of ileum gut. Samples placed in the cooled fixating solution and processed according to the standard scheme for histologic research (Figure 2).

Experiments clearly show that Oxidized PolyGraphene remains as a part of a himus and in the field of near wall of a mucous membrane of intestine. OPG does not enter the intercellular space in the epithelium, does not penetrate into the cells and doesn't get directly to a surface of cages of an epithelium that treats as large poly-particles of OPG (100-500 microns), and smaller poly-particles (10-50 microns). At one-time introduction of OPG, it goes as transit goods through a small intestine, without being late and without getting directly to a surface of an intestinal epithelium which is closed by a continuous dense mucous bed, and also in space between intestinal fibers. OPG works, mainly in a gleam of intestines and at a surface of a mucous layer, without having direct negative destructive effect on cells of an intestinal epithelium and OPG has a large capacity.

The results of tests OPG as acting basis for the enterosorbents of new generation indicate a good promising potential for wide medical applications of PolyGraphene.

Conclusion. The unique properties of graphene and its derivatives have generated significant interest for potential applications in biomedicine. While GO, rGO, FLG, and MLG exhibit similar properties to graphene, more research is necessary to address scalability and cost-effectiveness for practical applications. In the field of tissue engineering, graphene-based materials have shown remarkable potential in scaffolds, biosensors, and drug delivery systems, due to their ability to mimic the properties of natural tissues and cells. However, to translate these applications into clinical settings, optimizing the biocompatibility and functionalization strategies of graphene-based materials is crucial for safe and effective use.

Furthermore, understanding the complex interactions between graphene and biological systems is necessary to mitigate potential risks and optimize performance in biomedical applications. The dosage of graphene is an important factor that influences its effects on biological systems, and the biocompatibility and toxicity of graphene need to be carefully studied and optimized for safe use.

As such, further research is needed to develop reliable and effective methods for large-scale synthesis and production of graphene and its derivatives, as well as to optimize their properties and performance for specific applications. With continued innovation and development, it is possible that graphene-based materials will play a critical role in shaping the future of technology, medicine, and other industries.

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БЕЗОПАСНОСТЬ УГЛЕРОДНЫХ НАНОНОСИТЕЛЕЙ В БИОМЕДИЦИНСКИХ ПРИЛОЖЕНИЯХ: БИОСОВМЕСТИМОСТЬ ГРАФЕНА И ЕГО ПРОИЗВОДНЫХ

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Аннотация. В статье рассматривается один из важнейших факторов, позволяющих определить возможность широкого и безопасного применения графеновых нанообъектов в современной биомедицине - это фактор биосовместимости, а именно взаимодействие графенсодержащего вещества с заданным участком организма, который реализуется на разных масштабах и на разных уровнях организации живой материи. Графен и его производные продемонстрировали исключительные свойства и потенциал для различных применений. Хотя производные графена, такие как оксид графена (GO), восстановленный оксид графена (rGO), немногослойный графен (FLG) и многослойный графен (MLG), обладают свойствами, сходными со свойствами графена, необходимы дополнительные исследования для решения проблемы масштабируемости и экономической эффективности для практических применений. В тканевой инженерии материалы на основе графена показали себя многообещающими в качестве каркасов, биосенсоров и систем доставки лекарств, но оптимизация стратегий биосовместимости и функционализации имеет решающее значение для безопасного и эффективного использования. Эта работа представляет собой попытку лучше понять сложные взаимодействия между графеном и биологическими системами, включая клетки, ткани и органы, что необходимо для будущих исследований и расширения использования графена в биомедицинских приложениях.

Ключевые слова: *графен, биосовместимость, функционализация, биомедицинские приложения.*