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EDITORIAL

Dear colleagues!

We are pleased to present the first issue of The Eurasian Journal of Life Sciences, an initiative proposed by the co-chairs of the Association of Russian and Chinese medical universities.

The honor of publishing this inaugural issue has been given to Sechenov University, Russia's oldest medical institution with over 260 years of history. The University has long played a key role in shaping medical education and advancing biomedical research. As we build upon this legacy, we also see the growing need for new platforms that unite research efforts across borders.

Today, fields such as molecular biology, genetics, and biotechnology are reshaping healthcare. Leading universities are at the forefront of these changes. By combining their strengths, institutions from many countries can address some of the most complex biomedical challenges of our time.

We envision The Eurasian Journal of Life Sciences as more than a traditional academic journal. It is a shared space for dialogue, exchange, and collaboration. The journal will highlight developments in personalized medicine, pharmacology, genomics, AI in healthcare, and the convergence of biology and technology.

We hope it will serve as a dynamic platform where scientists and clinicians can share findings, perspectives, and set new directions for research. We warmly welcome our readers to this first issue and look forward to the collaborations it will inspire.

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REVIEW

Modern trends in laser non-invasive reconstruction of biological tissues

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ABSTRACT

The article focuses on contemporary methodologies for laser-based, non-invasive reconstruction of biological tissues. It examines the mechanisms of laser-tissue interaction, including photothermal processes and the formation of new molecular bonds. A range of laser systems – neodymium-doped yttrium-aluminum garnet laser (Nd:YAG laser), carbon dioxide laser (CO_2 laser), diode and their applications in vascular, micro- and plastic surgery are analyzed. The analysis is further enriched by a discussion of bioorganic solders, such as albumin and indocyanine green, and nanomaterials that have been shown to enhance bond strength and reduce thermal damage. Examples of successful applications of the technology for vascular and nerve repair, wound sealing, and plastic surgery are provided. Finally, future prospects are highlighted, including temperature control systems and personalized approaches. The text emphasizes the potential of laser methods as a minimally invasive alternative to traditional surgery.

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Introduction

Contemporary medicine is actively developing minimally invasive surgical methods, which are not only comparable in effectiveness to traditional approaches, but also provide less traumatic, reduced blood loss, minimal scarring, and shorter hospitalization and rehabilitation of patients. Thanks to the introduction of robotic systems, high-precision imaging, such interventions are becoming increasingly precise and safe, opening up new possibilities in the treatment of complex diseases. One of the most promising methods meeting these requirements is laser-assisted biological tissue reconstruction. This technology, based on the use of laser radiation in combination with biomaterials, demonstrates significant advantages over traditional surgical methods, such as suturing or stapling [1,2].

The aim of this article is to summarize current advancements in laser-assisted tissue repair, assess its benefits and limitations, and outline future research directions that could establish this technology as a standard in surgical practice.

Mechanism of interaction of laser radiation with biological tissues

When the process is exclusively laser-driven (laser tissue welding), it operates through a photothermal mechanism: laser energy induces structural rearrangements in the extracellular matrix components of connective tissue, leading to the formation of fusion bonds between opposing wound margins [3].

Thermal exposure induces unwinding of collagen's triple helices through hydrogen bond cleavage, resulting in denaturation and tissue contraction. Temperatures exceeding 60°C provoke covalent bond dissociation, disrupting the collagen fibers and modifying tissue characteristics, with complete relaxation achieved above 75°C [4,5].

The most common interpretation of the mechanism of operation of laser welding is the unravelling of collagen fibers at the cut ends, followed by intertwining of the fibers (interdigitation) across the cut under the action of laser radiation. As a result, fusion occurs either between the cut ends of collagen fibers or between their parallel edges. Also, new chemical bonds are formed during laser irradiation: formation of new covalent cross-links at the welding site and non-covalent interactions between unwound collagen filaments on both sides of the seam [6,7]. The operating temperature of laser welding is usually in the range of 60-65 °C.

Another effect occurring during laser welding of tissues is complete homogenization of the tissue (also called hyalinosis), in which the loose structure of collagen fibers is completely destroyed. In these cases, the temperature in the weld zone exceeds 75 °C. Denatured collagen and intracellular proteins photocoagulate, acting as endogenous glue (microsoldering) and forming new molecular bonds on cooling [8].

Photothermal soldering is based on the coagulation of protein solder due to a laser-induced temperature rise in the tissue. After cooling, non-covalent interactions between the solder and the collagen matrix in the tissue are responsible for the strength of the weld [9].

The higher the tissue's absorption coefficient, the more pronounced the photothermal effect. However, this also limits the penetration depth of laser radiation, making welding of deeper tissue layers considerably more challenging. Conversely, when tissues have low absorption coefficients, laser radiation can penetrate deeper, but the resulting photothermal effect is weaker, leading to lower tensile strength of the weld.

Laser systems for tissue reconstruction

One of the first lasers to be widely used in surgery is the Neodymium-doped yttrium-aluminum garnet laser (Nd:YAG laser) with a wavelength of λ=1064 nm. This wavelength coincides with the absorption peak of melanin and hemoglobin, giving it a hemostatic effect on soft tissue. At the same time, Nd:YAG laser radiation is poorly absorbed by water, allowing it to penetrate tissue to a depth of more than 5 mm. The benefits of the Nd:YAG laser also include its bactericidal and biostimulating properties. The positive effect of the Nd:YAG laser on cell proliferation and differentiation has also been demonstrated [10,11].

To study Nd:YAG laser tissue welding modes, Li et al. compared three techniques on porcine skin: continuous linear, zigzag, and segmented welding. The segmented method demonstrated superior outcomes, reducing thermal damage through intermittent exposure while preserving tissue regenerative potential. This approach achieved a weld strength of 0.37 MPa, outperforming linear (0.32 MPa) and zigzag methods, which exhibited energy concentration and heterogeneous joint strength, respectively [12].

The study of the effect of the Nd:YAG laser suture temperature on the tensile strength of the suture and the degree of denaturation of the reconstructed tissue showed that the strength of the sutures is maximum at a suture formation temperature close to 55 °C. At a temperature of 65 °C, the degree of protein denaturation becomes too great and the tensile strength of the sutures decreases [13].

The primary advantage of Nd:YAG lasers lies in their ability to penetrate deep into biological tissues. However, excessive energy density may cause uncontrolled thermal damage to surrounding tissues at depth. Consequently, the application of Nd:YAG lasers remains significantly limited in microsurgery and vascular surgery [14].

In contrast, the carbon dioxide laser (CO_2 laser) with a wavelength of λ=10,600 nm has found predominant application in microsurgery fields. This wavelength corresponds to water's peak absorption spectrum. Since water constitutes the primary component of most biological tissues, the laser energy gets predominantly absorbed in superficial tissue layers, with only exponentially diminishing energy available for deeper tissue heating [15].

A CO_2 laser system equipped with a fiber optic radiometer can be used for corneal integrity. Laser light is delivered via an optical fiber located directly over the treatment area. The system incorporates an infrared radiometer to monitor corneal temperature in real time, with the detector capturing thermal radiation from the tissue and transmitting the data to a computer. The laser targets only the superficial layers (less than 0.1 mm), thus avoiding damage to the deeper structures of the eye [16].

The most widely used lasers for soldering biological tissues are diode lasers with various wavelengths. Typically, semiconductor systems are more compact and consume significantly less energy than other laser technologies. The radiation from diode lasers is easily transmitted through fiber-optic delivery systems, which is crucial for applications in endoscopic surgery. However, the use of diode lasers has certain limitations, as their peak output power is significantly lower than that of CO_2 and Nd:YAG lasers. This drawback is minimized through the use of bioorganic solders and dyes that enhance tissue absorption [17].

In vascular surgery, an effective approach is the combination of a diode laser equipped with an optical fiber and a surgical microscope. One of the most commonly used wavelengths is $\lambda = 810 \pm 10$ nm. This wavelength interacts efficiently with indocyanine green (ICG), a cyanine dye incorporated into a chitosan patch. Initially, single pulses (100 J cm^2) were delivered to the tissue, with the fiber pressed firmly against the chitosan patch. Then, the patch was subjected to non-contact continuous-wave irradiation at an intensity of 20 W/cm^2 to ensure full adhesion of the patch to the outer vascular walls [18].

In the medical laser field, 970 nm radiation is widely used, especially for vascular repair. These units are equipped with a diode laser and a precision positioning system including a moving table with coordinate control (x, y, z) and a focusing lens with a fixed working distance of 18 mm, which ensures a stable laser spot diameter of 1.0 mm. The control mechanism is facilitated by a foot switch that incorporates a timer, while the integrated video system, equipped with a zoom function and an IR sensor, enables precise real-time control of the beam position, thereby mitigating the impact of human error. This configuration ensures a high degree of precision with minimal risk of damage to surrounding tissues [19].

To address the limited penetration depth of diode lasers, an intravascular approach was developed, utilizing a quartz fiber with a conical silver mirror to generate 360° ring radiation, delivered via a catheter to the anastomotic site. The procedure involved two sequential irradiation phases: primary soldering (0.41 W, 30 s, 1.52–4.1 W/cm^2) followed by reinforced treatment with additional solder application (0.55 W, 45 s, 2.04–5.5 W/cm^2). This method ensured uniform thermal diffusion across the vessel wall, achieving sutureless anastomotic integrity, as confirmed by histomorphological analysis demonstrating precise coaptation of vascular edges and controlled collagen denaturation within the irradiated zone [20].

Diode lasers with wavelengths in the 1900–1950 nm range are increasingly used in microsurgery because their penetration depth closely matches the thickness of microvessel walls (about 150 μm), enabling precise, solder- and dye-free vascular welding. This wavelength is strongly absorbed by water, resulting in shallow tissue penetration and highly localized thermal effects, which minimizes collateral damage and allows for effective vessel sealing-making it ideal for delicate procedures like microanastomoses in hand surgery [21,22].

One of the most promising laser soldering technologies is the integration of temperature feedback into laser systems. Temperature feedback allows a preset temperature to be maintained in the weld area, preventing overheating and necrosis of the surrounding tissue. The basis of such systems is an infrared bolometric matrix sensor that scans the laser weld area and determines the temperature at the most heated point. The data received is transmitted to a microcontroller which, using a proportional-integral-differential controller, corrects the laser power to maintain the set temperature with high accuracy

(up to 0.5°C). This avoids overheating the tissue and minimizes the thermal damage zone, providing optimal conditions for the formation of a strong and biocompatible joint. This technology is particularly effective in combination with biopolymer nanocomposite solders, as the feedback ensures uniform heating and stable transformation of the liquid dispersion into a solid framework material [23].

A comparison of the main types of laser radiation used in laser reconstruction of biological tissues is presented in Table 1.

Table 1. Comparison of laser systems for tissue reconstruction

Laser type	Wavelength, nm	Penetration depth, mm	Main advantages	Restrictions	Application
Nd:YAG [10-14]	1064	>5	Deep penetration, bactericidal properties	Risk of thermal damage	Dermatology
CO_2 [15,16]	10600	<0.1	High precision, minimal damage to surrounding tissues	Limited depth of penetration	Microsurgery, ophthalmology
Diode (near infrared) [17-20,23]	810-970	1-3	Compactness, safety, low cost	Low capacity	Plastic surgery, nerve repair
Diode [21-22]	1900	0.15	Spot treatment, no solder required	Narrow therapeutic window	Vascular microsurgery

Notes: Nd:YAG, neodymium-doped yttrium-aluminum garnet laser; CO_2, carbon dioxide laser

Materials for optimizing laser tissue reconstruction

The use of bioorganic solders in laser tissue repair significantly increased the strength of welds, reduced thermal necrosis of tissues and accelerated the repair process [23,24].

Blood protein serum albumin is the most widely used as a base for bioorganic solders. In experiments, bovine serum albumin (BSA) [13,25,26] and human serum albumin [24] are most commonly used. Albumin is a class of water-soluble proteins that have a globular structure. Albumin is found in the tissues of almost all animals and plants. Albumin acts as a bacteriostatic coating that simultaneously promotes attachment and proliferation of eukaryotic cells. These properties make albumin a major component of bioorganic solders [27].

In order to focus the laser impact in the incision zone and prevent thermal necrosis of the surrounding non-target tissues, a chromophore that absorbs the wavelength of laser radiation is added to the solder composition. The incorporation of chromophores enables the utilization of a more compact laser apparatus with reduced power, consequently reducing operational and financial expenditures while enhancing safety for the operating surgeon [28].

The most successful combination in laser soldering of biological tissues involves the use of ICG aired with an 810 nm diode laser ICG is a non-toxic fluorescent iodide dye characterized by rapid hepatic clearance. This pairing has gained widespread adoption because the peak absorption wavelength of ICG (800 nm) closely aligns with the laser's emission wavelength (810 nm), ensuring optimal energy absorption and efficient tissue bonding [28-30].

Another effective exogenous chromophore is methylene blue, which exhibits a peak absorption at 670 nm. methylene blue has found extensive use in oncology as a photosensitizer—when activated by laser irradiation, it promotes the destruction of cancer cells [31].

However, chromophores have several limitations: low stability in aqueous solutions, tendency to migrate into surrounding tissues (increasing necrosis risk), and absorption dependency on concentration, pH, and temperature [32]. To enhance stability, they are incorporated into biopolymer matrices such as chitosan. Chitosan films not only immobilize the dye but also promote healing by providing mechanical strength and electrical conductivity. Chitosan is a high-molecular-weight glucose polymer that is water-insoluble. Current research is actively exploring its applications in tissue engineering, gene therapy, and targeted drug delivery. ICG-doped chitosan films are used in laser-assisted end-to-end anastomosis. The anastomosis site is fully wrapped with a chitosan patch, which is then irradiated with a near-infrared laser [33].

An alternative technology to prevent chromophore run off into the surrounding tissue walls is the creation of frameworks based on polycaprolactone (PCL) and ICG by electrospinning. Electrospinning represents a method for the production of fibers in the nano- and micrometer range that is undergoing active development. Electrospinning frameworks find application in targeted drug delivery [34], tissue and cell engineering [35], supporting cell adhesion and the delivery of growth factors, and promoting wound healing [36].

To fabricate the PCL scaffold, PCL was first dissolved in chloroform while ICG was dissolved in methanol. Each solution was stirred for 24 hours to achieve homogeneity. The solutions were then combined to obtain a final ICG concentration of 0.1 wt.%. The soldering scaffolds were produced via electro-spinning. A high voltage was applied to the polymer solution to generate a fluid jet, resulting in the formation of long, thin fibers. During deposition, the solvent evaporated, causing the fiber diameter to significantly decrease from 100 μm to 3-9 μm. The jet was ultimately deposited onto a grounded collector, forming a random non-woven fibrous scaffold. Prior to laser soldering, the fabricated scaffold was soaked in a 40 wt.% BSA solution and air-dried for 15 minutes. The resulting scaffolds were flexible and moderately adhesive, making them suitable for use around vascular anastomoses [36].

Although polymer frameworks have greatly improved the efficiency of laser soldering, when PCL melts under laser irradiation, a significant portion of the chromophore penetrates into healthy tissue, leading to thermal necrosis [37].

The development of research in the field of nanoscale particles has made a significant contribution to the improvement of modern medicine in general, and surgery in particular. Addition of nanoparticles to solder leads to increased absorption of laser radiation by solder, localization of irradiation in the area of weld formation and prevention of thermal damage to surrounding tissues

Encapsulating ICG silicon dioxide (SiO_2) nanoparticles prevented chromophore migration from the repair site into surrounding tissues and increased the tensile strength of welded joints [33]. The porous nanoshells were created by polymerizing silicon around cetyltrimethylammonium bromide micelles. To counteract electrostatic repulsion between negatively charged ICG molecules and the SiO_2 nanoparticle framework, the nanoshells were coated with polyallylamine hydrochloride. The positively charged polyallylamine hydrochloride retains ICG within the pores through electrostatic attraction [38].

Gold nanoparticles are widely used in tissue engineering due to their high absorption capacity, stability in physiological environments, and biochemical versatility[33].Gold nanoparticles were employed to create a nanocomposite solder. Polyethylene glycol-modified gold nanorods were centrifuged in phosphate buffer. Hyaluronic acid was then added to the resulting suspension

to achieve a final concentration of 3 wt.%. The solder mixture was continuously stirred for 48 hours to obtain a homogeneous burgundy paste. The gold nanorod-based solder demonstrated low diffusion through the tissue matrix and highly localized laser energy absorption at the weld site. But it should be taken into account that gold nanoparticles can aggregate in biological fluids, which reduces their photothermal efficiency and consistency of tissue repair [39-42].

The addition of carbon nanotubes (CNT) to solder not only addresses the issue of laser radiation localization in the welding zone but also significantly enhances the tensile strength of welded seams [43]. Carbon nanotubes are actively used in regenerative medicine and diagnostics due to their size, which matches the main components of the cellular matrix, and their properties, which are comparable to protein structures [44]. CNT-based biopolymers exhibit low cytotoxicity and have a positive effect on cell differentiation and proliferation [45-46].

A three-dimensional nanocomposite for tissue integrity restoration was obtained by irradiating a biopolymer dispersion based on BSA and CNT with a pulsed femtosecond laser at a wavelength of λ = 810 nm. To create the nanocomposite, single-walled carbon nanotubes (SWCNT) with an average diameter of 1.4–1.6 nm and a length of 0.3–0.8 μm were used. An aqueous dispersion of SWCNT with a concentration of 0.001 wt.% was mixed with BSA powder until a protein concentration of 25 wt.% was achieved. The mixture was then sonicated in an ultrasonic bath until complete homogenization (for 40–60 minutes). The dispersion was irradiated with an unfocused laser beam. The pulse duration was 140 fs, with a frequency of 80 MHz. The laser output power was set to 2 W [47]. When using laser soldering technology for biological tissues in combination with this nanocomposite dispersion, the restoration strength achieved was 10 times higher than the tensile strength of sutures soldered using a solder based solely on BSA and ICG [23].

A description of the main components of solders used in laser reconstruction of biological tissues is presented in Table 2.

Table 2. Main compounds used in laser tissue reconstruction

Material	Purpose	Advantages	Disadvantages	Examples of applications
BSA [25-27]	Solder base, regeneration promoter	Biocompatibility, accessibility, promotion of cell proliferation	Low strength without additives	Vascular anastomoses, nerve repair
Chitosan [32,33]	Biopolymer matrix for solders	Biodegradability, antibacterial properties, healing promotion	Insoluble in water, requires modification	Anastomosis patches, drug delivery
ICG [28-30]	Chromophore for focusing the laser	High absorption at 800 nm, non-toxic, rapid clearance from the body	Migration into surrounding tissues, low stability	Plastic surgery, wound sealing
Carbon nanotubes [23,43-47]	Enhancing weld strength	High mechanical strength, biocompatibility, regeneration stimulation	Potential cytotoxicity at high doses	Reconstructing connective tissues
Gold nanoparticles [39-42]	Localization of laser action	Stability, high absorption capacity, biological inertness	Aggregation in physiological fluids	Skin reconstruction
Silicon nanoparticles [38]	Carrier for chromophores	Prevent dye migration, increase seam stability and strength	Complexity of synthesis, potential toxicity in case of improper functionalization	Vascular surgery, deep tissue soldering

Notes: BSA, bovine serum albumin; ICG, indocyanine green

Practical application of laser tissue reconstruction technology

The gold standard in vascular anastomosis is the classic suture method, but this method of tissue repair is time-consuming and in many cases is associated with hypoxia and tissue damage, as the supply of oxygenated blood to the operated and surrounding vessels is cut off during suturing. In addition, the effectiveness of microsurgical sutures depends on the skills of the surgeon. Laser methods of vascular repair have an advantage over suturing because they reduce the risk of stenosis, foreign body reaction and inflammation, require less surgical time, are less traumatic to surrounding tissues and limit the thrombogenicity of the anastomosis. Laser soldering provides immediate watertight wound closure [23,48].

Studies on laser-assisted tissue repair were conducted on porcine aortas. The vessels were divided into identical rectangular samples with an area of 3 cm^2 and cleaned of excess connective tissue to achieve a sample thickness of approximately 1 mm. For vascular anastomosis, two samples were pressed firmly together, and a polyetherimide membrane soaked in a solution of BSA (2 wt.%) and ICG (0.002 wt.%) was applied. The membrane was positioned to overlap approximately 10% of the surrounding healthy tissue. The weld was then treated with a diode laser at a wavelength of λ = 810 nm and a temperature of 80°C for 30 seconds [49].

The potential application of laser technologies for gum and oral mucosa restoration is being actively studied. For ex vivo experiments, pig gum tissue and oral soft tissues were used. The tissues were divided into samples with an area of 6 cm^2, and the average sample thickness was 1 mm. A 2 cm long incision was made in the center of each sample. ICG was applied to the incision, followed by exposure to laser radiation at a wavelength of λ = 808 nm. The results demonstrate that the use of an 808 nm diode laser in combination with ICG enables effective laser welding of oral soft tissues. The optimal bonding strength was achieved at an ICG concentration of 9% and a laser power of 4.5 W (10 Hz), with the weld strength comparable to that of conventional suturing. The average surface temperature reached 74 ± 5.4 °C, while the thermal damage zone remained within 333 μm. Histological analysis confirmed the localized thermal effect, indicating minimal collateral tissue damage [50].

Peripheral nerve injuries are one of the most common consequences of motor vehicle accidents and work-related injuries, resulting in sensory and motor impairment. Despite the advances made in neurosurgery over the last 10 years, effective reconstruction of peripheral nerve injuries is still a major challenge in regenerative medicine. A comparison of sciatic nerve repair using traditional needle-and-thread sutures versus an 810 nm diode laser (500 mW) with a protein solder based on 25 wt.% ICG and 62 wt.% BSA showed that the average operation time was significantly shorter in the laser repair group compared to the suture group. Electromyography revealed no differences between the experimental groups. However, the sciatic nerve function index was significantly better in the laser-repaired nerves compared to sutured nerves after 12 weeks. Histological evaluation showed no difference in inflammatory processes between the groups but demonstrated faster and more effective restoration of the peripheral nerve outer layer (epineurium) following laser repair compared to the suture method [51].

The most dangerous postoperative complication in thoracic surgery is alveolar air leaks. However, there is still no optimal method for eliminating

leaks. Laser soldering enables the formation of airtight seams, overcoming the limitations of traditional suturing. For lung sealing, a semiconductor pulsed diode laser with a wavelength of 808 nm was used in combination with a semi-solid solder based on 50 wt.% BSA and 0.1 wt.% ICG. In vivo studies were conducted on 14 pigs, where two types of lung injuries were created: a linear incision and a circular incision. The protein solder was applied to the incision site and irradiated with the laser. In all cases of laser repair (except for two requiring repeat closure), no postoperative air leaks were detected. By the seventh day, all animals showed complete healing of the lung lesions with fibrous scar formation and only minor inflammatory reaction in the adjacent lung tissue [52].

Due to its ability to rapidly provide tight wound closure, laser soldering is suitable for leak prevention in gastrointestinal surgical treatment. A gold-based nanocomposite solder (Au nanorods) and collagen at a wavelength of 800 nm was used for laser soldering. The pulsed mode of laser sealing with a pulse duration of 130 fs and an interval of 12.5 ns ensures minimal heating of adjacent tissues, which prevents thermal damage. As a result, the suture strength reaches 42% of the natural tissue strength, and the tightness is 64% of the physiologic norm [53].

One of the most promising applications of laser-assisted tissue repair is in plastic surgery, as laser soldering enables precise suture formation without scar formation. Studies, including experimental work on rats, have demonstrated that laser-assisted edge joining using solder composed of BSA, ICG, and SWCNT results in significantly less noticeable scarring. For instance, Scar assessment scale evaluation on postoperative day 21 showed only 1 point for the laser method compared to 4 points for conventional sutures. Laser treatment stimulates healing processes, as confirmed by histological data: experimental groups exhibited earlier appearance of hair follicles and reduced inflammatory infiltration compared to control groups [54].

Discussion

Improvement of laser systems, aimed at the introduction of temperature feedback, providing precise control of tissue heating (up to 0.5 °C) and minimizing thermal damage. Integration of Proportional–integral–derivative controller and infrared sensors allows to optimize the soldering process safety and efficiency of the technique.

To increase the strength of laser repair and enhance the proliferative properties of repaired tissues, new generation biocomposite solders include albumin, collagen, carbon nanotubes and nanoparticles (gold, SiO_2). These materials not only increase connection strength (up to 4±0.4 MPa), but also stimulate tissue regeneration, shortening healing time. Innovative approaches, such as encapsulation of dyes in nanoparticles or polymer matrices, solve the problem of chromophore migration and reduce the risk of necrosis of surrounding tissues.

At this stage of development, laser reconstruction is moving towards personalized solutions, including the selection of laser parameters and solder composition for different tissue types. This trend is supported by the development of machine learning to predict weld strength and optimize exposure modes [55].

Despite the successes, challenges remain, such as standardization of techniques, ensuring long-term stability of compounds, and scaling of technologies for mass clinical application. Further research should focus

on: in-depth study of molecular mechanisms of regeneration under laser exposure, development of universal biosimilars with programmable properties, and multicenter clinical trials.

Conclusion

Contemporary technologies of laser restoration of biological tissues demonstrate rapid development, opening new perspectives for reconstructive and plastic surgery.

Laser reconstruction of tissue is bringing the era of sutureless surgery closer, where precision, minimal invasiveness and aesthetics are becoming the standard. Already transforming approaches to wound care and reconstructive surgery, this technology may become the gold standard in plastic and microsurgery in the near future.

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REVIEW

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The potential possibility of nonlinear recurrence methods application for posttraumatic stress disorder investigation

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ABSTRACT

This article describes methods of nonlinear physics related to recurrent analysis that may be useful in studying the effect of posttraumatic stress disorder on sleep disorders. Traditional pharmacological and psychotherapeutic approaches widely used to treat post-traumatic stress disorder require long-term and painstaking work, combining the joint efforts of clinical specialists and the patient. The versatility and variability of the clinical picture of this disease makes the diagnosis and treatment of post-traumatic stress disorder syndromes particularly difficult. In particular, only in International Classification of Diseases 11th Revision was complex post-traumatic stress disorder isolated from the general group of dissociative disorders. However, one of the few unifying characteristics for such patients is significant disruption of night sleep. Currently, mathematical methods, pumped from nonlinear physics, are often used to analyze physiological signals and assess the condition of patients with various diseases, including depression, chronic migraines, and apnea syndrome. However, recurrent analysis has not been used to date in the study of post-traumatic stress disorder. We are confident, based on the successful application of this method to the study of patients with migraines, orthodontic disorders, and sleep disorders, that this is a major omission and scientists

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working on the problem of post-traumatic stress disorder should pay close attention to the methods proposed in this article for a comprehensive study of the problem. Careful application of the proposed methods will undoubtedly contribute to the study of the effect of various psychiatric diseases on sleep, including posttraumatic stress disorder, and will help to develop more advanced methods of gentle rehabilitation.

Key Words: sleep, polysomnography, nonlinear dynamics, physiological signals, recurrent analysis

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Introduction

Today, diagnoses such as post-traumatic stress disorder (PTSD) and/or complex post-traumatic stress disorder (cPTSD) are more relevant than ever in therapy, neurology and psychiatry, in light of the current global political and social situation. PTSD is a mental illness that significantly affects the quality of life of people suffering from it. It is described as a complex of symptoms caused by anxiety that occurs after a traumatic event. Simple post-traumatic disorder becomes complex when an individual, in addition to other post-traumatic symptoms, experiences self-devaluation [1]. PTSD affects many biological systems, such as brain activity cycles and neurochemical reactions, as well as cellular, immune, endocrine and metabolic functions. In the general human population the overall prevalence of these disorders is 1-15%, and among those wounded in military operations [2], the percentage increases to 20-30% [3], and in psychiatric institutions, the prevalence of PTSD can reach 50% [4]. Patients suffering from PTSD are at increased risk of suicide attempts [5, 6] and are more likely to experience difficulties in social relationships [7]. Currently, mathematical methods, pumped from nonlinear physics, are often used to analyze physiological signals and assess the condition of patients with various diseases, including depression, chronic migraines, and apnea syndrome. However, recurrent analysis has not been used to date in the study of PTSD. We are confident, based on the successful application of this method to the study of patients with migraines, orthodontic disorders, and sleep disorders, that this is a major omission and scientists working on the problem of PTSD should pay close attention to the methods proposed in this article for a comprehensive study of the problem.

Various events, such as hospitalization and medical procedures to which a person is subjected, such as non-invasive ventilation, can predispose to the occurrence of these pathologies [8]. In addition, this disorder is very common among military and civilians affected by counter-terrorism operations, military actions and/or other forms of violence, in the context of which it was identified as a separate diagnosis [3, 9]. Moreover, in the context of the COVID-19 pandemic, this disorder has spread among medical and social workers who have borne the brunt of anti-epidemic measures [10]. Traditional pharmacological and psychotherapeutic approaches widely used to treat PTSD require long-term and painstaking work, combining the joint efforts of clinical specialists and the patient. The versatility and variability of the clinical picture of this disease makes the diagnosis and treatment of PTSD syndromes particularly difficult. In particular, only in International Classification of Diseases 11th Revision (ICD

11) was cPTSD isolated from the general group of dissociative disorders [11]. However, one of the few unifying characteristics for such patients is significant disruption of night sleep [12].

Sleep is one of the points of attraction in interdisciplinary neuroscience and branches of fundamental medicine, from neuro- and psychophysiology to therapy. The quality and duration of sleep directly affect immunity, the preservation of cognitive functions and, in general, the maintenance of normal vital functions of the body [13]. Studies of electrophysiological signals of brain activity, the cardiovascular system and other functional systems during sleep are a powerful direction in the development of neuroscience, where methods of nonlinear dynamics are increasingly used for data processing. For example, today mathematical modeling of the interaction of the respiratory, cardiovascular and central nervous systems phenomenologically demonstrates the development of destructive processes associated with an increase in blood pressure [14] and the occurrence of cognitive impairment in obstructive sleep apnea syndromes [15, 16]. Moreover, studies of the features of oscillatory activity in the microstructure of night sleep make it possible to observe early markers of the development of neurodegenerative diseases [17-19], mental disorders [20, 21] and some somatic disorders [22, 23].

At the same time, the objective map of nocturnal sleep disorders from the point of view of polysomnography (PSG) is still covered with a large number of blank spots. Research aimed at establishing the relationship between sleep and PTSD is at an early stage. An empirically substantiated theory and mathematical model of this relationship have not yet been created, but this relationship is very strong [12, 24]. Today, studies of sleep disorders in PTSD include an analysis of the prevalence of sleep onset disorders, the frequency of nightmares, the content of nightmares, disorders in the paradoxical stage of rapid eye movement (REM) sleep (in particular, the development of motor disorders associated with increased muscle tone), changes in the threshold of arousal during sleep, motor disorders and respiratory failure during sleep [25]. Apparently, the emphasis on the treatment of nocturnal sleep disorders in PTSD and cPTSD is a beneficial strategy for psychotherapeutic care in these patients, or, in other words, treating nocturnal sleep problems alone also leads to an improvement in the general condition in PTSD [26].

Thus, the role of sleep restoration and control in PTSD is difficult to overestimate, and this is an important area for further elucidation of the factors of disease development and treatment of patients with this diagnosis. In addition, testing under PSG control of the proposed algorithm for physiotherapeutic treatment of sleep disorders based on the analysis and control of biophysical characteristics of signals of functional activity of the body will provide new fundamental data on some aspects of sleep development itself, as a unique phenomenon that unites various classes of living systems.

The paper examines the issue of how correct it is to use nonlinear dynamics methods such as recurrent transformations to diagnose changes occurring during sleep in patients with PTSD and cPTSD in comparison with the conventionally normal sleep of an adult. The study of physiological processes of night sleep in health and pathologies using information technologies attracts the attention of researchers both from the standpoint of assessing its general necessity and the possibility of reducing this time, which is unproductive from an economic and social point of view [27, 28]. On the other hand, broad prospects for the treatment and prevention of diseases are potentially opening up for clinical practice in connection with recent studies that have closely linked the sleep of a living system with the normal functioning of the immune system [29]. Moreover, fluctuations in the permeability of the blood-brain barrier (BBB)

that occur during night sleep in both animals and humans, identified in recent years, give hope for significant advances in neurorehabilitation technologies based on high-tech sleep analysis in real time [30, 31].

Characteristics of the relationship between sleep disorders and PTSD

Since the beginning of the 20th century, the number of different types and the total number of nocturnal sleep disorders has been constantly increasing. Such dynamics are caused by the increase in light pollution in cities and, in general, opportunities to "distract" from sleep, and, at the same time, by the growth in the power and number of stress factors in the social organization of modern urban life, which destroy the normal ability to have a full night's sleep and the normal sleep structure [32]. Despite a significant number of ongoing studies, there is still no unified understanding of such narrow points as, in particular, the relationship between the states of cognitive functions and sleep structure [33, 34], sleep in chronic pain [35], sleep disorders, primary and concomitant with other diseases in patients [36, 37]. In particular, an example of such a lack of complete clarity of the relationship between general pathologies and sleep disorders is PTSD.

Although the full understanding of the pathophysiological mechanisms underlying distress remains incomplete, it is generally recognized that key mediators in stress-related disorders involve the activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to glucocorticoid release, and the sympathoadrenal (SA) system, responsible for the secretion of adrenaline and noradrenaline. Different stressors impact the HPA and SA systems in varying ways, and the intensity and outcome of these responses are determined by the overall homeostatic state of the organism - shaped by genetic factors, internal and external environmental conditions, and the regulatory programming of glucocorticoids, biogenic amines, and other bioactive substances [38, 39].

Beyond the well-established HPA axis activation in response to stressors, research has identified that proinflammatory cytokines - such as interleukin-1, tumor necrosis factor, and interleukin-6 - can also stimulate the hypothalamus, contributing to the stress response [40]. Interestingly, the development of PTSD, particularly with severe clinical manifestations, is often accompanied by reduced cortisol levels in the acute aftermath of trauma [41–44]. Furthermore, this reduction in circulating glucocorticoids is currently viewed as a potential objective biomarker for the onset of PTSD [45, 46]. In other words, PTSD symptoms apparently correlate with those arising as a result of uncontrolled growth of proinflammatory factors, in particular glucocorticoids, caused by a distressing situation. Glucocorticoid receptors are found in almost all nuclear cells, but the density of glucocorticoid receptors is especially high in the brain, in particular in the hippocampus [47]. Within the framework of PTSD pathogenesis, the emerging neuroinflammation has the character of a pathological uncontrolled chronic process. It is possible that there is positive feedback between the chronicity of such neuroinflammatory processes in different areas of the brain and the occurrence of disturbances in the normal permeability of the BBB [48]. It is important to note that current data regarding the direct impact of stress on the BBB remain inconsistent. For instance, P. Esposito et al. reported that acute immobilization stress in rats led to increased BBB permeability in the diencephalon and cerebellum, while no such changes were observed in the cerebral cortex [49]. Conversely, M. Roszkowski et al., after applying various acute and chronic stress models in mice, did not observe any significant alterations in BBB permeability [50].

In individuals diagnosed with PTSD - as well as in those with schizophrenia and depression – both structural and functional disruptions have been identified in neural pathways linking the hippocampus and prefrontal cortex [51]. Moreover, it has been established that the prefrontal cortex, hippocampus, amygdala, locus coeruleus, and several other brain regions play key roles in the development and persistence of pathological anxiety [52, 53], and are also critically involved in the pathogenesis of depression [54]. At the same time, the locus coeruleus is one of the leading centers of the central nervous system regulating sleep and wakefulness processes. Not least, the sleep disorders observed in PTSD may be associated with neuroinflammatory processes, including in this area of the brain [52].

At the same time, not many works are devoted directly to a full analysis of polysomnographic studies of PTSD patients. This space of the scientific map still shows many blank spots. However, it is already obvious that lack of sleep, disturbances in its structure and microstructure lead to further chronization of problems with consolidation of traumatic memories and an increase in the general level of anxiety of the patient [55]. Interestingly, sleep disruption immediately after, as well as prior to trauma exposure could both increase the risk of PTSD development, suggesting a perpetual circle with pre-existing sleep disturbances increasing the risk for PTSD and vice versa [56-60]. Posttraumatic sleep and circadian disruptions, in turn, affect the neuroendocrine, immune and autonomic systems, leading to impaired adaptive mechanisms, increased sensitivity to stress, and thus may be a cause or at least a powerful factor in the development of stress-related disorders and PTSD in particular [59, 60, 61]. Thus, assessment of sleep quality and circadian patterns should be a priority in the routine clinical assessment of individuals exposed to distress factors and trauma.

Repantis et al. suggest a potentially important role for objective PSG monitoring of sleep stages in individuals in acute distress on the first night after trauma [62]. Identification of objective sleep-related functional parameters in trauma using easily applicable electroencephalography (EEG) devices may improve the ability to correctly predict the potential development of PTSD and guide the way to new sleep interventions to prevent PTSD. In addition, the authors suggest a potential role for modulatory interventions during REM sleep in the prevention of PTSD, such as behavioral sleep deprivation and selective pharmacological (e.g., serotonergic, noradrenergic, cholinergic) suppression or enhancement of REM sleep. Moreover, there is work devoted to the disruption of normal chronorhythms of the body due to acute distress and the occurrence of PTSD, for example, there is evidence that sleep and circadian disruption may represent a vital pre-existing risk factor in the prediction of PTSD development and circadian dysregulation after trauma exposure may represent a core feature of trauma-related disorders mediating enduring neurobiological correlates of traumatic stress through a loss of the temporal order at different organizational levels [60, 63].

At the same time, classical PSG analysis requires specific equipment, premises and an expert – a somnologist, which makes these studies a very expensive and complex procedure. An alternative to classical PSG analysis can be provided by the development of automatic systems based on information technologies using methods of nonlinear physics, artificial intelligence and machine learning, allowing to recognize various stages of sleep and determine pathological changes in the microoscillatory structure of sleep without the participation of a clinical specialist. Good prospects for the development of realistic systems of such analysis are provided by methods of recurrent analysis.

Classical recurrent analysis in problems of polysomnography data processing

Currently, neuroscience uses a large number of nonlinear dynamics methods for processing physiological signals. One of the simplest and most versatile is recurrent analysis, which allows one to establish relationships and correlations between signals in complex distributed systems [64]. Recurrent analysis can be used for both stationary signals and chaotic or noisy signals. In particular, recurrent analysis allows one to identify similar structures in various signals, including EEG, electrocardiography (ECG), and photoplethysmogram (PPG) signals, which form the basis of the PSG recording [65, 66]. It is well suited for processing night sleep data and identifying anomalies in sleep structure, since it is focused on identifying relationships between different signals [67]. Various modifications of the basic analysis and calculation of accompanying metrics make this method very versatile.

The implementation of recurrent analysis is quite simple from a mathematical point of view. The first step is to construct a recurrent matrix, each element of which is determined by the following formula [66]:

$$RP_{i,j} = \Theta\left(\varepsilon - \left|x_i - x_j\right|\right), \quad i,j \in 1,\ldots,N \tag{1}$$

Where RP – recurrent rate, ε is neighborhood of the time series value under consideration, determined empirically, x_i and x_j are the elements of the data series with the corresponding times i and j, N is the number of elements of the series, Θ is the Heaviside function, which results in 0 if the argument is negative and 1 if it is non-negative [66]:

$$\Theta(z) = \begin{cases} 0, if\ z < 0 \\ 1, if\ z \geq 0 \end{cases} \tag{2}$$

Based on this formula, we can obtain a recurrent matrix consisting of zeros

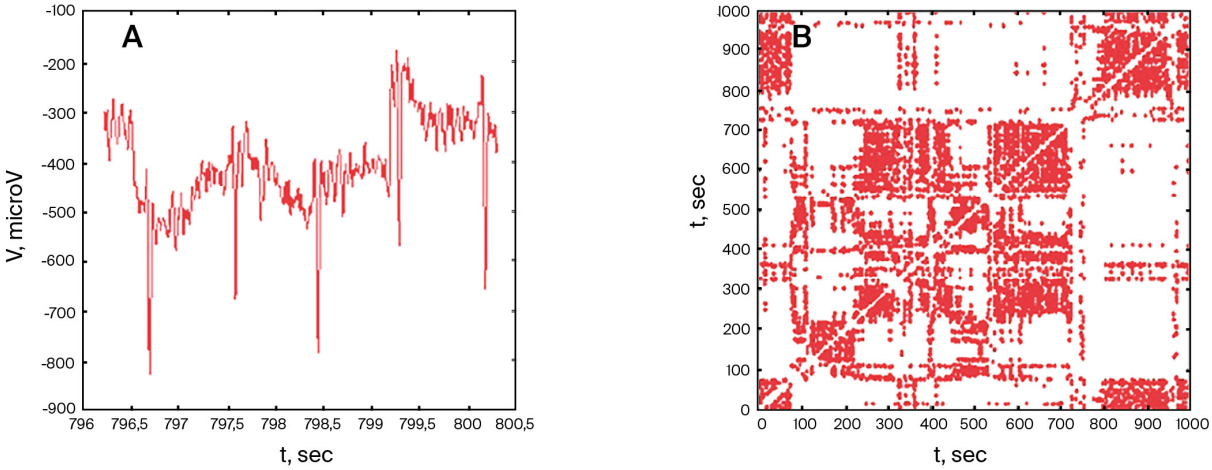
$$\mathbf{R}^X = \begin{array}{c} \\ i-1 \\ i \\ i+1 \\ j-1 \\ j \\ j+1 \end{array} \begin{array}{c} \begin{array}{ccccccc} i-1 & i & i+1 & & j-1 & j & j+1 \end{array} \\ \begin{pmatrix} 1 & \vdots & & & \vdots & 0 & \vdots \\ \vdots & 1 & \vdots & \cdots & 0 & 1 & 0 \\ & \vdots & 1 & & \vdots & 0 & \vdots \\ \vdots & 0 & \vdots & & 1 & \vdots & \\ 0 & 1 & 0 & \cdots & \vdots & 1 & \vdots \\ \vdots & 0 & \vdots & & & \vdots & 1 \end{pmatrix} \end{array}$$

and ones, which has the following form, shown in Figure 1.

FIG. 1. General form of a recurrent matrix

In Figure 1, we can see that each nonzero element with the number i,j or j, i corresponds to the case when the distance between the elements x_i and x_j is less than ε, or, in other words, the element x_j is in the given ε-neighborhood of the element x_i. From the obtained recurrent matrix, we can obtain a recurrent

diagram by coloring all the points with the moments of time that coincide with the numbers of nonzero elements in the matrix and additionally excluding the main diagonal from consideration, since it will always be filled with ones [66]. An example of such a diagram for a short fragment of the EEG recording of one of the experiments with sleep recording is shown in Figure 2. Time is plotted



on both axes of the obtained diagram, which increases to the right and upward.

FIG. 2. Electroencephalography signal recorded during sleep (A) and its corresponding recurrence diagram (B)

The most important parameter when using recurrent analysis is the size of the ε-neighborhood, for this reason its selection is approached with special attention. If the ε-neighborhood is too small, then the number of ones in the recurrent matrix may be very small or may not be there at all, then it is impossible to learn anything about the dynamics of the system under consideration. On the other hand, if the ε-neighborhood is too large, then most of the time implementation points will be included in the neighborhood of each of the points under consideration, thus the recurrent matrix will be filled mainly with ones, which again leads to low information content when studying the system due to a large number of artifacts. It is also necessary to take into account the influence of noise, which can distort the structure of the recurrent diagram. Thus, there is a problem of adequately choosing the size of the ε-neighborhood for the systems under study.

The literature suggests various empirical methods for selecting the ε-neighborhood value, depending on the type of system being studied. The ε-neighborhood can be selected depending on the maximum diameter of the phase space, the density of points in the recurrence diagram, and the signal-to-noise ratio [67, 68]. There are no objective criteria that would allow one to always universally select the ε-neighborhood value for any system being studied, and therefore the choice of the method for determining ε often changes for each individual system. When working with PSG records, the value of the ε parameter was calculated empirically so that the density of points on the recurrence diagram was about 1% (in accordance with N Marwan et al.) for the vast majority of EEG, ECG, or PPG signals being studied [66].

In recurrence diagrams, structures of different types can be observed depending on the system under consideration. In total, eight main patterns can

be observed in recurrence diagrams [69]:

- Uniform filling of the recurrence diagram with points. Such a structure is typical for stationary systems whose relaxation time is small compared to the time covered by the recurrence diagram.
- Periodic structures. They are characteristic of systems with periodicity. In particular, for single-frequency signals, the recurrent diagram will look like a lattice of diagonal lines, the lattice period will correspond to the oscillation period. For multi-frequency signals, the recurrent diagram will be obtained from the superposition of lattices of different periods, corresponding to each of the signal frequencies, due to which a more complex, but still periodically repeating structure can be obtained.
- A gradual decrease in the number of points on a recurrence diagram with distance from the main diagonal, attenuation in the upper left and lower right corners can be observed in systems with variable parameters, that is, in non-stationary ones.
- White areas or stripes are a signal that the system is experiencing sudden changes in the system dynamics that differ greatly from the average time implementation.
- Isolated points can be observed in the presence of significant fluctuations in the system or when considering an uncorrelated random process.
- Diagonal lines parallel to the main diagonal are characteristic of systems whose evolution is the same in different periods.
- Diagonal lines perpendicular to the main diagonal are observed in systems in which evolution is the same, but in reverse time.
- Vertical and horizontal lines are observed when the system does not change over time or changes very slowly, and are also an indicator of a laminar process in the system.

In addition, there are a number of recurrence analysis measures, some of which are based on counting the number of diagonal lines, and some are associated with counting vertical lines.

Measures of recurrence analysis based on diagonal lines

The ratio of recurrence points that form diagonal structures (of at least length l_{min} – threshold of lines that are formed by the tangential movement) to all recurrence points [66]:

$$DET = \frac{\sum_{l=l_{min}}^{N} lP(l)}{\sum_{l=1}^{N} lP(l)} \quad (3)$$

is introduced as a measure of determinism (DET) (or predictability) of the system. Where $P(l)$ (in general it also depends on) – is a diagram of diagonal lines of length l: [66]:

$$P(l) = \sum_{i,j=1}^{N}\left(1 - R_{i-1,j-1}(\varepsilon)\right) \left(1 - R_{i+1,j+1}(\varepsilon)\right)\prod_{k=0}^{l-1} R_{i+k,j+k}(\varepsilon) \quad (4)$$

The average line length of diagonal lines (L) which means that the attractor trajectories in the phase space remain close for a long time, relative to the other side, can be determined by the formula [67]

$$L = \frac{\sum_{l=l_{min}}^{N} lP(l)}{\sum_{l=l_{min}}^{N} P(l)} \quad (5)$$

The REM measure indicates how quickly the trajectory segments diverge and is related to the exponential divergence of the phase space trajectory [66]:

$$DIV = {}^{1}\Big/_{max\left([l_i]_{i=1}^{N_l}\right)} \quad (6)$$

For demonstrate complexity of the recurrence diagram with respect to the diagonal lines use are quantitative measurements of the entropic characteristics of systems, in particular, those related to Shannon entropy (ENTR), as $p(l) = P(l)/N_l$, that haw follow view

To demonstrate the complexity of the recurrence diagram with respect to the diagonal lines, quantitative measurements of the entropic characteristics of systems are used, in particular, those related to ENTR, as $p(l) = P(l)/N_l$, which follows from the representation [66]:

$$\mathrm{ENTR}=-\sum_{l=l_{min}}^{N} p(l)\ \ln\ p(l), \quad (7)$$

Recurrence Analysis Measures Based on Vertical Lines

Laminarity (LAM) is calculated in a similar way to DET [66],

$$LAM = \frac{\sum_{v=v_{min}}^{N} vP(v)}{\sum_{v=1}^{N} vP(v)} \quad (8)$$

This measure demonstrates the frequency of occurrence of laminar structures in the system. Here $P(v)$ - total number of vertical lines of length v in a recurrence diagram [66]

$$P(v) = \sum_{i,j=1}^{N}\left(1 - R_{i,j}\right)\left(1 - R_{i,j+v}\right)\prod_{k=0}^{v-1} R_{i,j+k} \quad (9)$$

In addition, the metrics of trapping time (TT) and length of the longest vertical line (v_{max}) are often used, which are calculated as [66]

$$TT = \frac{\sum_{v=v_{min}}^{N} vP(v)}{\sum_{v=v_{min}}^{N} P(v)},\ v_{max} = max\left([v_i]_{i=1}^{N_v}\right), \quad (10)$$

TT also called the capture time. This metric estimates the average time the system will stay in a certain state. Unlike measures based on diagonal lines, these measures are able to detect «chaos-to-chaos» transitions. Therefore, they allow one to study intermittency even for rather short and non-stationary data series [66].

Applied Application of Recurrent Analysis Methods in Sleep Research Problems

Thus, we can conclude that recurrent diagrams allow us to quite fully and deeply study the dynamics of systems of the most diverse nature. As practice shows, even such simple measures can help in studying the dynamics of sleep. For example, the Emelyanova et al. article shows that sleep stages are

characterized by different values of the recurrent indicator [70]. The metric of the recurrent indicator is one of the main ones and is the sum of all non-zero elements in the recurrent matrix [66]:

$$RR = \sum_{i=1}^{N} \sum_{j=1}^{N} R_{i,j} \quad (11)$$

For REM sleep stages, the recurrent index increases, while for slow sleep stages 3 and 4, the recurrent index decreases significantly. For slow sleep stages 1 and 2, the index remains normal, i.e., on average, it corresponds to wakefulness. These simple patterns not only help to create a mathematically simple algorithm for automatic hypnogram marking, but also to conduct more in-depth studies of various sleep disorders. For example, with a high apnea/hypopnea index, significant changes in the dynamics of recurrent indices during the night are noticeable for different sleep stages [71].

Statistical analysis of changes in recurrent indicators can be a powerful tool for finding sleep disorders caused by various problems, including PTSD. Thus, based on the median and average value, using modern machine learning methods, it is possible to identify groups with normal sleep and with sleep-disordered breathing [72]. Such methods can be used both for early diagnosis of the disorder and for monitoring the rehabilitation process.

An equally important method of processing physiological signals using recurrent analysis is the use of joint recurrent indices and cross-recurrent indices. For signals $x(t)$ and $y(t)$, the values of which are known at the same moments of time t_i, where $i = 1, ..., n$, the cross-recurrent rate (CRR) can be found using the formula [66]:

$$CRR = \frac{1}{N^2} \sum_{j=1}^{N} \sum_{i=1}^{N} \theta(\varepsilon - ||\mathrm{y}(t_i) - \mathrm{x}(t_j)||), \quad (12)$$

The formula for finding the joint recurrent rate (JRR) is slightly different [66]:

$$JRR = \frac{1}{N^2} \sum_{j=1}^{N} \sum_{i=1}^{N} \theta(\varepsilon - ||\mathrm{x}(t_i) - \mathrm{x}(t_j)||) \quad (13)$$

$$\theta(\varepsilon - ||\mathrm{y}(t_i) - \mathrm{y}(t_j)||) ,$$

The CRR and JRR indicators have fundamentally different meanings. Thus, the value of the CRR increases if at times t_i and t_j the values of the two signals are in the same ε-neighborhood. For the value of the JRR to increase, it is necessary that the pairs of signal values $(\mathrm{x}(t_i), \mathrm{x}(t_j))$ and $(\mathrm{y}(t_i), \mathrm{y}(t_j))$ be close (within the ε-neighborhood). In this case, the values of the signals $\mathrm{x}(t_i)$ and $\mathrm{y}(t_i)$ may differ greatly from each other.

These indices can be used simultaneously to compare the dynamics of physiological signals to determine the degree and objective characteristics of sleep disturbance. It can be expected that the CRR will show the degree of complete synchronization of signals when their values, taking into account the normalizations, coincide. Whereas the JRR will allow us to detect deeper connections between signals when both signals simultaneously change their dynamics.

The calculation of JRR and CRR is especially useful for comparing several channels with each other. However, there is also a modification of the JRR method that estimates the number of repetitions in one channel during identical events. For cognitive tests, this method works similarly to the idea of constructing evoked potentials [73].

In this case, identical types of events are compared with each other and the average JRR is calculated. In the case of PSG processing, sleep stages can be

used as identical events, calculating the average index for each. This will allow us to estimate the number of returns for each channel for each sleep stage. At the same time, a high value of the index, as a rule, indicates the presence of stable patterns in physiological signals. Thus, the use of this method for patients with PTSD will allow us to consider how and in which channels the destruction of habitual sleep patterns occurs first.

Conclusion

This article describes methods of nonlinear physics related to recurrent analysis that may be useful in studying the impact of PTSD on sleep disorders. Currently, mathematical methods, pumped from nonlinear physics, are often used to analyze physiological signals and assess the condition of patients with various diseases, including depression, chronic migraines, and apnea syndrome. However, recurrent analysis has not been used to date in the study of PTSD. We are confident, based on the successful application of this method to the study of patients with migraines, orthodontic disorders, and sleep disorders, that this is a major omission and scientists working on the problem of PTSD should pay close attention to the methods proposed in this article for a comprehensive study of the problem. The proposed methods are very flexible and allow one to evaluate both the overall dynamics of polysomnographic data and to identify sleep stages, consider their changes in case of serious circadian rhythm disturbance, and determine the degree of destruction of normal sleep patterns. Methods based on recurrent analysis are usually not associated with complex mathematics and do not require much time for calculations, unlike frequency methods. The methods are flexible enough to conduct simultaneous analysis of the entire PSG record, including EEG, ECG, and PPG. Careful application of the proposed methods will undoubtedly contribute to the study of the effects of PTSD on sleep and will help to develop more advanced methods of gentle rehabilitation.

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REVIEW

Strategies for the development of photosensitizers

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ABSTRACT

Conventional photosensitizing agents have inherent limitations regarding their effectiveness, selectivity, and potential adverse effects, which can hinder their clinical application in oncological practices. This study delves into innovative strategies aimed at the development of advanced photosensitizers that promise improved performance for clinical use. We present a comprehensive analysis of a range of molecules with diverse chemical structures, including novel nanomaterials and conjugated systems. These compounds demonstrate remarkable photostability and possess a high capacity for selectively targeting tumor tissues, which is crucial for enhancing therapeutic outcomes. In addition to discussing the improved properties of these next-generation photosensitizers, we provide an in-depth examination of their mechanisms of action, highlighting how they induce cytotoxic effects in cancer cells while minimizing harm to adjacent healthy tissues. The potential toxicity of these compounds has been scrutinized, considering both acute and long-term effects, with a focus on strategies to mitigate adverse side effects. Our research advocates for the importance of continued investigation into the development and optimization of photosensitizers, emphasizing their multi-disciplinary applications. By integrating insights from chemistry, pharmacology, and oncology, we aim to increase the overall effectiveness of photodynamic therapy. Furthermore, we explore the potential of these agents to extend their applicability beyond traditional treatment settings, suggesting their integration with other therapeutic modalities, such as chemotherapy and radiotherapy, which could lead to synergistic effects and significantly improve patient outcomes in cancer treatment.

Keywords: porphyrins, synthesis, reactive oxygen species, photodynamic therapy

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Introduction

Conventional photodynamic therapy (PDT) has been widely accepted and supported by numerous medical organizations all over the world [1]. This treatment is based on the unique ability of certain substances, known as photosensitizers (PS), to specifically accumulate in target tissues. When these tissues are exposed to light at a wavelength appropriate to PS, the cells start to generate reactive oxygen species (ROS) and other powerful radicals and leads to the process of necrosis or apoptosis [2]. This process also triggers an immune response, causing localized inflammation and changes in blood vessels permeability in the affected area [1].

The evolution and implementation of PDT as a treatment for various pathologies presents a significant challenge, primarily due to the complexity involved in developing effective pharmaceutical agents [1,4]. Despite the limitations of the first generation of photosensitizing drugs, novel compounds have been developed, although many of them have failed in clinical trials [5,6]. However, there has been an increasing emphasis on the development of soluble forms of PS These not only reduce the time needed for administration but also simplify the treatment planning process. There is a particular focus on developing novel targeted delivery systems for PS, such as nanoparticles and monoclonal antibodies (mAb). Some of these PS are being investigated for use in intraoperative photodynamic imaging, where they could be used to visualize tumors during surgical procedures. The development of newer generations of photosensitive drugs with specific physicochemical properties presents the possibility of their use in therapeutic applications that combine imaging and treatment methods in the field of oncology [5,6].

The objective of this review article is to systematically explore the development of advanced photosensitizers that overcome the limitations of conventional agents in terms of effectiveness, selectivity, and potential adverse effects, which can restrict their clinical application in oncology.

Porphyrin-based compounds for photodynamic therapy

Porphyrin-based compounds hold significant promise for PDT. These compounds, with their tetrapyrrole structure, are actively being investigated and integrated into clinical practice [1]. Over the past several decades, porphyrins have been extensively studied for their application as agents in PDT. A significant breakthrough occurred in 1942 when it was observed that hematoporphyrin (Hp) accumulates selectively in tumor tissues [7]. Further research has validated the specific effects that porphyrins have on cancer cells [8,9]. The mechanism behind this selective accumulation can be partly attributed to low-density lipoprotein (LDL) receptors, which are highly expressed in rapidly proliferating tumor cells. The lipophilic nature of porphyrins allows them to bind to the LDL receptor's core, which is structured for apolipoprotein B, facilitating their entry into the cell [10]. Research indicates that tumor cells generally exhibit a lower pH level, typically ranging from 5.85 to 7.68, in contrast to normal tissues that usually have a pH between 7.0 and 8.0 [10]. The porphyrin molecule maintains a delicate equilibrium between protonation and deprotonation, which enables porphyrins to passively diffuse through cell membranes. This diffusion process becomes increasingly effective as the pH decreases. Consequently, a drop in pH contributes to a higher accumulation of porphyrins specifically within tumor tissues. In a tumor with a pH of 6.5, approximately 44% of the porphyrins are in a neutral state, compared to only about 3% in healthy tissue with a pH of 7.4. Neutral molecules are better able to pass through cell membranes than

charged ones, emphasizing the importance of pH in maintaining the presence of porphyrin-protein conjugates within cells and affecting their concentrations in tumors (Fig. 1).

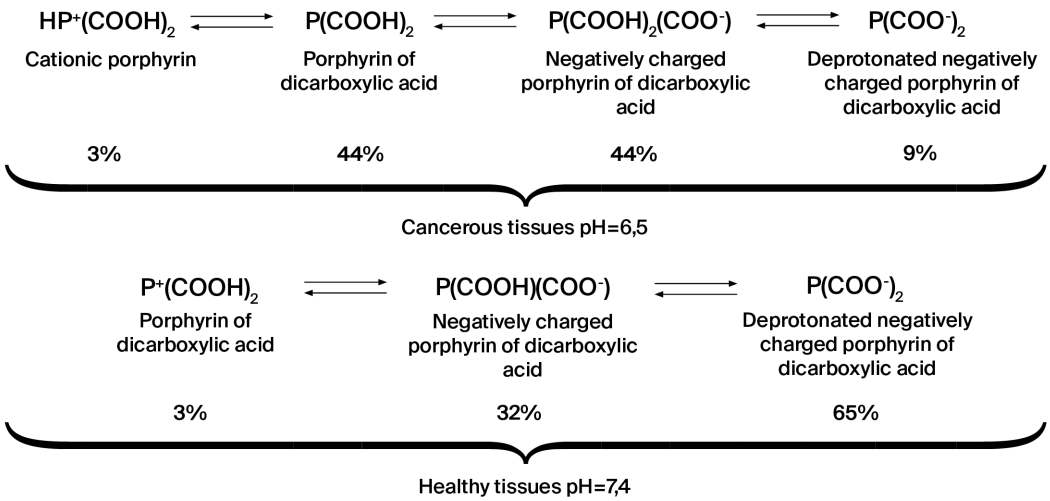

FIG. 1. Acid-base balance in the porphyrin structure in healthy and malignant tissues

Typical Classification of Porphyrin-Based Photosensitizers

The demand for novel pharmaceutical products arises from the need to improve the effectiveness of existing medications. Currently, PS, which are derived from the porphyrin family, are divided into three generations (Fig 2).

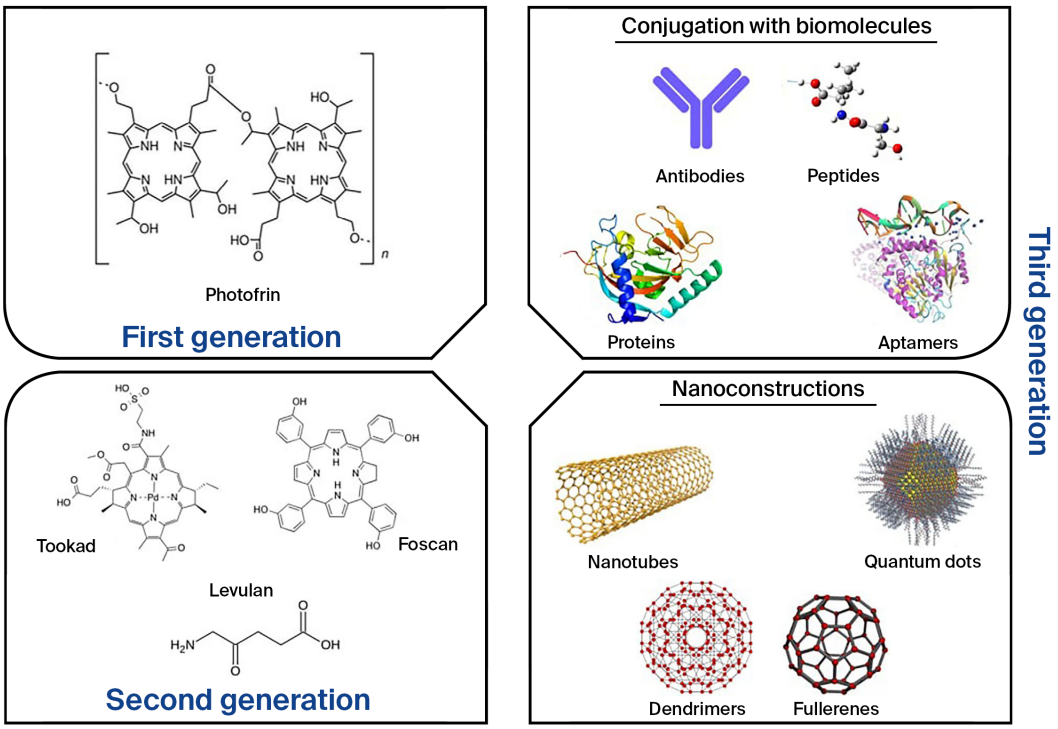

FIG. 2. Generations of tetrapyrrole photosensitizers

The first generation of PS is characterized by Hp [11]. This compound has a sophisticated chemical composition, featuring two highly reactive rings. This complexity makes it difficult to achieve purity, as Hp can exist as a mixture of various forms, including monomeric porphyrins, dimers, and high-molecular-weight oligomers. Attempts to purify Hp using a 5% solution of sulfuric and acetic acids at room temperature for 15 minutes resulted in the formation hematoporphyrin derivative (HpD) I. Prior to administration, HpD I underwent an alkaline treatment, and its pH was adjusted to 7.4 using hydrochloric acid to produce HpD II [12].

Hp play a crucial role in the landscape of PDT, particularly through their predominant use in the formulation known as Photofrin, as recognized in Canada by Axcan Pharma. Notably, these products are characterized by a significant red absorption peak at a wavelength of 630 nanometers but possess low extinction coefficients. A low extinction coefficient indicates that the photosensitizer does not absorb light very efficiently, meaning it requires higher concentrations or longer exposure times to achieve the desired activation for therapeutic or experimental purposes [13]. The effectiveness of Photofrin in cancer treatment is due to its exceptional affinity for LDL, which enhances its selectivity for cancer cells. Research has shown that this substance accumulates primarily in the membranes of mitochondria, the endoplasmic reticulum, and the Golgi apparatus in cancerous tissues [14]. When exposed to laser light at the specific wavelength of 630 nm, Photofrin triggers the production of ROS, a highly reactive form that induces apoptosis by releasing cytochrome C from mitochondria, ultimately leading to the programmed death of cancer cells. In Russia, a similar substance to Photofrin, known as Photogem, was created at Moscow State University in 1990. This substance is a blend of single-molecule and multi-molecule derivatives of Hp, and it has been approved for medical use, demonstrating similar effects to Photofrin in terms of its potential for targeting tumors [15].

Advancements in the field have led to the development of second-generation photosensitizing agents. It is shows higher photostability, so they are more resistant to decomposition under the influence of light, which leads to a longer-term preservation of therapeutic activity. The improved photostability also allows the use of lower doses of these compounds, which reduces the risk of possible toxicity and makes treatment safer for patients. Modern second-generation photosensitizers often have a wider light absorption range, which allows using different wavelengths of illumination to activate their activity [13]. This expands the application possibilities by allowing the use of light sources more suitable for clinical conditions and providing deeper penetration of light into tissues. This enhancement significantly increases the therapeutic impact on tumors, primarily facilitated through the conjugation of these agents with various targeting molecules such as antibodies, proteins, and carbohydrates. As a result, second-generation agents exhibit a higher capacity for ROS generation, thus optimizing their therapeutic effectiveness in the intricate microenvironment of tumors [16].

The innovation continues with third-generation PS, which are engineered to be encapsulated in various carrier media, enhancing their selectivity for tumor cells. Modern carrying agents include liposomes, micelles, gold nanoparticles, and other formulations that enable targeted delivery [17]. Among these, chlorin e6 (Ce6) has surfaced as a leading candidate for research and development in the realm of new pharmaceuticals [18,19]. By combining Ce6 with biocompatible amphiphilic polymers such as polyethylene glycol (PEG) and polylactic acid (PLA), stable nanoparticles (e.g., chlorin e6-conjugated methoxy-poly(ethylene

glycol)-poly(d,l-lactide) (mPEG-PLA-Ce6) are created [20]. Extensive studies reveal that these nanoparticles yield a significantly enhanced level of ROS production in both two-dimensional cellular monolayer, three-dimensional multicellular tumor spheroids and in vivo animal experiment of solid hypoxic tumor cells compared to free Ce6, showing improved cellular uptake and cytotoxic effects [21]. Recent advancements in immunogenic phototherapy highlight the use of advanced structures like core-shell nanoparticles to effectively target colorectal cancer cells while increasing oxygen levels in the tumor tissue [21]. These engineered particles, comprising gold nanoparticles coated with manganese dioxide (MnO_2) and hyaluronic acid, produce ROS when stimulated with infrared radiation, culminating in tumor cell death and fostering dendritic cell development, which is critical for a robust immune response against cancer. This method increases oxygen levels in the tumor tissue via a MnO_2 that catalyzes hydrogen peroxide (H_2O_2) breakdown and generates ROS, enhancing the photodynamic effect under laser irradiation at a wavelength of 635 nm [22].

The expanding field of theranostic medicine is currently experiencing the emergence of multifunctional nanobiomaterials. An example includes conjugated nanoparticles like polyethylene glycol-copper bismuth sulfide-Ce6-folate (PEG-Cu_3BiS_3-(Ce6)-folate), where the nanoparticles are designed to target folate receptors highly expressed in certain tumor cells [23]. Preclinical studies have underscored the promising synergistic effects of these nanoprobes in both photothermal therapy and PDT, showing significant therapeutic efficacy in glioma xenograft models. Another noteworthy PS, meta-tetra-(hydroxyphenyl)chlorin (mTHPC), known for its tendency to aggregate in biological fluids, has been tackled by creating polymer micelles to preserve its potent properties [24]. Through encapsulation in micellar structures conjugated with targeting molecules, mTHPC can achieve efficient cellular uptake in cancer cells expressing the epidermal growth factor receptor, significantly enhancing phototoxicity.

In summary, the evolution of PS from the initial generation through advanced formulations highlights a remarkable trajectory toward enhanced specificity, efficacy, and multifunctionality in cancer treatment, thereby holding substantial promise for future therapeutic applications.

Strategies for the development of next-generation photosensitizers

Porphyrins can be integrated with biological molecules through bioorthogonal chemical methods, such as phosphoramidite chemistry, solid-phase synthesis, and post-synthetic modifications like amidations and hydrazide-carbonyl reactions [25]. When it comes to the conjugation of porphyrins with oligonucleotides, there are two main approaches: the modification of porphyrin molecules using phosphoramidites and the post-synthetic conjugation [25,26]. The incorporation of porphyrins into oligomers enhances their solubility and allows them to interact with nucleic acids. This process also creates a chiral center due to the helical structure of deoxyribonucleic acid (DNA). DNA-porphyrin constructs have a wide range of applications, including the detection of specific nucleotide sequences, the staining of nuclei, and their use as antimicrobial chemotherapeutics [27].

Solid-phase synthesis is a method that can be used to modify porphyrins by integrating them into a sugar ring through the use of phosphoramidite chemistry [25]. This process involves replacing the nucleoside at the first

position of the sugar ring with a porphyrin, or linking porphyrins to nucleosides through amino functionalization of the third carbon of the sugar. This results in the formation of duplex structures containing zero to three porphyrin units using solid-phase techniques.

The post-synthetic modification of porphyrin is a novel approach in synthetic chemistry that allows for the direct conjugation of these molecules with nucleic acid bases or other specific positions within the molecule [25]. This is achieved through the use of functional linkers after the initial synthetic process, which opens up opportunities for modifying oligonucleotides after synthesis [26].

Particularly promising in this regard is the area of peptide conjugation. Peptides offer a wider range of functional reactive groups than oligonucleotides, making them an attractive target for post-synthetic modifications. There are four main methods for conducting these reactions: Staudinger ligation, copper-assisted alkyne-azide cycloaddition (CuAAC), strain-promoted alkyne–azide cycloaddition, and olefin metathesis [28]. The Staudinger ligation reaction is a rapid and highly specific process that relies on the complex interaction between azides and phosphine compounds. In 2010, N. Umezawa et al. used this technique was to synthesize 5,10,15,20-tetrakis-(3-azidophenyl)-porphyrin by combining 3-azido-benzaldehyde with an equivalent amount of pyrrole [29]. The CuAAC method has demonstrated excellent selectivity and a wide range of applications in various pH and temperature environments for the coupling of peptides with porphyrins. Porphyrin-peptide conjugates generated through the CuAAC process have shown promise for applications in PDT, tumor imaging, and targeted drug delivery. However, the use of CuAAC for the conjugation of porphyrins and peptides is limited by the inherent toxicity of copper-based catalysts towards living cells [30].

Eggleston's team also investigated the strategy of using Staudinger ligation for peptide crosslinking to produce conjugates based on Cell-Penetrating Peptide with Triphenylphosphine (CPP-TPP) [31]. This conjugate demonstrated the highest phototoxicity among other conjugation methods (such as CuAAC and thiol-maleimide), due to the presence of an extended triazole-based linker between the hydrophobic porphyrin and the polycationic peptide. Phototoxicity was assessed in a monolayer culture of human breast cancer cells, and the concentration of porphyrin needed to induce 50% cell death after 5 min of light exposure was approximately 40 nM. To further investigate the effect, a protein toxin called saporin, which inactivates ribosomes with a mass of 30 kDa, was used in conjunction with the CPP-TPP conjugate. These experiments demonstrated that cell viability decreased significantly (about 3-fold) when saporin was added, compared to exposure to the CPP-TPP conjugate alone. It's worth noting that the decrease in viability with saporin alone was negligible (approximately 10%) [31].

The process of native thiol–maleimide chemical ligation entails the selective coupling of thiol side chains from peptides containing cysteine residues with modified maleimides, culminating in the creation of novel PS belonging to the porphyrin family [32,33]. Liu et al. employed this methodology to combine protoporphyrin IX (PpIX), a photosensitizing agent, with a carrier molecule known as lipopolysaccharide and an antimicrobial peptide known as YI13WF, renowned for its capacity to eradicate bacteria [34]. Initially, the PpIX molecule underwent modification by the addition of a bismaleimide moiety. Subsequently, the modified PpIX was subjected to reaction with YI13WF in the presence of diisopropylamine and dimethyl sulfoxide, resulting in the formation of PpIX- YI13WF. The fluorescence and antimicrobial characteristics of the resulting compound were subsequently evaluated. It has been discovered that

when subjected to a concentration of 0.5 mM and illuminated with an energy density of 30 J/cm^3, the conjugate effectively eliminates 99.9% of gram-negative bacteria [34].

With regard to amino group ligation, one common method for labeling peptide amino groups is the combination with carboxylic acid derivatives, which results in the formation of stable amide or thiourea conjugates [35]. For example, porphyrin with pyridine units can react with poly-l-lysine to form a mono-amino-porphyrin thiourea conjugate that exhibits low toxicity in darkness at a concentration of 10 mM (Inhibitory Concentration 50% > 250 μg) [36]. In the presence of porphyrins, α-polypeptides can adopt secondary structures such as α-helices.

The field of antibody conjugation has been a subject of intense research since the late 1980s and early 1990s [37]. This research has led to the development of photoimmunoconjugates, such as the conjugation of Hp with a mAb that targets a protein expressed by myosarcoma M1 cells. The mAb is covalently attached to the carboxyl group on the lysine side chain of Hp. The mAb-M1-Hp conjugate demonstrates remarkable efficacy in the treatment of myosarcoma when administered at a low dose of 0.268 mg/kg, surpassing the efficacy of higher doses ranging from 2,5-5 mg/kg [38].

A benzoporphyrin derivative has been conjugated to a tumor-targeting mAb that binds to the epidermal growth factor receptor through a thiol–maleimide linkage [39]. In experimental studies conducted on Syrian golden hamsters bearing carcinomas, it has been demonstrated that administering this specific conjugate in combination with radiation therapy leads to substantial tumor necrosis. One example of such a conjugate involves linking a Ce6 derivative to a mAb specific for CA125 [40]. This antibody is then converted into polyglycolic acid through a carbodiimide reaction and subsequently modified with hydrazines. The resulting chlorin–polyglycolate–hydrazine subsequently reacts with the aldehyde group on the mAb, forming stable hydrazones.

In 2011, K. Smith et al. combined isothiocyanate-functionalized cationic porphyrins with tumor-specific antibodies and differentiation cluster receptor antibodies, such as CD104, CD146, and CD326 [41]. Low-dose conjugates, with a concentration of 10 nM/kg demonstrated comparable efficacy to high-dose Photofrin, which was administered at a dosage of 8.3 mM/kg. Furthermore, meso-tripyridyl-mono(4-carboxyphenyl) porphyrins have been synthesized in combination with amino forms of serum albumin and mAb against carcinoembryonic antigen (CEA). Ultraviolet–visible spectroscopic analysis has shown that the porphyrin labeling reaches its peak when the ratio of porphyrin to protein is 30:1, measured in terms of molar amounts [42]. For porphyrin-mAb-CEA conjugates and porphyrin–mAb complexes targeting CD104, the maximum values of the drug-to-ligand ratio have been recorded at 0.81 and 0.79, respectively [43].

A novel bifunctional linker was synthesized using a site-specific cysteine conjugation method [44]. The linker consists of bromopyridine and a cyclic acetylene, and it was designed to be used in PDT. Trastuzumab, an approved mAb for breast cancer treatment, had its eight free thiol groups reacting with bromopyridine, resulting in the formation of novel bonds between the antibody and the linker. When exposed to light at a wavelength of 625 nm, the conjugate demonstrated efficacy against HER2+ cell lines. This conjugate represents a significant advancement in the field of PDT, as it opens up new possibilities for the development of more effective treatments [44].

One such example is β-Mannose-Ce6 , which has shown comparable antitumor activity to β-glucocerebroside against human glioblastoma cells of

U251 line [45]. Additionally, it surpasses the photosensitizing capacity of first-generation agents like Talaporfin sodium (a photosensitizing agent consisting of Ce6 and L-aspartic acid). β-Mannose-Ce6 exhibits a more rapid rate of absorption compared to Talaporfin sodium, and its primary localization is within organelles such as the Golgi apparatus and mitochondria [45].

Metalloporphyrins have been identified as potential candidates for the development of future generation PS. A series of metalloporphyrin-indomethacin conjugates linked by PEG were synthesized and investigated: indomethacin-conjugated porphyrin, palladium porphyrin complex (PdPor), platinum porphyrin complex (PtPor), zinc porphyrin complex (ZnPor) [46]. Generation of ROS was assessed using 2',7'-dichlorofluorescein as a probe. Due to the effect of heavy atoms, metalloporphyrin complexes exhibited a higher quantum yield of singlet oxygen than that of porphyrin with a free base: PtPor > PdPor > ZnPor > Porphyrin. The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) analysis using HeLa cells confirmed the low cytotoxicity of porphyrin–indomethacin conjugates in the dark. When irradiated, PtPor demonstrated the highest therapeutic activity among these conjugates. The results showed that conjugates are mainly localized in the lysosomes of HeLa cells [46].

Conclusion

The recent advances in structural chemistry, in particular the development of new porphyrin derivatives and their combinations with other active substances, hold great potential for improved selectivity and efficacy. By modifying the structure of porphyrins by incorporating functional groups, for example, we can enhance their interaction with target cells and increase their responsiveness to light. Additionally, metallized porphyrins provide a novel application opportunity, as the addition of metal ions alters the electronic properties of the molecule and enhances its photodynamic properties. It is important to note that the successful clinical application of porphyrin PS depends on a comprehensive approach that includes optimizing the chemical structure, understanding the mechanism of action at the cellular level, developing effective delivery methods for targeted delivery to tumor tissues, and studying the interactions between PS and biological systems. These aspects require a multidisciplinary approach and an interdisciplinary research methodology in order to develop safe and effective therapeutic agents for PDT. Despite current challenges, research into porphyrins continues, presenting new opportunities for PDT and other biomedical applications. Advances in technology and development of photosensitizing agents, coupled with a better understanding of cellular biology and tumor genesis, could lead to significant improvements in cancer treatment and other medical conditions.

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REVIEW

Study of mechanisms and approaches to incretin-based therapy for obesity in children

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ABSTRACT

This study highlights data on the increasing role of incretins in interdisciplinary therapy for endocrinopathies, particularly glucagon-like peptide-1 (GLP-1), which affects carbohydrate metabolism, insulin secretion, and other metabolic processes. The mechanisms of secretion, biological activity, and degradation of these peptides are described, along with their role in regulating appetite, gastrointestinal motility, and carbohydrate metabolism. This information allows for a comprehensive understanding of the effects of synthetic GLP-1 analogs. We also explore modern approaches to treating obesity in children and adolescents, including the use of GLP-1 receptor agonists such as liraglutide. It presents the results of a clinical study confirming the effectiveness and safety of liraglutide in reducing body weight and improving metabolic indicators in

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children with obesity. It is shown that liraglutide not only promotes weight loss but also has cardioprotective effects, improving lipid profiles and reducing blood pressure. The efficacy of liraglutide in children aged 12–18 with obesity was amount to 43.3 - 76.5%. The prevalence of hypertension in obese children decreased from 30.9% to 4.8%, carbohydrate metabolism disorders from 41.1% to 19.4%, dyslipidemia from 20.6% to 9.7%. Liraglutide reduces the risk of major adverse cardiovascular events by 13–22% in patients with type 2 diabetes and high cardiovascular risk. This effect is attributed to moderate blood pressure reduction, improved lipid profiles, enhanced endothelial function, and anti-inflammatory and antioxidant actions. Additionally, the article discusses the prospects for using GLP-1 receptor agonists in cardiology, including their ability to reduce the risk of cardiovascular events in patients with type 2 diabetes and obesity.

Key Words: GLP-1 receptor agonists, liraglutide, obesity, children

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The Role of Incretins in the Body

Incretins are hormones produced by intestinal cells in response to food intake, contributing to 50–70% of postprandial insulin secretion in healthy individuals. This process in referred to as the incretin effect. Glucagon-like peptide (GLP) and gastric inhibitory polypeptide (GIP) (also known as glucose-dependent insulinotropic polypeptide) both belong to the glucagon protein family, sharing significant amino acid homology [1]. GIP is secreted by K-cells in the upper small intestine (duodenum and proximal jejunum) in response to carbohydrate and fat intake. GLP-1, GLP-2, and glicentin (the intestinal form of glucagon) are produced by L-cells, predominantly located in the distal intestine. Additionally, GLP-1 is also expressed in pancreatic alpha cells and neurons in certain brain regions, including hypothalamus, pituitary, reticular nucleus [2]. Despite the distal location of L-cells in the gastrointestinal tract, GLP-1 is released into the bloodstream within minutes after food intake. This indicates an indirect neuroendocrine regulation, rather than direct nutrient stimulation. Experimental studies in animals have confirmed the important role of the parasympathetic nervous system, particularly the vagus nerve, in transmitting neuroendocrine signals through muscarinic receptors [2].

The concentration of GLP-1 and GIP in fasting plasma is extremely low but increases significantly after meals. Both peptides are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), which is expressed in capillary endothelial cells. As a result, a large portion of GLP-1 and GIP is inactivated before entering the portal bloodstream, explaining their short half-life. Studies with intravenous administration of GIP and GLP-1 in healthy volunteers and patients with diabetes have shown that the half-life of GIP is 5–7 minutes, while that of intact GLP-1 is 1–2 minutes [3].

GIP receptors are expressed in pancreatic islet cells, the intestine, adipose tissue, the heart, the pituitary, and various brain regions. GLP-1 receptors, in turn, are found in the gastrointestinal tract, the endocrine pancreas (alpha and beta cells), the lungs, kidneys, heart, and various brain regions [4] (Fig. 1).

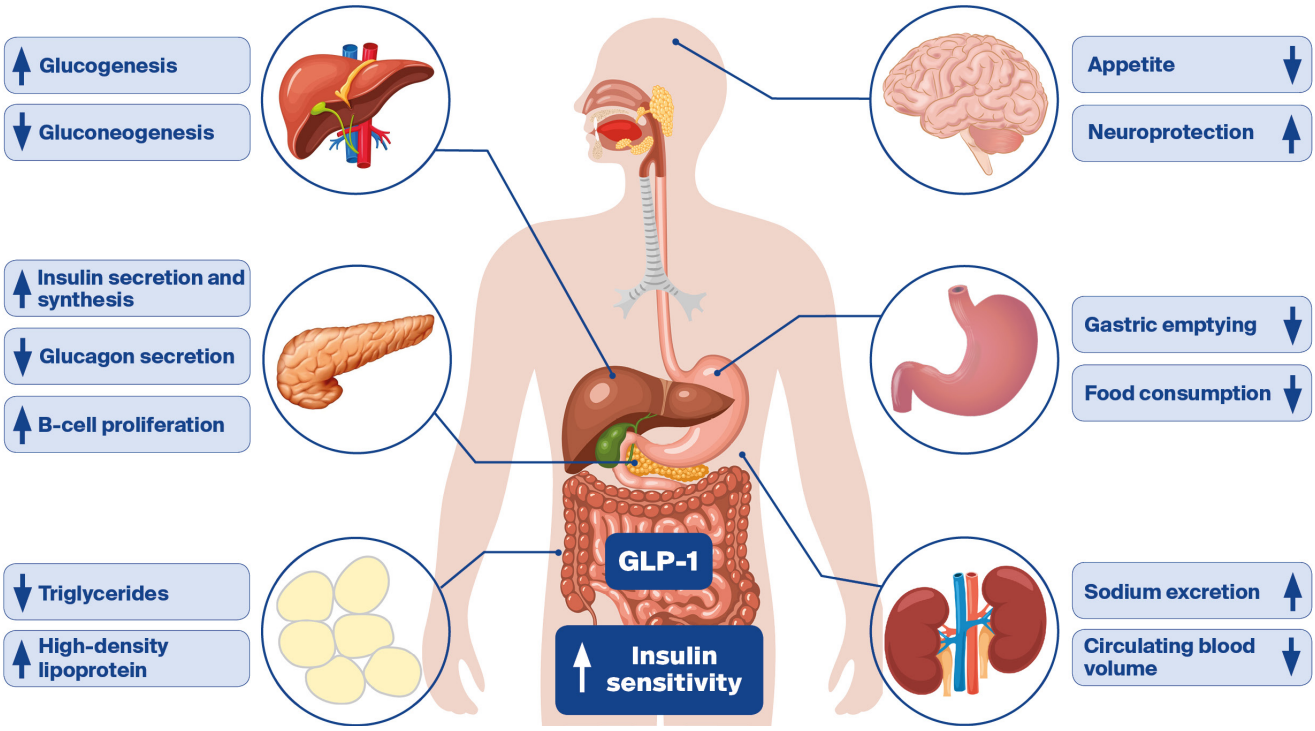

FIG. 1. Metabolic effects of glucagon-like peptide-1 (GLP-1)

A significant portion of secreted GLP-1 is inactivated in the intestine before entering the systemic circulation, suggesting that its biological activity may occur locally or through interaction with afferent sensory nerve fibers transmitting signals to the central nervous system. This interaction modulates the activity of efferent parasympathetic fibers of the vagus nerve, regulating key intestinal functions such as secretory and motor activity, as well as pancreatic secretion [4].

Under physiological conditions, the intake of small amounts of food or easily digestible nutrients primarily stimulates the release of GIP, an incretin secreted in the proximal intestine [5]. Conversely, the digestion of larger volumes of food or complex nutrients activates both GIP and GLP-1. GLP-1 secretion correlates with insulin release throughout the day. Importantly, the action of GLP-1 is strictly glucose-dependent, meaning its effects are directly linked to blood glucose levels. The minimal threshold for glycemia at which GLP-1's effect on insulin secretion ceases is approximately 4.5 glycemia. This indicates that GLP-1's influence on insulin secretion is not associated with a risk of hypoglycemia, as its effect diminishes as glucose levels approach normal. In addition to directly stimulating insulin secretion, GLP-1 promotes insulin gene transcription and all stages of insulin biosynthesis, helping to replenish insulin stores, especially when depleted. GLP-1 is also a potent stimulator of somatostatin secretion, an effect independent of blood glucose levels [5].

GLP-1 inhibits glucagon secretion, likely mediated by increased insulin and somatostatin secretion. Direct effects on alpha cells, which express GLP-1 receptors, also play a role. This inhibition of glucagon secretion is glucose-dependent, ensuring that GLP-1 does not impair the counter-regulatory response to hypoglycemia [6].

GLP-1 slows gastric emptying by inhibiting gastrointestinal motility and secretory functions, likely through neural mechanisms involving the vagovagal reflex pathway [7]. This physiological role of GLP-1 helps regulate intestinal absorption, synchronizing the movement of food with secretory activity. In pathological conditions such as diabetes, delayed gastric emptying can reduce postprandial glucose fluctuations.

One of the key properties of GLP-1 is its ability to reduce food intake by promoting satiety [8]. This effect is mediated by central mechanisms, with GLP-1 acting on brain regions such as the hypothalamus and nucleus tractus solitarius. Peripheral GLP-1 also influences afferent fibers of the parasympathetic nervous system, transmitting signals to the central nervous system to modulate food intake.

Incretin-Based Therapies for Pediatric Obesity

The first line of therapy for constitutional-exogenous obesity involves diet and lifestyle modifications [9]. However, this approach is often ineffective, as it fails to address all the consequences of obesity [10,11]. This is due to low patient engagement, rapid weight gain, having eating disorders, and poor parental compliance. Additionally, obesity-related comorbidities in childhood tend to progress more aggressively than those developing later in life [12]. This situation necessitates the consideration of pharmacotherapy.

The treatment of obesity in children and adolescents aims to achieve two goals: maintaining the BMI SDS (body mass index standard deviation score) in the short term (for 6–12 months) and significantly reducing BMI SDS while controlling and preventing complications in the long term [9]. According to clinical guidelines in Russia, pharmacotherapy (combined with lifestyle changes) is recommended for children aged 12 and older when lifestyle interventions over at least one year have not yielded the desired results [9].

Currently, five medications are the United States Food and Drug Administration (FDA) approved for treating obesity in children and adolescents [13]. Prior to 2022, only three drugs were available: orlistat (for adolescents over 12), phentermine (in individuals over 16), and liraglutide (for adolescents over 12). In 2022, the FDA approved the combination drug phentermine/topiramate in a controlled-release form for once-daily use in adolescents over 12 with obesity. However, the efficacy and safety of these drugs do not fully meet desired outcomes. In January 2023, the FDA also approved semaglutide (a GLP-1 receptor agonist) for adolescents over 12 with obesity.

Liraglutide, a GLP-1 receptor agonist, mimics the action of endogenous GLP-1, which is produced in the intestine in response to food intake [14]. Its mechanism of action involves activating GLP-1 receptors in various organs and tissues, including the pancreas, gastrointestinal tract, and central nervous system. In the pancreas, liraglutide stimulates beta cells, enhancing glucose-dependent insulin secretion and improving glycemic control. It also suppresses glucagon release from alpha cells, reducing hepatic glucose production and preventing hyperglycemia. In the gastrointestinal tract, liraglutide delays gastric emptying, prolonging satiety and reducing appetite. In the central nervous system, particularly the hypothalamus, liraglutide acts on satiety centers, reducing hunger and food intake. Additionally, liraglutide exhibits cardioprotective effects by lowering blood pressure and improving lipid profiles through reduced cholesterol and triglyceride levels. Liraglutide has fewer contraindications and better tolerability compared to other weight-loss medications, making it a safer option for pediatric patients [14].

The efficacy and safety of liraglutide has been demonstrated in a large randomized SCALE Teen trial. It involved 251 patients (126 received liraglutide). A body weight loss of ≥5% was achieved in 43.3% in the liraglutide group versus 18.7% in the placebo group [14].

In the study of Vitsebskaya A.V. and Popovich A.V. 10 patients with obesity and gastrointestinal diseases were included. The use of liraglutide for 3 months resulted in a significant decrease in BMI SDS to 2.8 kg/m^2. The severity of obesity decreased by 0.4 kg/m^2 BMI SDS. During liraglutide therapy, there was a statistically insignificant decrease in fasting glucose, glycated hemoglobin, cholesterol, triglycerides and transaminases [15].

The efficacy of liraglutide in children aged 12–18 with obesity was demonstrated in a single-center, observational, single-arm, prospective, uncontrolled study conducted at the Endocrinology Department of the Burdenko Voronezh State Medical University [16]. The study included 68 children with grade II–III obesity and morbid obesity (BMI SDS ≥ 2.5) and a body weight of at least 60 kg. Positive dynamics, defined as a reduction in BMI SDS by 0.25 or more, were observed in 47 children (69.1%). Five patients (7.4%) showed a reduction in BMI SDS of less than 0.25, while 3 children (4.4%) had no change in body weight (BMI SDS change ± 0.05), and 7 patients (10.3%) experienced weight gain (BMI SDS increase > 0.05). During the first month of therapy, 2 patients (2.9%) transitioned from morbid to grade III obesity, 9 children (13.2%) from grade III to grade II, and 3 patients (4.4%) from grade II to grade I. Pairwise comparisons of BMI SDS before treatment and at 1, 4, and 8 months showed statistically significant differences ($p < 0.001$), indicating meaningful changes rather than random fluctuations. Average weight loss was 4.8 kg (4.6%) at 1 month, 8.1 kg (7.7%) at 4 months, 9.7 kg (9.2%) at 8 months, and 6 kg (5.7%) at 12 months. Some patients lost over 20 kg (23–25%) [16].

Adverse effects were reported by 10 patients (14.7%) during dose escalation. Nausea occurred in 8 patients (11.7%), vomiting in 4 (5.9%), abdominal pain in 4 (5.9%), diarrhea in 3 (4.4%), and belching in 1 child (1.5%). One patient (1.5%) with non-alcoholic fatty liver disease developed cholelithiasis after one month of liraglutide therapy. No cases of hypoglycemia were reported.

Liraglutide demonstrated significant efficacy in addressing the primary goals of obesity treatment: positive weight loss dynamics were achieved in 76.5% of patients, and weight stabilization in 4.4% of children. The greatest effect was observed after 8 months of therapy, particularly in children with higher BMI SDS values but not morbid obesity. Weight normalization was accompanied by a reduction in obesity-related complications. The prevalence of hypertension decreased from 30.9% to 4.8% ($p < 0.004$); carbohydrate metabolism disorders from 41.1% to 19.4% ($p = 0.004$); dyslipidemia from 20.6% to 9.7%; and non-alcoholic fatty liver disease from 60.3% to 50% [16].

The use of liraglutide for the treatment of obesity in children in younger age groups is being studied. Thus, when 56 children aged 6-12 years were treated for 56 weeks, the average percentage change in body mass index from baseline was -5.8% among those receiving liraglutide, compared with 1.6% in the placebo group [17].

Cardioprotective Effects of Incretins

Beyond obesity treatment, another promising area is their application in cardiovascular diseases. The cardioprotective effects of GLP-1 receptor agonists (e.g., liraglutide, semaglutide, dulaglutide) are a key focus in modern cardiology and endocrinology. Initially developed for type 2 diabetes, these

drugs have shown significant benefits for the cardiovascular system. Large clinical trials (e.g., LEADER, SUSTAIN-6, REWIND) have demonstrated that GLP-1 agonists reduce the risk of major adverse cardiovascular events, such as myocardial infarction, stroke, and cardiovascular death [18-21]. For example, liraglutide reduces the risk of major adverse cardiovascular events by 13–22% in patients with type 2 diabetes and high cardiovascular risk. This effect is attributed to moderate blood pressure reduction, improved lipid profiles (lower triglycerides and higher high-density lipoproteins (HDL)), enhanced endothelial function, and anti-inflammatory and antioxidant actions [21] (Fig. 2).

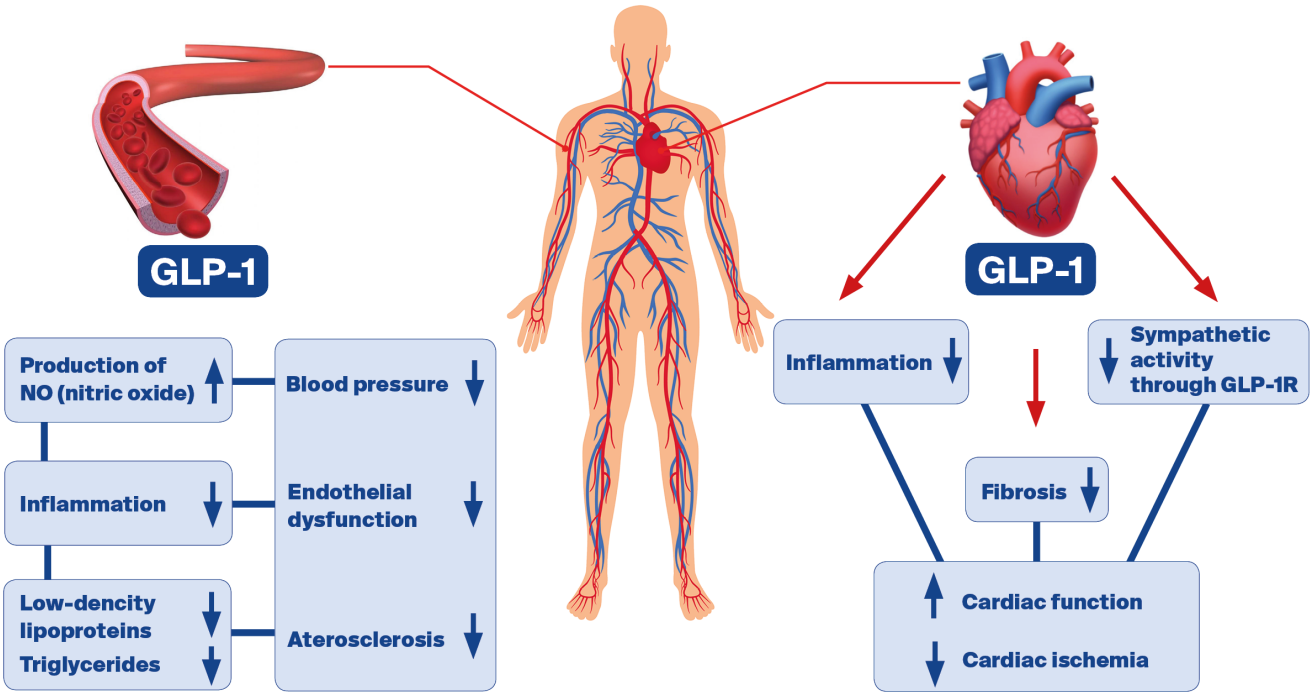

FIG. 2. Cardioprotective effects of incretins on the cardiovascular system

GLP-1 receptor agonists lower blood pressure through multiple mechanisms, including direct and indirect effects on the cardiovascular system. GLP-1 receptors are expressed in vascular smooth muscle cells and cardiomyocytes. Activation of these receptors increases intracellular cyclic adenosine monophosphate (cAMP) levels, activating protein kinase A, which induces smooth muscle relaxation and vasodilation, thereby reducing blood pressure. cAMP also activates endothelial nitric oxide synthase, increasing nitric oxide (NO) production, which further promotes vasodilation. Additionally, GLP-1 reduces pro-inflammatory cytokines by inhibiting the Nuclear factor kappa-light-chain-enhancer of activated B cells signaling pathway, a key regulator of inflammatory gene expression, including cytokine genes such as tumor necrosis factor α, interleukin-6, interleukin-1β [22-25]. It is worth noting that GLP-1 suppresses macrophage activation and their transition into a pro-inflammatory state, thereby contributing to a reduction in pro-inflammatory cytokines [22,23,25,26].

GLP-1 modulates sympathetic nervous system activity, which plays a crucial role in blood pressure regulation. GLP-1 and its agonists can cross the

blood-brain barrier or act on brain regions with higher permeability (e.g., area postrema). In the central nervous system, GLP-1 receptors are expressed in key areas regulating sympathetic activity, such as the hypothalamus, nucleus tractus solitarius, and rostral ventrolateral medulla [24,27,28,29]. Activation of these receptors reduces sympathetic activity, heart rate, and blood pressure [29]. GLP-1 receptors are also expressed in the nephron, where their activation increases sodium and water excretion, reducing blood volume and pressure. GLP-1 receptors are also expressed in various segments of the nephron, including the proximal tubules and collecting ducts. Activation of these receptors increases sodium excretion by suppressing the activity of the Na+/H+ exchanger type 3in the proximal tubules, which reduces sodium reabsorption and enhances its urinary elimination, as well as increases water excretion by decreasing sodium reabsorption (osmotic diuresis) [30]. This leads to a reduction in circulating blood volume and, consequently, a decrease in arterial blood pressure.

GLP-1 positively influences lipid metabolism by increasing HDL levels and reducing triglycerides [31]. It suppresses key lipogenic enzymes, such as acetyl-CoA carboxylase and fatty acid synthase, through adenosine monophosphate activated protein kinase activation. GLP-1 also enhances lipoprotein lipase activity, which breaks down triglycerides in very low-density lipoproteins and chylomicrons. Increased HDL levels result from enhanced apolipoprotein A1 synthesis, the primary structural protein of HDL [32-34].

These mechanisms contribute to GLP-1's beneficial effects on the myocardium. GLP-1 improves energy metabolism in cardiomyocytes, enhances mitochondrial function, reduces ischemia-reperfusion injury, and decreases pro-inflammatory cytokines in the myocardium. It also prevents or reduces myocardial hypertrophy by lowering blood pressure and sympathetic activity, and it inhibits fibrosis by suppressing transforming growth factor-beta activity [35].

GLP-1 receptor agonists do not replace standard cardiovascular therapies (e.g., statins, antihypertensives) but serve as valuable adjuncts. Their multifaceted cardioprotective effects, including blood pressure reduction, improved lipid profiles, and anti-inflammatory and antioxidant actions, make them important additions to standard cardiovascular disease management.

Conclusion

The article presents key directions for the development of incretin-based therapy. The study confirmed the high efficacy of liraglutide in treating obesity in children and adolescents, with significant weight reduction in 76.5% of patients and weight stabilization in 4.4%. The cardioprotective properties of liraglutide were also demonstrated, with improvements in lipid profiles and blood pressure, reducing the risk of cardiovascular complications. These findings align with international studies showing liraglutide's ability to lower cardiovascular risk in patients with obesity and type 2 diabetes. GLP-1 receptor agonists may become an essential component of comprehensive obesity treatment, particularly in patients at high cardiovascular risk. Further research with longer follow-up periods will clarify the long-term effects of liraglutide and its role in preventing obesity-related complications.

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REVIEW

Treatment of cardiac contusion: experimental basis for pathogenetic therapy and emerging approaches in cardioprotection

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ABSTRACT

Myocardial contusion is a serious consequence of blunt thoracic trauma, most commonly resulting from traffic accidents, falls, sports injuries, and combat-related events. It is associated with impaired myocardial contractility, fibrosis, and systemic inflammation, and carries a high risk of complications, with mortality rates reaching up to 10%. Despite advances in understanding the pathogenesis, the development of effective therapeutic strategies remains a key priority in experimental cardiology.

A promising direction involves the development of targeted approaches that address both myocardial injury and the optimization of adaptive responses. The first aspect focuses on counteracting bioenergetic hypoxia, restoring energy and ionic homeostasis, suppressing secondary damage in the context

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of inflammation, and regulating apoptosis and autophagy. The second aspect targets the modulation of stress-activating and stress-limiting systems, including tissue-level adaptation mechanisms.
Particular attention has been given to cardioprotective agents, which have demonstrated efficacy in ischemic heart disease, myocardial infarction, and ischemia–reperfusion injury. However, their impact on post-traumatic myocardial remodeling remains insufficiently explored. Phytopreparations from the Chinese Pharmacopoeia, characterized by multitarget activity on key pathological processes — such as bioenergetic deficiency, oxidative stress, and dysregulation of cellular homeostasis — may offer a viable alternative. Integrated strategies combining anti-inflammatory effects, metabolic support, and control of fibrogenesis may enhance therapeutic outcomes.
Further research is necessary to assess the synergistic interactions of individual components, dose-dependent responses, and the long-term impact on myocardial structure and function. Multimodal approaches may improve therapeutic efficacy and help overcome the limitations of monotherapy, opening new avenues for the management of post-traumatic cardiac complications.

Key Words: commotio cordis; blunt cardiac trauma; blunt cardiac injury; blunt chest trauma; heart contusion; cardioprotection; stress-activating systems; stress-limiting systems

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Introduction

Myocardial contusion primarily results from mechanical trauma to the thoracic cage, typically occurring in the context of road traffic accidents, high-energy falls, sports-related injuries, as well as mine-blast and behind-armor (blast wave) trauma [1, 2]. The epidemiology of myocardial contusion remains poorly characterized, largely due to the lack of standardized diagnostic criteria and the absence of consistent reporting mechanisms in national health statistics. In most cases, the prevalence of this condition is inferred indirectly through general thoracic trauma indicators. According to the Ministry of Health of the Russian Federation (2023), in 2022, thoracic injuries, including those caused by road traffic accidents and other external factors, were reported at rates of 599.5 and 530.6 cases per 100,000 population, respectively[1]. The average mortality rate associated with blunt chest trauma is approximately 17.5%; however, when the injury involves simultaneous damage to the lungs, heart, and major vessels, the mortality rate increases significantly, leading to a markedly poorer prognosis [3]. According to the National Trauma Data Bank, myocardial contusion is diagnosed in 7–55% of chest trauma cases and accounts for approximately 10% of all admissions to trauma departments [4]. A meta-analysis by Kyriazidis et al. showed that myocardial injury following blunt chest trauma occurs in 18.3% of cases [5]. Particular attention should be given to the rare but extremely life-threatening complications associated with this condition. A retrospective analysis of 20,000 trauma cases revealed that blunt cardiac and pericardial rupture occurs in 0.002% of cases, yet is associated with a mortality rate of 89.2% [6].

Post-traumatic morphological changes are typically classified into three phases: the acute phase, reparative regeneration, and post-traumatic

[1] Здравоохранение в России. 2023: Статистический сборник/Росстат. Москва: Росстат; 2023. / Healthcare in Russia. 2023: Statistical book/Rosstat. Moscow, 2023. 179 p. (In Russ.). Accessed 05.04.2025. http://ssl.rosstat.gov.ru/storage/mediabank/Zdravoohran-2023.pdf

cardiosclerosis [7, 8]. Clinically, four stages are identified in the post-traumatic course of myocardial contusion: the stage of primary traumatic disturbances, traumatic myocarditis, restoration of impaired functions, and the outcome stage [7]. In Russia, myocardial contusion is classified based on severity, which is determined by the extent of hemodynamic disturbances (mild, moderate, or severe) [7].

Patients presenting with clinical or echocardiographic signs of severe cardiac trauma, such as valve, septal, or ventricular wall injury resulting in cardiac tamponade, require immediate surgical intervention. However, even when diagnosed promptly, subsequent surgical treatment carries considerable risks. First, data from existing case series reported in the literature involving patients who underwent surgical intervention indicate that the extent of preoperative hemodynamic instability may represent the most significant prognostic factor, with survival rates reported to range from 39% to 100% [9]. Second, the use of anesthetic agents with cardiodepressive effects, along with positive pressure ventilation following intubation, may further compromise cardiac function in these patients [9].

At the same time, early diagnosis of myocardial contusion is often challenging. Seemingly minor injuries to the chest wall may be accompanied by severe closed cardiac trauma, and vice versa: symptoms of rib fractures, pulmonary injuries, or chest wall contusions may predominate, thereby masking the signs of myocardial contusion [7].

Delayed diagnosis and management of myocardial contusion can substantially increase the risk of poor outcomes following chest trauma. However, treatment of myocardial contusion remains symptom-oriented, as pathogenetic therapeutic strategies are still under development, primarily due to incomplete understanding of the underlying mechanisms. This review aims to systematize pathogenetically based approaches to the treatment of cardiac contusion and to highlight promising areas of pharmacological cardioprotection for further study of their efficacy in experimental models.

Pathogenesis of cardiac contusion: current status of the issue

The pathogenesis of myocardial contusion is characterized by a complex interaction between injury and adaptive mechanisms. Primary damage is primarily caused by the direct mechanical impact on the heart [10]. However, secondary injury – driven by hypoxia, energy deficiency, and inflammation – can be equally significant, and in some cases, even more harmful [11]. Direct damage to the microvascular network contributes to ischemia and bioenergetic hypoxia. In the affected tissue, anaerobic glycolysis becomes predominant, leading to hyperlactatemia, acidosis, decreased oxidative phosphorylation rates, depletion of high-energy phosphates, and consequently, increased lipid peroxidation in the damaged myocardium [11–13]. Local acidosis contributes to the suppression of mitochondrial respiratory chain enzyme activity and promotes the activation of proteolytic enzymes, which can exacerbate secondary injury to cardiomyocytes. Impaired efficiency of the electron transport chain not only lowers production of reduced form of nicotinamide adenine dinucleotide, but also leads to increased generation of reactive oxygen species (ROS), such as superoxide and hydrogen peroxide [14]. Concurrently, adaptive mechanisms are activated to restore homeostasis; however, their effectiveness is dependent on the dynamic interplay between stress-activating systems (such as the sympathoadrenal and hypothalamic–pituitary–adrenal axes) and stress-limiting

systems (including gamma-aminobutyric acid (GABA)ergic, opioidergic, and antioxidant pathways). When this balance is disrupted, physiological stress shifts to pathological distress, which exacerbates myocardial injury, promotes cardiomyocyte apoptosis, and compromises the heart's functional reserves.

ROS are recognized as critical pathogenic factors that contribute to endothelial dysfunction. These species impair calcium uptake by the myocardium, trigger arrhythmias, and promote cardiac remodeling and apoptosis [15]. It is well-established that maintaining cellular function relies on a delicate balance between ROS and antioxidant defenses [15]. Experimental studies have shown that myocardial contusion is associated with a reduction in the levels of reduced glutathione within injured cardiomyocytes, thereby exacerbating secondary tissue damage [16]. However, when selecting pharmacological agents to mitigate lipid peroxidation in myocardial contusion, it is essential to recognize that ROS signaling during hypoxia also plays a pivotal role in activating various cellular defense mechanisms [17].

Previous experimental studies have demonstrated that myocardial contusion in the post-traumatic period is associated with disturbances in central hemodynamics, which are driven by two key components: reflex responses and myocardial alterations, the latter of which has been detailed in the preceding section [18]. The reflex component is closely linked to neural reflexes mediated by activation of the parasympathetic nervous system. However, the role of these reflexes during the early post-traumatic phase of myocardial contusion should not be viewed solely as a pathogenic factor but also as a potential adaptive mechanism. Notably, the Bezold–Jarisch reflex may function as a form of myocardial adaptation, a concept supported by experimental data [19]. For example, studies have indicated that the administration of atropine – a substance that reduces parasympathetic activity – during the post-traumatic phase of myocardial contusion leads to an increased incidence of ventricular arrhythmias following the injury [20].

As a result of both primary traumatic and secondary hypoxic alterations in the myocardium, pain emerges as a key manifestation of the local inflammatory response, which is initiated in the injured tissue by the presence of damage-associated molecular patterns. Concurrently, pain can trigger emergency adaptive responses in the body, designed to create optimal conditions for survival under life-threatening circumstances. The General Adaptation Syndrome, the conception, proposed by G. Selye, describes a classical defense-compensatory strategy that facilitates the body's adjustment and may be used for characterization of processes during the post-traumatic phase of myocardial contusion [16]. Successful adaptation depends on the balanced interaction between stress-activating and stress-limiting systems, which together give rise to the classical protective response known as «stress». However, when stress-activating systems dominate excessively or stress-limiting systems are insufficient, this adaptive mechanism may transition into a maladaptive process, referred to as «distress».

The two principal stress-activating systems in mammals are the sympathoadrenal system and the hypothalamic-pituitary-adrenal axis. The sympathoadrenal system has a wide range of significant effects on the heart and cardiovascular system, including positive chronotropic (increased heart rate), inotropic (enhanced contractility), lusitropic (accelerated relaxation), dromotropic (improved conduction), and bathmotropic (increased excitability) effects. Furthermore, it contributes to elevated blood pressure by enhancing venous and arteriolar tone [21]. Activation of the hypothalamic-pituitary-adrenal axis involves stimulation of parvocellular neurons in the paraventricular nucleus of

the hypothalamus, leading to increased production of corticotropin-releasing hormone, adrenocorticotropic hormone, and the subsequent release of corticosteroids. These hormones play a crucial role in maintaining homeostasis by optimizing carbohydrate metabolism, regulating immune responses, normalizing fluid and electrolyte balance, and modulating behavioral and emotional responses – ultimately contributing to the effective execution of the body's protective stress response [22].

Closely interacting with the stress-activating systems are the stress-limiting systems, which include central components, such as the GABAergic and opioidergic systems, and peripheral components, including the prostaglandin system and tissue antioxidants [23]. The GABAergic system plays a key role in modulating the effects of the sympathoadrenal system. Experimental studies have shown, for instance, that chronic stress in male rats may weaken GABAergic activity within the paraventricular nucleus and alter autonomic cardiac regulation [24]. One of the key effects of GABA is its ability to suppress the secretion of corticotropin-releasing hormone in the hypothalamus [25]. The opioidergic stress-limiting system comprises neurons located in the thalamus, amygdala, hypothalamus, striatum, nucleus accumbens, pituitary gland, as well as in the cerebral cortex and olfactory bulbs. These structures are involved in the synthesis of endogenous opioids, such as endorphins, enkephalins, and dynorphins, whose physiological effects are mediated through the activation of opioid receptors [26]. Peripherally, opioid receptors are expressed in the adrenal cortex, on the membranes of immunocompetent cells, and in the vascular endothelium [27].

Despite their functionally opposing roles, the opioidergic and stress-activating systems are unified by a common objective: facilitating the organism's adaptation to environmental stressors. Their interaction reflects a finely tuned homeostatic balance, wherein mutually antagonistic pathways dynamically modulate each other in accordance with internal and external demands. This interdependence is evident at the metabolic level, where both adrenocorticotropic hormone and β-endorphin are derived from the common precursor proopiomelanocortin. Importantly, activation of opioid receptors has been shown to suppress adrenal glucocorticoid secretion, underscoring a feedback loop that modulates the activity of both systems [28].

The opioidergic system is characterized by effects that are partially opposite to those of the sympathoadrenal system. In contrast to the vasoconstrictor action of catecholamines, opioids cause moderate vasodilation and exhibit antiarrhythmogenic activity, but the severity of these effects depends on the type and localization of receptors [29]. The key role of the opioidergic system in stress-limiting processes is associated with the suppression of anxiety and fear, states that are enhanced by catecholamines. An equally important characteristic of opioids is their analgesic effects realized through activation of the serotoninergic antinociceptive system [30].

The prostaglandin stress-limiting system, the key components of which are prostaglandin E and prostaglandin I_2, realizes its protective effects through three main mechanisms. The first, it suppresses sympathetic activity by directly inhibiting norepinephrine production. The second, prostaglandin E and especially prostaglandin I_2 cause marked vasodilation of coronary arteries, improving myocardial perfusion [31]. The third, prostaglandins limit lipid peroxidation, preventing damage to cell membranes and organelles, which enhances antioxidant defense [32].

Although a resilient adaptive strategy is established in all rats during the post-traumatic period, regardless of their baseline stress resilience, individual

stress reactivity plays a crucial role in modulating the balance between stress-activating and stress-limiting systems following cardiac injury [16]. Experimental studies in rats have shown that inherent stress tolerance is a key determinant of the efficacy of adaptive mechanisms [16]. The post-traumatic phase of experimental myocardial contusion is characterized by a reduction in both force-generating and velocity-dependent indices of myocardial contractility, along with a decline in myocardial functional reserves, independent of baseline stress resilience. However, high baseline stress resilience is associated with better preservation of myocardial contractile function and reserves, whereas low stress resilience is linked to greater myocardial dysfunction and a more pronounced reduction in the functional reserves of the injured heart [33]. The observed differences in the severity of contractile dysfunction between high- and low-resilience phenotypes can likely be attributed to varying degrees of secondary myocardial injury within the contusion zone. These differences are probably mediated by the distinct balance between stress-activating and stress-limiting mechanisms involved in the pathogenesis of secondary damage [33].

In animals with high stress resilience, an optimal adaptive strategy is established, effectively mitigating secondary myocardial injury and preserving cardiac function during the post-traumatic period [16]. In contrast, individuals with low stress resilience exhibit a predominance of stress-activating system activity, leading to the development of a distress syndrome [16]. This imbalance results in pronounced secondary myocardial damage, characterized by reduced contractile performance and diminished functional cardiac reserves, a disruption in cellular homeostasis marked by a shift toward apoptosis over autophagy, and a significant depletion of reduced glutathione levels in cardiomyocytes, thereby intensifying oxidative stress. Collectively, these pathological alterations contribute to the elevated mortality observed in low-resilience animals [16, 33].

Immunohistochemical analysis revealed activation of both autophagy (Beclin-1) and apoptosis (Caspase 3) within the myocardial injury zone following experimental contusion, irrespective of the animals' baseline stress resilience [34]. However, the expression dynamics of these markers differed markedly between groups. In high-resilience individuals, a progressive increase in Beclin-1 expression was observed, indicative of enhanced autophagic flux. In contrast, low-resilience animals exhibited a decline in Beclin-1 levels. Caspase 3 expression was elevated across all groups, although baseline levels were significantly higher in low-resilience rats. These findings suggest that autophagy may serve an adaptive, cytoprotective function in the context of less severe myocardial injury, as observed in stress-resilient animals, whereas apoptosis predominates in the setting of more extensive damage, characteristic of low-resilience phenotypes [34].

In a model of experimental myocardial contusion, the post-traumatic period was characterized by a statistically significant reduction in desmin expression ($p<0.0001$) and the number of intercalated discs ($p<0.0001$) within the injury zones of animals in the experimental group, as compared to controls, regardless of their baseline stress resilience. Notably, the subgroup of low-resilience animals exhibited significantly lower values for both parameters when compared to their high-resilience counterparts [35].

Secondary myocardial damage in the posttraumatic period caused by inflammation, bioenergetic hypoxia, and activation of lipid peroxidation is completed by fibroblast activation and replacement of damaged areas in the heart with connective tissue. Activated fibroblasts, forming connective tissue in previously damaged areas, change the structure of the myocardium.

Posttraumatic myocardial fibrosis disturbs bioenergetic exchange in the myocardium, as connective tissue increases energy dissipation during the conversion of metabolic energy into effective myocardial contraction. Cardiac remodeling occurring in the posttraumatic period contributes to the progression of structural-functional and spatial-geometric abnormalities, which may cause the development of arrhythmias and even heart failure in the remote period. Cardiac fibrosis is well studied on the model of myocardial infarction, however, the process of fibrosis as a result of cardiac contusion, which is conditioned, among other things, by the ratio in the posttraumatic period of primary, secondary damage and adaptive mechanisms, remains poorly understood [36].

The use of recombinant human fibroblast growth factor 21 (rhFGF21) is a promising direction for the correction of excessive connective tissue overgrowth in the myocardium. Experimental data demonstrate the ability of rhFGF21 to exert a protective effect against cardiac fibrosis induced by myocardial infarction [37], which may ultimately reduce the risk of arrhythmia development in the postinfarction period [36, 38]. However, there are no data on the evaluation of rhFGF21 efficacy in the posttraumatic period of experimental cardiac contusion in the literature.

Cardiac contusion: proven efficacy of pharmacotherapy and prospects for experimental design

Despite substantial advances in understanding the pathogenesis of myocardial contusion, the development of effective pathogenetically targeted therapies remains a pressing scientific challenge. Contemporary research emphasizes the need for an integrated approach aimed at addressing key mechanisms of injury, including bioenergetic hypoxia, energy deficiency, inflammation, and cellular imbalance involving apoptosis and autophagy [11, 16, 34]. The initial mechanical impact in myocardial contusion triggers a cascade of pathological events that closely parallel the processes underlying ischemic and reperfusion-related myocardial injury. Both conditions are marked by bioenergetic hypoxia, disturbances in ionic homeostasis, inflammatory activation, and impaired regulation of adaptive cellular responses. This pathogenetic convergence provides a compelling rationale for investigating, in the post-traumatic context of myocardial contusion, therapeutic strategies that have demonstrated efficacy in the treatment of ischemic heart disease and reperfusion-reoxygenation syndromes. Experimental data reinforce the promise of this translational approach. In particular, trimetazidine, a pharmacological agent widely employed in cardiology, has shown cytoprotective activity in models of myocardial contusion [39]. Nevertheless, the effective translation of these therapeutic strategies into routine clinical practice for the treatment of myocardial contusion necessitates further comprehensive experimental and clinical investigations. These studies should be directed toward establishing optimal dosing protocols, elucidating the therapeutic potential of combination regimens, and examining the long-term outcomes associated with such interventions.

Promising therapeutic directions involve targeted strategies that integrate two fundamental approaches:

1) Correction of myocardial injury, encompassing the mitigation of bioenergetic hypoxia, restoration of energy and ionic homeostasis, suppression of secondary damage driven by inflammation within the injured tissue, and regulation of cell death pathways, specifically apoptosis and autophagy;

2) Optimization of adaptive mechanisms, including modulation of the activity of stress-activating and stress-limiting systems, as well as fine-tuning of tissue-level adaptive responses such as apoptosis and autophagy.

Correction of myocardial injury

Correction of myocardial injury includes the use of metabolic cytoprotectors (trimetazidine, glutamine, mildronate, succinate-containing drugs, coenzyme Q10) [39-43].

The use of trimetazidine in an experimental model of myocardial contusion has demonstrated substantial cardioprotective effects. Our study demonstrated that pre-administration of trimetazidine helps maintain cardiomyocyte membrane integrity and supports myocardial contractility during the post-traumatic period. These results were further confirmed by *ex vivo* data from a model of the isolated isovolumically contracting heart [39]. In addition, an antiarrhythmic effect of trimetazidine, similar to that observed with glutamine, was detected in another our study [42]. Both compounds, when administered as monotherapy, significantly reduced the incidence of early post-traumatic arrhythmias. The authors attributed these effects to the metabolic cytoprotective properties of these agents, which enhance reparative processes [42]. These findings underscore the multifaceted beneficial impact of trimetazidine on both the structural and functional integrity of the myocardium, further supporting its potential clinical application in managing myocardial contusion.

The use of sodium polydihydroxyphenylene thiosulfonate in an experimental model of myocardial contusion has yielded conflicting results. We demonstrated previously that pre-traumatic administration of this antihypoxic effectively suppressed the onset of sinus arrhythmia, paroxysmal ventricular tachycardia, and intraventricular conduction disturbances, with its efficacy found to be independent of baseline arterial pressure [18]. However, the same study revealed a significant limitation of the therapy: a majority of animals receiving sodium polydihydroxyphenylene thiosulfonate developed pronounced arterial hypotension and a substantial reduction in cardiac output, primarily due to bradycardia. These hemodynamic disturbances persisted throughout the post-traumatic period, resulting in a tenfold increase in mortality compared to the control group [18]. These findings suggest that while sodium polydihydroxyphenylene thiosulfonate exhibits notable cardioprotective effects against arrhythmias, its destabilizing impact on systemic hemodynamics significantly reduces its therapeutic utility in the context of myocardial contusion.

Metabolic correction using succinate-based agents, such as meglumine sodium succinate, combined medication, containing inosine, nicotinamide, riboflavin and succinic acid, and ethylmethylhydroxypyridine succinate, represents a promising therapeutic strategy for managing myocardial contusion. Numerous studies have demonstrated the clinical efficacy of these compounds in conditions involving ischemic, hypoxic, and toxic myocardial injury, primarily by optimizing energy metabolism and enhancing antioxidant defenses [39, 40, 44]. However, the evidence supporting their use in the context of myocardial contusion remains limited. While Meglumine sodium succinate has been successfully employed in clinical cardiology practice, its ability to modulate reparative processes following traumatic myocardial injury requires further experimental validation. Additional research is crucial to elucidate the role of these agents in attenuating post-traumatic remodeling,

preventing arrhythmias, and improving clinical outcomes in the aftermath of myocardial contusion [40].

A substantial body of research has investigated the effects of pro-inflammatory cytokine inhibitors, such as anakinra and tocilizumab. Tocilizumab, in particular, has demonstrated variable outcomes in cardiology. In patients with ST-elevation myocardial infarction, the drug was shown to improve clinical prognosis without significantly altering levels of circulating endothelial or platelet-derived chemokines, although these concentrations were found to correlate with concomitant heparin administration [45]. Moreover, tocilizumab was reported to reduce levels of citrullinated histone H3, a key marker of neutrophil extracellular trap (NET) formation (NETosis), thereby mitigating secondary myocardial injury [46]. The randomized ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction (ASSAIL-MI) trial, which included 101 patients with acute ST-elevation myocardial infarction, confirmed the beneficial effects of tocilizumab, including an increase in salvaged myocardial tissue volume [47].

However, the use of tocilizumab in patients with non-ST-elevation myocardial infarction has been associated with increased levels of citrullinated histone H3, indicative of enhanced NETosis activity [48]. These findings underscore the need for further investigation into the dual role of tocilizumab in modulating inflammatory pathways in the setting of myocardial infarction. In the context of myocardial contusion, experimental evaluation of such effects is particularly relevant, given the potential impact of NETosis on myocardial remodeling and post-traumatic outcomes.

Another emerging avenue in anti-inflammatory therapy for cardiac pathology involves the inhibition of the nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain- containing receptor 3 (NLRP3) inflammasome, which has been identified as a potential key regulator at the intersection of energy metabolism, inflammation, and gut microbiota–derived metabolites. Elucidating the interplay among these factors may facilitate the identification of novel molecular targets for the prevention and treatment of cardiovascular disease, ultimately influencing disease progression [49]. Inhibition of NLRP3 activation has been shown to exert beneficial effects on metabolic pathways and autophagic flux in the hearts of mice fed an obesogenic diet. Thus, targeting NLRP3 activation holds promise for the treatment of both metabolic and cardiovascular conditions — including myocardial contusion [50]. Testing such inhibitors in experimental models of myocardial contusion appears to be both scientifically justified and therapeutically promising.

Although the potential efficacy of statins in the context of myocardial contusion requires further experimental validation, their well-established anti-inflammatory properties suggest a potential cardioprotective effect. A meta-analysis of statin therapy in patients with myocardial infarction and non-obstructive coronary artery disease (n=11,171, including 9,129 receiving statins) demonstrated a significant reduction in mortality and the incidence of fatal cardiovascular events [51]. These findings support the consideration of statins as a promising pathogenetic approach to mitigate the inflammatory sequelae of traumatic myocardial injury.

Pharmacological regulation of autophagy using agents such as rapamycin and spermidine represents a promising therapeutic strategy in the management of myocardial injury. Of particular interest is the role of mammalian target of rapamycin (mTOR), a key regulatory protein involved in amplifying the inflammatory response. Clinical studies have shown that early inflammation

following ST-elevation myocardial infarction significantly influences infarct size and the trajectory of left ventricular remodeling. In this context, mTOR inhibition has demonstrated potent cardioprotective effects. This was substantiated by a study conducted by Stähli et al., which reported a significant reduction in infarct size following acute myocardial infarction through targeted mTOR blockade [52].

Experimental data additionally reveal the mechanisms of this effect. In model of acute myocardial infarction, rapamycin, being a classical mTOR inhibitor, causes activation of autophagic processes in the damaged myocardium. As demonstrated by Aisa et al., this leads to a significant reduction in infarct area and improvement of cardiac contractile function after coronary artery ligation [53]. It is noteworthy that cytoprotective properties of rapamycin are also manifested in cell therapy. The study by Li et al. showed that preliminary activation of autophagy by rapamycin significantly improves survival and differentiation of transplanted mesenchymal stem cells in the model of ischemia-reperfusion [54].

Recent studies have opened new avenues for mTOR inhibition through the application of nanotechnology-based strategies. An innovative approach developed by Kwon et al. involves the use of liposomal nanoparticles encapsulating both myocardial injury–associated antigens and rapamycin. This system promotes the formation of tolerogenic dendritic cells and activates regulatory T cells that limit cardiac inflammation. Regulatory T cells, in turn, promote the phenotypic transformation of macrophages from a pro-inflammatory to a reparative profile, thereby mitigating adverse cardiac remodeling and ultimately improving cardiac function [55].

Taken together, current evidence strongly supports the potential of targeted mTOR inhibition and the modulation of autophagic processes as an effective strategy to limit myocardial injury, prevent excessive inflammation, and optimize reparative responses. It is crucial to note that these mechanisms may be relevant not only in the context of ischemic or reperfusion-induced myocardial damage but also in cases of traumatic cardiac injury. However, further experimental studies are necessary to validate this hypothesis and define the most effective approaches for autophagy modulation in the setting of myocardial contusion.

Optimization of adaptation processes

The second strategic direction in the treatment of myocardial contusion may be aimed at optimizing adaptation processes in cardiac contusion, which usually focuses on reducing hyperactivation of stress-releasing systems (β-blockers, glucocorticoid receptor antagonists) and enhancement of stress-limiting mechanisms through GABAergic (aminophenylbutyric acid), opioid (tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate) [16], and antioxidant (rutin, also termed rutoside) pathways [56]. Additionally, ferroptosis inhibitors (ferrostatin-1) and autophagy stimulators that can improve cardiomyocyte survival can be studied.

One of the primary clinical manifestations of myocardial contusion is the occurrence of diverse arrhythmias. In cases where the patient exhibits a predisposition to tachyarrhythmias, the use of β-adrenergic blockers is considered a rational therapeutic strategy [57]. The cardioprotective effects of this drug class have been extensively characterized and are mediated through multiple intracellular signaling cascades initiated by distinct G-protein subunits [58]. β-blockers reduce myocardial hypertrophy and fibrosis caused by excessive

activation of sympathetic nervous system and renin-angiotensin-aldosterone system. Furthermore, by limiting catecholamine overload, β-blockers protect the myocardium from necrosis and apoptosis, thereby reducing the extent of injury to cardiomyocytes.

Another potential target for pathogenetically oriented therapy in myocardial contusion is the activation of GABA receptor pathways. This class includes benzodiazepines (e.g., diazepam, phenazepam, midazolam), barbiturates (e.g., thiopental sodium, phenobarbital), as well as baclofen, aminophenylbutyric acid, and sodium oxybate. Some of these agents may be employed for analgesia following trauma, including myocardial contusion; however, data on their direct effects in the context of myocardial contusion pathogenesis are currently lacking. Nevertheless, activation of the GABAergic system has been associated with downregulation of sympathoadrenal activity. In a rat model of ischemia–reperfusion injury, stimulation of central GABAergic structures was shown to reduce circulating catecholamine levels and myocardial injury markers, while also decreasing the extent of myocardial necrosis [59].

The following effects have been described for opioid receptor agonists, which may be of interest from the standpoint of pathogenetic therapy of cardiac contusion: antiarrhythmogenic, cardioprotective, counterinsulatory, vasoactive, anti-stressor, antioxidant, analgesic [60]. Notably, the effects of opioids on vascular tone and heart rate are ambiguous, given the diversity of opioid receptors and their localisation. To a large extent, these effects depend on the ability of the substance to penetrate the blood-brain barrier [61].

Opioid receptors μ- and δ- are able to increase the expression of type 1 glucose transporters on the cell surface [62]. This mechanism likely enhances myocardial metabolic adaptation in the context of traumatic injury. In a polytrauma model in pigs, including blunt chest trauma, it has been shown that in contrast to physiological conditions, when free fatty acids are the main energy substrate for cardiomyocytes, the use of glucose as an energy substrate in cardiomyocytes increases after injury [63]. Excitation of opioid receptors causes modulatory effects of adrenaline and noradrenaline on the heart

In the majority of studies reporting beneficial effects of opioid receptor agonists, the compounds employed were those with high permeability across the blood–brain barrier, a property closely linked to the clinically valuable analgesic effects of this pharmacological class. However, in experimental settings aimed at elucidating the local, peripheral actions of opioids, the use of opioid peptides with limited blood-brain barrier penetration may be more appropriate, allowing for a more selective assessment of their direct cardiotropic and vasoregulatory effects [16].

During the 1970s and 1980s, researchers in the Union of Soviet Socialistic Republics developed tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate, a synthetic analog of leucine-enkephalin. In contrast to the endogenous peptide, tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate features a substitution of glycine with D-alanine, which significantly slows its enzymatic degradation by enkephalinases. Additionally, an arginine residue was appended to the C-terminal region of the molecule. This positively charged modification was introduced to prevent tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate from penetrating into higher centers of the central nervous system, thereby restricting its activity to peripheral targets [64].

In addition, an effect on the processes of collagen synthesis and breakdown in the liver has been described for tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate [65], which may be interesting, given the importance of fibrosis in the pathogenesis of cardiac injury. In turn, intense inflammation

occurring after cardiac injury may aggravate the development of myocardial fibrosis. A decrease in neutrophil phagocytosis activity has been described for tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate [66], which may also be useful for cardioprotection.

Antioxidant therapy represents a pathogenetically sound strategy in the treatment of myocardial contusion, given the central role of oxidative stress and inflammation in its pathogenesis. The positive effect of rutin on the state of myocardial antioxidant systems was demonstrated on the model of blunt cardiac trauma in rats [56], which opens prospects for further study of this group of drugs. However, uncontrolled use of drugs whose effects are aimed at suppressing the production of ROS can cause the so-called antioxidant stress. The essence of this process is that ROS in the cell are not only a damaging factor but also an important intracellular messenger that regulates such processes as apoptosis and autophagy. Antioxidant stress in tumor cells may be responsible for the formation of drug resistance in tumor cells [67]. The obtained data on the role of oxidative stress in the pathogenesis of cardiac contusion justify the need for experimental studies to verify the therapeutic potential of antioxidants.

A multi-level therapeutic approach to myocardial contusion may not only interrupt the vicious cycle of injury progression but also enhance endogenous mechanisms aimed at myocardial protection during the post-traumatic period. Such strategies open new avenues for the restoration of cardiac structure and function, the prevention of post-traumatic cardiosclerosis and pathological remodeling, and, ultimately, the reduction of mortality associated with myocardial contusion.

Traditional herbal medicines in the treatment of myocardial contusion: therapeutic potential of the Chinese Pharmacopoeia

A promising direction in the pathogenetically oriented treatment of myocardial contusion is the use of herbal preparations listed in the Chinese Pharmacopoeia. The efficacy of these compounds in models of ischemia, reperfusion injury, and heart failure has been experimentally validated, offering a foundation for their potential adaptation to the context of traumatic myocardial injury. The key classes of these agents are outlined below, categorized according to two principal therapeutic strategies:

The first therapeutic strategy focuses on counteracting hypoxia, oxidative stress, and inflammation:

1) *Salvia miltiorrhiza* (Dan Shen), a widely studied herbal remedy exerts multiple cardioprotective effects, primarily attributed to a unique class of bioactive compounds known as tanshinones. These compounds have been shown to inhibit the generation of ROS and suppress lipid peroxidation [68]. *S. miltiorrhiza* also improves microcirculatory flow by reducing thromboxane A_2 levels and inhibiting platelet aggregation [69]. Furthermore, it exhibits anti-inflammatory activity through downregulation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cell) signaling and subsequent decreases in pro-inflammatory cytokine levels, including tumor necrosis factor α and interleukin-6 [70]. In ischemia–reperfusion models, *S. miltiorrhiza* has been shown to reduce the extent of secondary myocardial injury [71].

2) *Astragalus membranaceus* (Huang Qi) contains a class of active compounds known as astragalosides, which contribute to its multifaceted

cardioprotective profile. First, astragalosides enhance endogenous antioxidant defenses by stimulating the synthesis of superoxide dismutase and glutathione [72]. Second, they exert anti-inflammatory effects by reducing levels of pro-inflammatory cytokines such as tumor necrosis factor α and interleukin-6 [70]. Additionally, *A. membranaceus* has been shown to improve myocardial contractile function in models of heart failure [73].

3) *Curcuma longa* (Jiang Huang) contains active compound curcumin, possessing cardioprotective properties, particularly in the context of ischemic and hypoxic myocardial injury [74]. Experimental studies have demonstrated its ability to suppress pathological processes such as myocardial hypertrophy and fibrotic remodeling. The active compound contributes to the normalization of ventricular structural and functional parameters by modulating key pathways involved in cardiac remodeling [74]. Moreover, curcumin has been shown to reduce pharmacologically induced cardiotoxicity and provide therapeutic benefits in models of cardiomyopathy associated with diabetes mellitus [74]. Additional mechanisms of curcumin's action include the correction of endothelial dysfunction, inhibition of foam cell formation, and suppression of excessive proliferation of vascular smooth muscle cells. Collectively, these effects broaden its potential applications in the prevention and treatment of various cardiovascular pathologies [74].

The second therapeutic strategy focuses on the optimization of endogenous adaptive mechanisms. Within this domain, the following agents show potential efficacy:

1) The effect of *Eleutherococcus senticosus* (Ci Wujia) has been demonstrated in models of ischemia-reperfusion syndrome [75]. Its established effects include the reduction of cortisol levels and modulation of the hypothalamic-pituitary-adrenal axis [76], thereby contributing to the rebalancing of activity between stress-activating and stress-limiting systems – an essential component in adaptive cardioprotection.

2) *Panax ginseng* (Ren Shen) is recognized as an effective cardioprotective agent, a property that correlates with its capacity to modulate tissue-level adaptive responses under conditions of ischemia–reperfusion injury. Its active constituents selectively inhibit key signaling pathways associated with programmed cardiomyocyte death, thereby preserving cellular homeostasis [77]. The cardioprotective effects of *P. ginseng* are mediated, in part, by the attenuation of oxidative stress through suppression of ROS-generating systems, as well as the indirect inhibition of pro-inflammatory cytokine synthesis. These actions collectively enhance anti-apoptotic signaling, thereby increasing myocardial resistance to ischemia–reperfusion damage [77]. Furthermore, studies have demonstrated that ginsenosides derived from *P. ginseng* regulate protein acetylation, contributing to mitochondrial function and offering additional protection to cardiomyocytes [78].

3) *Ginkgo biloba* (Yin Xing/ Yin Xing Ye) may enhance adaptive responses through several mechanisms. First, it exerts an anxiolytic-like effect, which can mitigate stress-induced physiological dysregulation [79]. Second, its well-characterized anticholinesterase activity, particularly that of the *G. biloba* standardized extract, prevents acetylcholine degradation, thereby enhancing cholinergic transmission and alleviating stress-related impairments [80]. Notably, *G. biloba* standardized extract is also recognized as a natural antagonist of platelet-activating factor. Clinical studies have demonstrated the efficacy of Ginkgo biloba extract in the treatment of various cardiovascular and cerebrovascular conditions, as well as in the management of reperfusion and reoxygenation syndromes [81].

4) *Schisandra chinensis* (Wu Wei Zi), known for its cardioprotective effects in ischemia-reperfusion syndrome [82], contains the active compound Schisandrin B. This compound exhibits antioxidant and anti-inflammatory properties, as well as inhibition of RAGE/NF-κB/MAPK (receptor for advanced glycation end products / nuclear factor kappa-light-chain-enhancer of activated B cells / mitogen-activated protein kinase) signaling and modulation of autophagy markers [83]. Research on the efficacy of *S. chinensis* in treating idiopathic pulmonary fibrosis suggests that its antifibrotic effects may be linked to the activation of autophagy through the AKT/mTOR (protein kinase B / mTOR) pathway [84].

A promising direction in therapeutic strategy involves the use of combination therapies. A combined approach allows for the effective exploitation of synergies between herbal compounds. For example, a combination of *P. ginseng* and *G. biloba* extracts has demonstrated significant neuroprotective effects, making it an effective treatment for various neurological disorders, including stroke [85]. The combined use of *P. ginseng* and *G. biloba* has shown neuroprotective properties, mediated by the inhibition of neuronal apoptosis. This effect was linked to improvements in neuronal structure and subcellular organelles, enhancement of cellular proliferative activity, and suppression of Caspase 3 overexpression in neurons [86].

Conclusion

Contemporary research into the pathogenesis of myocardial contusion has led to substantial progress in elucidating the fundamental mechanisms of myocardial injury following mechanical trauma. Despite these advances, the search for effective therapeutic strategies for this condition remains an urgent and unresolved task. The pathogenetic processes that unfold during the post-traumatic phase of myocardial contusion, such as bioenergetic hypoxia, disturbances in ionic homeostasis, inflammatory responses, and patterns of tissue adaptation, closely parallel the mechanisms observed in myocardial damage caused by ischemia and subsequent reperfusion. This conceptual parallel forms a theoretical basis for considering the use of established cardioprotective agents during the post-traumatic phase of myocardial contusion, particularly those with proven efficacy in the context of ischemic and reperfusion-related myocardial injury. However, translating these therapeutic strategies into clinical practice for patients with myocardial contusion requires thorough experimental validation. Of particular importance is the investigation of dose-dependent effects, the synergistic potential of combination therapy, and the long-term impact on the structural and functional integrity of the myocardium. A promising direction in the management of myocardial contusion is the development of comprehensive treatment regimens that integrate anti-inflammatory, metabolic, and antifibrotic components. In this context, particular attention should be given to traditional herbal remedies from the Chinese pharmacopoeia, which are distinguished by their polyvalent effects on key pathogenic pathways. Their ability to simultaneously modulate oxidative stress, energy metabolism, and cellular homeostasis offers new opportunities to overcome the limitations of monotherapy. Further research in this area may make a significant contribution to improving therapeutic strategies for myocardial contusion by enabling a more comprehensive correction of the complex disturbances characteristic of post-traumatic myocardial injury.

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