

Dual Application of Nanotechnology of Pine Needles Catalyst and Graphene-Based System for Cardioprotective Application

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ABSTRACT

The most widespread cause of death in the world, cardiovascular diseases (CVDs), require the development of new therapeutic approaches that would overcome the current constraints of management, in terms of responding to the oxidative tissue damage, as well as facilitating regeneration. The article represents a new integrative nanotechnological method that combines a pine needle-derived nanocatalyst with a graphene-based system in the context of prerequisites of cardioprotection. The platform takes advantage of a green synthesis process, in which the phytochemical-rich Pinus extract produces multi-enzyme (SOD, catalase, peroxidase) mimetic metal nanozymes. The bioactive nanocatalysts are conjugated on the functionalized graphene oxide (GO) and reduced graphene oxide (rGO) sheets, which are famous because of their high electrical conductivity, mechanical strength, and surface area. The dual-system nanohybrid that results is a synergistic combination of the ability of the graphene component to deliver therapeutics precisely, condition electrically, and provide mechanical strength with the high-potency, catalytic ability of the pine nanozyme to scavenge reactive oxygen species (ROS). The synthesis, characterization, and multi-target of this hybrid system (such as the regulation of the Nrf2 antioxidant system, NF- κ B/NLRP3-mediated inflammation, and cardiomyocyte-apoptosis) are provided. In addition, we discuss the most recent applications of graphene-based materials to drug delivery, cardiac tissue engineering, and bioelectronic interfaces, which are the basis of the rationale behind this integration. This dual-uses approach is based on the groundbreaking, theranostic platform of ischemia-reperfusion injury mitigation, cardiotoxicity in relation to drugs, and myocardial repair, which is supported by emerging human safety data on graphene oxide, one of the major steps toward catalytic and regenerative cardiovascular nanomedicine.

Keywords- Nanotechnology, nanocatalyst, cardioprotective, cardiovascular disease, pine needle, graphene.

I. INTRODUCTION

According to the World Health Organization, cardiovascular diseases (CVDs) are the cause of death in the world and the foremost global health challenge of the 21st century, which causes the estimated 17.9 million deaths per year and 32 percent of all mortality in the world in 2025. This is not equally distributed with more than 75% of the CVD deaths being in the low- and middle-income countries, which points at a very crucial disparity in the access of health care and resources. The financial burden is also equally appalling, as CVDs present the world economy with hundreds of billions of dollars worth of direct healthcare costs, cost of medications, and due to lost productivity through disability and early death. Ischemic heart disease and stroke are the two most frequent forms of the epidemiological spectrum of CVDs, but heart failure, cardiomyopathies, and arrhythmias are also possible, and they all involve complex pathophysiological pathways, including endothelial dysfunction, atherosclerotic plaque formation, myocardial ischemia, and cellular damage by oxidative stress. This burden is expected to be further increased by the aging world population and the escalating occurrence of metabolic risk factors, which include high blood pressure, diabetes and obesity, making the need to know more effective, accessible and specific therapeutic modalities an urgent and unsatisfied necessity. Although there are certainly positive effects of current standard-of-care therapies, they are rife with enormous limitations, which do not allow to achieve optimal patient management. Pharmacological regulars such as statins, anticoagulant drugs, beta-blockers, and angiotensin-converting enzyme are used to control primarily the symptoms and risk factors but in most cases do not prevent or reverse the underlying tissue damage. In particular, the non-compliance rate with statins is still high because of such side effects as myopathy, and their effectiveness is not always consistent. Percutaneous coronary angioplasty with stenting and coronary artery bypass grafting are radical interventions in acute coronary syndrome, but are traumatic procedures and inherently perioperative in nature, which treat macrovascular obstructions but leaves untreated the microvascular dysfunction and the endemic inflammatory and oxidative environment that remains to compromise the myocardium.

Moreover, an additional shortcoming of most systemic medications is the inability to specifically strike diseased heart tissues, which results in sub-therapeutic levels at the site of injury and intolerable off-target side effects. A burst of reactive oxygen species (ROS) is recognized as the central event in such conditions as doxorubicin induced cardiotoxicity or myocardial ischemia-reperfusion injury, but we do not yet have clinically useful agents capable of selectively inhibiting such an oxidative cascade at the cellular level in the heart without interfering with the signal transduction of

important redox processes elsewhere in the body. It is against this background of waiting universal necessity and treatment insufficiency that nanotechnology now stands as a very promising form of radical change in the context of cardiovascular medicine.

The potential of nanotechnology is in its basic ability to create materials and devices with the scale of biological molecules and cellular structures, making it possible to exercise control over therapeutic interactions like never before. These systems can be used to address biological barriers at the nanometer scale (generally 1-100 nm) and to interact with specific cells or organelles and react to the specific pathophysiological microenvironment of diseased tissue. In cardiology, this could translate to a number of translational potential applications, namely, controlled drug delivery to infarcted or inflamed myocardium, reduced systemic exposure; regenerative medicine with nano-structured scaffolds that guide the growth and electrical incorporation of new cardiac tissue; advanced biosensing to real-time cardiac biomarker or electrophysiology; and cytoprotection via nanozymes that catalytically ascorb by harmful ROS. The overall objectives are to enhance the efficacy of therapy, minimize the side effects, and introduce completely new types of treatment that are not focused on managing symptoms but rather repairing and regenerating. Graphene-based materials (GBMs) such as graphene oxide (GO) and reduced graphene oxide (rGO) have become the subject of immense attention among the profusion of nanomaterials and there is a particular overlap of properties that are ideal in biomedical applications. Their two-dimensional and atomically thin nature offers a spectacular surface area of loading drugs or functionalization. Their high electrical conductivity is most useful in cardiac applications, since they can be useful in the conduction of electrical signals between the cardiomyocytes, which any tissue engineering construct hoping to repair the electrically synchronous myocardium must be capable of doing. In addition, GBMs are incredibly strong in a mechanical sense and remarkably flexible, which, in turn, enables incorporation with flexible patches or coatings capable of sustaining the dynamic beating of the heart. Scholars have already shown the applicability of GBMs in the development of conductive scaffolds to improve the differentiation of stem-cell-derived cardiomyocytes, in the development of sensitive biosensing cardiac troponin biosensors, and in the development of efficient gene/drug delivery vectors. Nevertheless, a mono-culture of graphene system does not tend to offer any physical or conducting functionality, without the presence of an intrinsic, strong biological catalytic activity to directly regulate the pathological biochemical pathways of CVDs.

It is here that a novel idea of a dual-system, where a bio-catalytic pine needle-derived nanozyme is paired with a graphene-based system has the potential to open up a very high capability of synergy. Pine needles

(Pinus species) is a valuable renewable natural source of bio-activity phytochemicals such as flavonoids, phenolics and terpenes that are antioxidant, anti-inflammatory and anti-microbial. Pine needle extracts can be exploited by a green synthesis process to produce metallic or metal oxide nanoparticles (e.g. selenium, zinc oxide, cerium oxide) or serve as catalytic centers themselves. Such nanoparticles can be used as nanozymes, nanomaterials which mimic the activity of enzymes. In particular, they can be designed to replicate the activity of important endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, or glutathione peroxidase, that are overloaded in the case of cardiac ischemic activity. In the proposed dual-system, the suggested nanocatalysts, which are so powerful and consist of plants, are envisioned to be anchored to a huge surface of a piece of graphene oxide. This merger results in formation of a multifunctional theranostic agent: the graphene component is a high drug-loading platform, electrically conductive, structurally stable, and capable of targeted delivery and the pine needle nanozyme is a continuous, enzyme-based protection against oxidative and inflammatory injury at a cellular scale.

In one example, a hybrid system could be designed to work in the ischemic zone in the case of a model of myocardial infarction. The nanozyme component would provide a catalytically sustainable neutralization of the deluge of ROS, potentially preserving viable cardiomyocytes, minimizing the size of an infarct, and triggering the hostile inflammation microenvironment to repair, which is possible with the help of the graphene base to restore electrical functionality to the damaged tissue frontier. Such a strategy combines a set of advantages of existing therapy: it offers a localized, targeted response; offers a catalytic, prolonged antioxidant defense, by far better than single-molecule antioxidant drugs; and provides a combination of biochemical cyto-protection and biophysical assistance to tissue functionality. Therefore, the merging of material performance with the innate biological wisdom of the plant-derived nanocatalysts is one of the frontiers of cardioprotective approach, in which the goal is not only to control cardiovascular disease, but to intelligently and comprehensively stimulates the healing and regeneration process on the most fundamental cellular level that the body can create.

II. GRAPHENE-BASED MATERIALS (GBMS): STRUCTURE, DERIVATIVES, AND PROPERTIES

The basic unit of GBMs, graphene is one layer of carbon atoms bonded in the form of a two-dimensional honeycomb network. This is a simple but powerful structure that gives a set of exceptional

physical and chemical characteristics. The individual carbon atoms are sp² hybridized and as such, the strong in-plane s-bonds make it be exceptionally strong intrinsically, with the out-of-plane p-electrons making it famous with its electrical conductivity and chemical reactivity. Nonetheless, in biomedical uses, pure graphene is typically functionalized to enhance its processability, physiological stability, and biocompatibility and this has resulted in two major derivatives, graphene oxide (GO) and reduced graphene oxide (rGO).

Graphene Oxide (GO) and Reduced Graphene Oxide (rGO)

Graphene oxide (GO) is the result of the severe oxidation of graphite, which has added oxygen-based functional groups (e.g., epoxy, hydroxyl, carbonyl, carboxyl) to the basal plane and edges of the sheet of graphene. This oxidation interferes with the native sp² carbon structure making GO an electrical insulator, but converting it into a hydrophilic, easily dispersible compound in aqueous solutions. This aqueous solubility is a vital strength in biomedical uses as it allows simple mixing with polymers, incorporation of therapeutic factors as well as interacting with biological systems. The high number of functional groups on the surface of GO serves as anchoring points to the covalent modification of drugs, proteins, targeting molecules or in the present study, as nanocatalysts.

GO is reduced to reduced graphene oxide (rGO) by thermal or photothermal reduction or chemical reduction which removes a large fraction of the oxygen groups. This reinstatement to some degree restores the conjugated sp² network, thus retrieving much of the high electrical conductivity characteristic of pristine graphene- a characteristic that is central to cardiac applications. The hydrophobicity of the material and its interfacial properties are also changed during the reduction process. The range of insulating, hydrophilic GO to conductive, more hydrophobic rGO offers a controllable material platform. An example can be a cardiac patch with an underlay of GO, which allows the cells to adhere well to the substrate, and rGO network to supply pathways of electrical conductivity to cardiomyocytes.

III. KEY PROPERTIES FOR BIOMEDICAL USE: ELECTRICAL CONDUCTIVITY, MECHANICAL STRENGTH, AND FLEXIBILITY

Electrical Conductivity: rGO restored sp² network has high charge carrier mobility. This is a must in the case of cardiac tissue engineering. The electrically excitable cells are known as cardiomyocytes which need to transmit action potentials swiftly and synchronously to be able to coordinate the contraction. GBMs on scaffold or patches form conductive microenvironment

that promotes electrical connectivity between neighbouring cells to form more mature tissue phenotypes and synchronous beating, which is essential to repair infarcted myocardium where conductive tissue is substituted with scar tissue that is non-conductive. Mechanical Strength and Flexibility: Graphene is one of the strongest materials even though it is atomically thin. GBM reinforce the tensile strength and toughness of macro-scale structures, such as hydrogels or polymeric patches, when introduced as nano-reinforcements, which enhance tensile strength and toughness exponentially. More to the point, such composites are capable of reaching the mechanical compliance of the soft, dynamic, and continuously contracting cardiac tissue. This helps to eliminate mechanical mismatch which may lead to inflammation, scar formation or even harm the fragile myocardium.

High Surface Area and Functionalizability: The interaction surface area of two-dimensional geometry is immense. This enables the loading of therapeutic molecules with ultra-high loading capacity. Moreover, the chemical versatility of GO/rGO surfaces allows bi-functionalization of surfaces, i. e., conjugation of particular peptides to be delivered to injured endothelial cells or cardiomyocytes or to tether catalytic nanozymes as is investigated in this integrated system.

IV. THE PINE NEEDLE CATALYST: AN INTRODUCTION TO PLANT- DERIVED NANOTECHNOLOGY

To replace engineered carbon material with nature-inspired synthesis, pine needles (*Pinus* spp.) represent a renewable, ecologically clean material to synthesize functional nanomaterials. This is a green form of synthesis and is compatible with sustainable nanotechnology and it makes use of the non-toxic and capping properties of plant phytochemicals that are bio-reductive in nature.

Phyto-constituents that have Anti-oxidant and Anti-inflammatory Potential

The pine needles contain a wide range of bioactivity compounds, such as phenolic acids (caffeic and ferulic acid), flavonoid (catechins), proanthocyanidins, and volatile terpenes. Together, these compounds account for the identified antioxidant, anti-inflammatory, antimicrobial, and heart protective effects of pine needle extracts in traditional and conventional phytotherapy. Their biological activity is mostly associated with the donation of electrons or hydrogen atoms to neutralize the free radicals and reactive oxygen species (ROS). These natural characteristics of pine needle extracts present the extracts as a perfect biological template to the development of therapeutic nanocatalysts in the context of cardiovascular pathology, where oxidative stress is a key mediator of ischemia-reperfusion injury, doxorubicin-induced cardiotoxicity, and chronic heart failure.

Synthesis and Characterization of Metallic/Enzyme-Mimetic Nanoparticles from Pine Extracts

Green synthesis of nanoparticles using pine needle extract is a one-pot reaction at ambient temperature in a single pot. The extract has a triple role: that of reducing agent (reducing metal ions in a salt precursor to zero-valent metal or metal oxide nuclei), capping agent (to stabilize the growing nanoparticles and prevent their aggregation), and functionalizing agent (to entrap its own phytoconstituents on the nanoparticle surface). An example is when silver nitrate (AgNO_3) solution or selenous acid (H_2SeO_3) solution is mixed with pine needle extract, silver (Ag) and selenium (Se) nanoparticles are formed. It can be tuned; the extract concentration, pH, temperature and reaction time determine the size, shape and crystallinity of the resulted nanoparticles. The characterization procedure would include multiple methods, among them UV-Vis spectroscopy to verify that the formation was carried out through surface plasmon resonance peaks, Transmission Electron Microscopy (TEM) to determine the size/morphology, X-ray Diffraction (XRD) to assess crystallinity, and fourier-Transform Infrared Spectroscopy (FTIR) to determine the phytochemicals attached to the nanoparticle surface, which is the key factor in maintaining its stability and bioactivity.

V. THE NANOZYME CONCEPT: A TRANSITION BETWEEN NATURAL CATALYSIS AND NANOMATERIAL FUNCTION

The nanoparticles produced using the pine needles are not just carriers of their phytochemical constituents; they can be modified to act as nanozymes nanomaterials with inherent catalytic properties of enzymes. This is the key point that makes the hybrid system no longer a mechanism of passive delivery, but an active, catalytic therapeutic agent. Nanozymes are synthetic enzymes that replicate the activity of natural enzymes, including peroxidase (POD), catalase (CAT), superoxide dismutase (SOD) and oxidase (OXD). They typically use Fenton-type or Haber-Weiss reactions in which the nanomaterial acts to convert harmful ROS to less toxic or nontoxic products. A SOD mimetic catalyzes the disproportionation of superoxide anion ($\text{O}_2^{\bullet-}$) to hydrogen peroxide (H_2O_2) and oxygen (O_2). A later catalase mimetic would then catalyze the decomposition of hydrogen peroxide (H_2O_2) producing water and oxygen. This cascade of multi-enzymes is much better and more stable as compared to the plain antioxidant molecules such as vitamin C because nanozymes are not utilized in it and they can catalyze the reaction over a long duration of time.

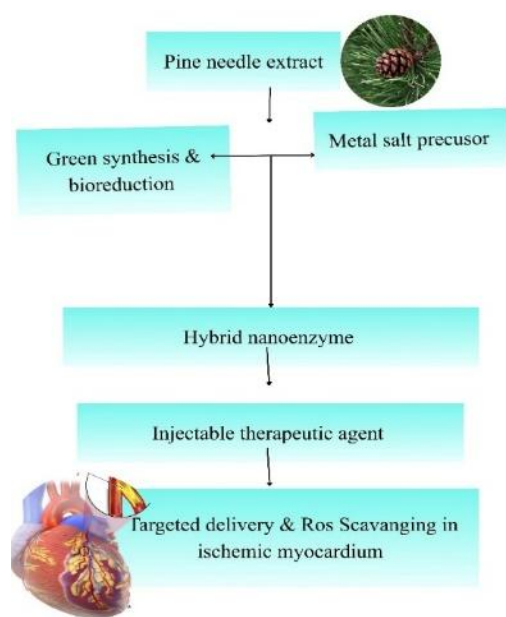


Fig: 1 Dual-System Hybrid Nanoplatform of pine needle

Cardioprotective role of graphene-based Fe_2O_3 nanozymes

The cardioprotective nanozymes are already being proven. Graphene-based Fe_2O_3 (iron oxide) nanozyme has been shown to be effective in a myocardial ischemia-reperfusion injury model. In a single paradigm, a hybrid of nanoparticles of Fe_2O_3 on sheets of graphene was produced. This architecture utilized the high surface area property of graphene to anchor and disseminate the nanozyme, and the Fe_2O_3 gave a strong catalase-mimetic capability, which broke down harmful H_2O_2 that forms during reperfusion. When this nanozyme composite was administered to animal models, it reduced the size of infarcts, malondialdehyde (a marker of oxidative stress), and cardiac functioning were better than in the controls. The thesis statement, which is central, is that catalytic nanozyme can be combined with a graphene platform to form a synergistic system with the graphene facilitating delivery and structural/conductive support and the nanozyme directly and catalytically mitigating the pathological oxidative burden. This two-systems strategy combines tunable material superiority of graphene derivatives, the green-synthesized catalytic potency of pine needle nanozymes, and the integrative architecture of nanozyme chemistry to create an advanced toolkit of targeted, catalytic, and regenerative intervention of cardiovascular disease.

VI. GRAPHENE-BASED SYSTEMS IN CARDIOVASCULAR APPLICATIONS: STATE OF THE ART

Graphene-based materials (GBMs) biomedical applications have provided a new frontier in

cardiovascular therapy because of their translation by the materials science lab to the biomedical field. Their physicochemical property- including unrivaled surface area, controllable surface chemistry, unprecedented electrical conductivity, and mechanical toughness- is exactly what is needed to solve multifactorial problems in the areas of cardiology. This subdivision will describe the state-of-the-art applications and how transformative the application can be as well as the ongoing research that supports the reasoning behind using GBMs with bioactive catalysts such as pine needle nanozymes.

Therapeutic Agent Delivery and Targeting

One of the major GBMs uses in cardiovascular medicine is the use of GBMs as advanced, multifunctional nanocarriers to deliver drugs and genes. Graphene oxide (GO) exhibits a large loading capacity of therapeutic agents due to high-loading capacity of both p-p stacking (aromatic drugs, such as doxorubicin) and covalent conjugation to oxygen functional groups. This ability is essential to counteract the weaknesses of the traditional systemic approach in drug administration, which can lead to a lack of appropriate drug concentrations in the cardiac focus and high off-target toxicity. GBMs may be stimuli-responsive to release their payload into a target pathological microenvironment of diseased cardiac tissue. As an illustration, a GO-based nanocarrier can be programmed to deliver an anti-inflammatory drug when there is an increase in reactive oxygen species (ROS) or acidic pH of an ischemic myocardium or atherosclerotic plaque inflamed. More so, the surface of GO can be targetable with targeting ligands, including peptides that interact with the particular markers on activated endothelial cells or the cardiomyocytes in ischemic heart disease, which will allow the active targeting of GO. This increases local concentration, increases the effectiveness of therapy and reduces systemic adverse effects- a very important factor in potent but toxic drugs in cardiology, such as chemotherapeutic drugs that are known to cause cardiotoxicity.

Cardiac tissue engineering and regenerative medicine

The most visual and possibly the most functional use of GBMs is, perhaps, in the area of cardiac tissue engineering. The death of the cardiomyocytes following a myocardial infarction results in the development of non-conductive, mechanically weak fibrous scar which is a condition that interferes with the functioning of the heart and may cause heart failure. To produce functional tissue patches that can be used to replace or repair this damaged region, a scaffold that recapitulates the native cardiac extracellular matrix structurally and electrically is needed.

Graphene-based 2D and 3D scaffolds for supporting cardiomyocyte maturation

It has been shown that GBMs have a significant effect on the growth and the activity of cardiac cells. GO and rGO two-dimensional films have been demonstrated to facilitate the growth and adhesion of cardiomyocytes.

More importantly, cellular maturation is a critical event that is driven by the intrinsic electroconductivity of rGO. Cardiomyocytes grown on conductive rGO substrates have organized sarcomeric structure and increased the expression of gap junction proteins (such as Connexin 43) and more synchronized and vigorous contractions than cardiomyocytes grown on non-conductive substrates. The real potential is, however, achieved in three dimensional constructs. Hydrogels (e.g., gelatin, chitosan, alginate) or porous foam scaffolds are loaded with GBMs to form hybrid materials.

These three dimensional scaffolds offer: Structural Support: They provide a biocompatible, mechanically resilient structure that direct the cell infiltration and tissue organization. Electrical Bridging: The scaffold is a graphene network, which forms micro-conductive channels, to promote the rapid transmission of electrical signals between seeded or invading cardiomyocytes. This is necessary to coordinate contractions over a patch that is of clinical relevance. Motivated Maturation: The use of human stem-cell-derived cardiomyocytes in studied with 3D graphene-containing scaffolds have demonstrated that 3D graphene-containing scaffolds can trigger a robust response in genes associated with cardiac contractility, calcium transportation, and electrical connection with the cell pulling the cells closer to an adult-like state. A conductive mechanical support of graphene-composite hydrogel that is injectable, e.g., could be used both to inhibit negative left ventricular remodeling and as a cell delivery system that leads to regeneration in the infarct region itself.

Bioelectronic interfaces and conductive implants

In addition to tissue replacement, GBMs are leading a new generation of bioelectronic interfaces to the heart. They have the advantage of being flexible, strong and conductive and therefore suitable in ensuring the development of smooth interfaces with the dynamic cardiac surface. Applications High-Fidelity Sensing: Ultra-thin arrays made of graphene can be laminated onto the epicardium, to give high-resolution and multi-point mapping of electrophysiology (electrocardiography) features, with high precision of localizing arrhythmic substrates, compared to conventional electrodes. Implantable Conductive Coatings: Medical implants such as pacemaker leads or stent wires can be coated with layers of graphene. This enhances their biocompatibility (by preventing biofouling and corrosion) and the conductive coating can also be functionalized with drugs (e.g. anti-proliferative agents to stents) to elute locally. Smart Patches: The involvement of graphene-based sensors and actuating elements would result in the so-called closed-loop therapeutic systems. One such example is a smart patch that is able to keep track of the electrical activity in the area and can sense the beginning of arrhythmia and provide a therapeutic shock or electrical pacing to stop it at the appropriate time.

In vivo safety and biocompatibility assessment

Translational route of any nanomaterial depends on the conclusive and strict safety testing. In the case of GBMs, biocompatibility is not an inherent feature but depends on the particular physicochemical properties such as lateral size, number of the layers, surface chemistry, and purity and the dose and route of failure.

Important biocompatibility interferences

Key structure-activity relationships have been determined using both in vitro and in vivo. Smaller, sharp-edged GO nanosheets in general have a greater potential of causing mechanical damage of the membranes and the generation of reactive oxygen species (ROS) in cells. However, bigger sheets and well-functionalized materials, dispersed and large in size, exhibit better biocompatibility. The most important conclusion of cell culture research is that, although high levels of GBMs may be toxic, lower, therapeutic doses may be highly biocompatible and even pro-regenerative, e.g., stimulating stem cell differentiation. The route of administration is the most important; direct injection of tissue or embedding into an implant poses another risk profile compared to systemic intravenous injection, where the interaction with blood constituents and biodistribution to other organs such as the liver and the spleen need to be seriously considered.

Insights from first-in-human inhalation studies

Although the majority of cardiac applications consider direct implantation or injection, systemic safety data is priceless. A series of pioneering studies of the first-in-human controlled exposure, including the GRAPHENE project of the Graphene Flagship have made first insights. These experiments involved the exposure of healthy human volunteers to ultrapure and specifically engineered graphene oxide to these experiments through controlled inhalation. These findings, which were presented in the main journals, were revolutionary. No Acute Clinical There was no significant acute pulmonary inflammation under the influence of carefully measured and low-dose inhalation of GO, and no significant alteration of the lung functions, blood pressure, and coagulation parameters. Dose- and Size-Dependent Response The experiments proved that material characteristics play an important role. They gave first-hand human information indicating that well-characterized GO, when generated under controlled conditions is tolerable without apparent acute toxicity. A Groundbreaking to Translation It is through these human trials that animal models are now substituted with human data. They provide a base safety profile of a particular type of GBM and offers a methodological framework with which future graphene-based medical devices or therapeutics can be tested which greatly decreases the risky pathway of their development.

Table 1: Summary of Graphene-Based Cardiovascular Applications

Application Area	Key Functions of Graphene	Example Forms/Systems	Development Stage
Drug/Cell Delivery	High surface area, functionalizable surface, targeting	GO/rGO nanosheets, composite particles	Pre-clinical research
Tissue Engineering	Electroconductivity, mechanical support, topographical cues	3D porous scaffolds, hydrogel composites	Pre-clinical & <i>in vitro</i> research
Bio-sensing & Imaging	Electrical sensitivity, fluorescence quenching, surface plasmon resonance	GO-based sensors, quantum dots	Early-stage research
Medical Implants	Anti-thrombogenicity, strength, flexibility	Coatings for stents, grafts, pacemaker leads	Early-stage R&D

Pine needle-derived nanocatalysts: synthesis, characterization, and cardioprotective mechanisms

The complexity of the proposed development of the dual-system lies in the high-technology incorporation of a plant-derived component that is biologically active. Pine needle-derived nanocatalysts are a new area of interest in the field of green nanotechnology, in which the phytochemistry of *Pinus* species is exploited to produce functional nanomaterials with inherent therapeutic properties. This part explains the environmentally friendly synthesis, strict characterization, and the multi-targeted effect of the molecular nature by which these nanocatalysts protect the vulnerable myocardium.

VII. GREEN SYNTHESIS METHODS AND OPTIMIZATION

A bottom-up fabrication strategy (green) and the synthesis of metallic and metal-oxide nanoparticles with pine needle extract exemplifies an exemplary strategy. This approach is a sharp departure to the traditional top-down physical/or severe chemical synthesis, which typically requires high input of energy, use of toxic reducing agents (e.g., sodium borohydride), and stabilizers that may leave cytotoxic residues. Pine needle aqueous extract is a bioreactor that is benign and

renewable as well as multifunctional. It is done by incubating an aqueous extract of pine needles (dried or fresh) that has been filtered with a precursor salt solution (e.g., silver nitrate, selenous acid, zinc acetate or chloroplatinic acid) at moderate temperatures (25-80°C). A color shift of the reaction mixture, such as to deep red with selenium nanoparticles (SeNPs) or brown with silver nanoparticles (AgNPs), is a visual indication of the formation of the nanoparticles.

The pine needle extract performs three critical roles simultaneously

The abundance of polyphenols, flavonoids, and terpenes serve as potent reducing agents, giving out electrons to transform ionic metal (M^+) to their zerovalent form of nanometallic (M^0) or to create metal oxide nuclei. Capping and Stabilization: The same phytoconstituents spontaneously attach themselves to the surface of the nascent nanoparticles to form a stabilizing corona. This green capping layer not only inhibits aggregation but also provides colloidal stability in aqueous media as well as, most importantly, it is directly involved in the biological activity of the nanoparticle. Functionalization The capping coating introduces the native bioactive compounds of pine to the biological surroundings, which allows the intrinsic antioxidant properties and antiinflammatory effects. This synthesis is the most important to be optimized to control the size, morphology, crystallinity, and eventually, the catalytic efficacy of the resulting nanozyme. Extract Concentration and pH A increased extract concentration usually results in a faster rate of reduction and smaller nanoparticles, whereas pH affects the ionization of the phytochemicals, which affect reducing power and reaction with metal ions. Precursor Salt Concentration The molar ratio of metal salt to extract is what determines the nanoparticles yield and may also determine size distribution. Reaction Temperature and Time Higher temperatures would increase the kinetics, including nucleation and growth stages, which control the ultimate size of particles and polydispersity. Precursor Type This option determines the activity of the core catalyst, the type of metal ion selected. Selenium (Se), cerium (CeO_2), platinum (Pt) and manganese (Mn_3O_4) are of the most interest as cardioprotective nanozymes as they have been widely studied regarding their redox-cycling and enzyme-mimetic properties. The optimization will be to generate a monodisperse population of nanoparticles in the optimal 10-50 nm size, sufficiently small enough to be internalized into cells and sufficiently large to be catalytic and to be cleared.

VIII. PHYSICOCHEMICAL AND CATALYTIC CHARACTERIZATION

Comprehensive characterization is essential to correlate the synthetic parameters with the material's

structure and function, ensuring reproducibility and therapeutic predictability.

Physicochemical Characterization: UV-Visible Spectroscopy: Real-time monitoring of the reduction reaction, surface plasmon resonance (SPR) peaks (in case of noble metals such as Ag and Pt) or absorption edges can be used to provide the initial evidence of nanoparticle formation. Dynamic Light Scattering (DLS) and Zeta Potential: DLS measures the hydrodynamic diameter and size distribution in solution, and the zeta potential measures the surface charge and colloidal stability. Having a large negative or positive zeta potential (Usually more than ± 30 mV) indicates good aggregation resistance, which is essential in biomedical use. Electron Microscopy: Transmission Electron Microscopy (TEM) is obligatory to see the actual size, shape (spherical, rod-like, triangular), and crystallinity of individual nanoparticles. SEM offers topographical information about nanoparticle aggregates or composites. X-ray Diffraction (XRD): This tests the crystallinity of the nanoparticles, and their structure, so that it is possible to distinguish between amorphous, crystalline, or mixed-phase nanoparticles (e.g., cubic versus hexagonal SeNPs). Fourier-Transform Infrared Spectroscopy (FTIR): Determines the functional groups of the pine phytochemicals (e.g., -OH, C=O, C-O-C) found on the nanoparticle surface, which directly determines the nature of the green capping layer. X-ray Photoelectron Spectroscopy (XPS): Measures both the elemental compositions of the nanoparticles and the chemical state (e.g. SeO₂ vs. SeO, Ce₃⁺ vs. Ce₄⁺ ratio in ceria) of the nanoparticles, which is directly correlated with the redox catalytic activity.

Catalytic Characterization (Nanozyme Activity Assays): This is the main functional validation. In standard biochemical assays, the nanoparticles are analysed to measure their enzyme-mimetic activities. Superoxide Dismutase (SOD) Mimetic Activity: This is measured as the capacity to prevent reduction of nitroblue tetrazolium (NBT) or cytochrome c by a flux of superoxide radical generated photochemically or by an enzyme. Catalase (CAT) Mimetic Activity: Determined by spectrophotometric measurement of H₂O₂ breakdown at 240 nm. Peroxidase (POD) Mimetic Activity: This activity was measured using chromogenic substrates such as 3,3',5,5'-tetramethylbenzidine (TMB) or o-phenylenediamine (OPD) in the presence of H₂O₂ where the oxidation of the substrate by the nanozyme converts into a color change that is measured by absorbance. Glutathione Peroxidase (GPx) Mimetic Activity: The activity was assessed in a coupled enzymatic assay, which determines the use of NADPH, as the glutathione (GSH) oxidized by the nanozyme using cumene hydroperoxide or hydrogen peroxide. The kinetics (Michaelis-Menten: Km and Vmax) of these nanozymes is determined and usually compared to those of their natural counterparts. The ideal pine needle-derived nanocatalysts especially SeNPs and CeO₂

nanoparticles are often optimized to exhibit robust multi-enzyme mimetic functions, and thus, they constitute powerful and broad-spectrum redox modulators.

Core Cardioprotective Mechanisms of Action

The therapeutic potential of these nanocatalysts is found in the fact that they can act at several, united points of the cardiovascular injury cascade and be used as catalytic self-regenerative cytoprotective agents.

Reactive Oxygen Species (ROS) Scavenging

The initial and the direct line of defense is this. In the case of ischemia/reperfusion (I/R) injury, doxorubicin therapy, or chronic heart failure, a pathogenic explosion of ROS such as, superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), and the extremely destructive hydroxyl radical (OH) overwhelm the natural antioxidant protection systems of the heart. Nanozymes produced by pine needles serve as catalytic sinks of these species. As an illustration, a selenium nanozyme may be able to have SOD as well as GPx-like activity. It catalytically breaks the O₂⁻ down to H₂O₂ and subsequently, with the aid of reduced glutathione (GSH) as a co-substrate, it goes on to further reduce H₂O₂ to water. This cascade of enzyme-mimetics, which is more efficient than stoichiometric antioxidants (such as vitamin C or E), is possible because only a single nanoparticle can respond to millions of ROS molecules without being depleted. In Ceria (CeO₂) nanoparticles, the reversible redox on/off interchange between Ce³⁺ and Ce⁴⁺ on the surface of the nanoparticles is used to catalytically scavenge O₂⁻, H₂O₂, and OH as an efficient regenerative antioxidant nanomaterial.

Modulation of endogenous antioxidant defense enzymes

In addition to direct scavenging of ROS, these nanocatalysts have the capacity to stimulate the inherent protective mechanisms of the heart. The Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is the main controller of oxidative stress because this antioxidant pathway controls the whole antioxidant response. Pine needle nanocatalysts with their phytochemical corona have been demonstrated to enhance the dissociation of Nrf2 caused by its cytoplasmic inhibitor Keap1 followed by translocation of Nrf2 to the nucleus in response to oxidative insult. It binds to the Antioxidant Response Element (ARE) there initiating the transcription of a cascade of cytoprotective genes, such as SOD, catalase, glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1). It is an excellent positive feedback loop: the nanozyme will neutralize the instantaneous, catalytic ROS response and increase the overall antioxidant capacity in the cell in the long-term, which will develop long-term resistance to injury.

Anti-inflammatory effects

Inflammation and ROS are closely interconnected in a vicious circle in the cardiac pathology. ROS stimulate major pro-inflammatory signaling centers, which are the NF- κ B (Nuclear Factor kappa-light-chain-enhancer of activated B cells)

pathway and the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome. Pine needle nanocatalysts interrupt this cycle. They eliminate a major inhibitor of NF- κ B by the scavenging of ROS. Moreover, their capping layer (e.g. flavonoids) can inhibit the I κ B kinase (IKK) directly, avoiding degradation of I κ B and nuclear translocation of NF- κ B. This inhibits the transcription of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6. At the same time, the nanozymes prevent the assembly of the NLRP3 inflammasome and its activation by reducing the mitochondrial ROS and potassium efflux, which are two major stimuli in myocardial infarction and heart failure.

Anti-apoptotic Signaling in Cardiomyocytes

The nanocatalysts prevent apoptosis in a combination of mechanisms Mitochondrial Protection By lowering mitochondrial ROS, they preserve mitochondrial membrane potential (DPsm), which prevents the permeability transition pore opening (mPTP) point of no return in cell death. Apoptotic Pathway Modulation They affect the ratios of Bcl-2 family proteins and downmodulate pro-apoptotic Bax and upmodulate anti-apoptotic Bcl-2. This maintains the integrity of mitochondria and the leakage of cytochrome c into the cytoplasm is avoided. Caspase Activation Inhibition The liberation of cytochrome c will activate caspase-9 and executioner caspase-3. This caspase cascade is blocked by the antioxidative and anti-inflammatory environment generated by the nanozymes and, thus, prevents cell death and the disruption of contractile units.

IX. CONCLUSION

The steadily increasing load of cardiovascular diseases makes the shift towards a shift in paradigm toward palliative management to curative, regenerative therapy inevitable. Such a shift is reflected in the dual-application nanotechnology combining pine needle-derived nanocatalysts and graphene-based systems which have been detailed in this article. The platform has a level of innovation that is beyond the abilities of individual materials by allowing a synergistic nanohybrid in which each component of the system fulfills an essential role in cardiac pathophysiology: the electric conductivity of graphene is regenerative of the synchronous delivery of electrophysiological signals to damaged myocardium, its mechanical integrity provides compliant support, and its surface can be functionally modified to target and deliver stimulus-responsive molecules to the injury site. At the same time, the pine needle-produced nanozyme is a potent and catalytic bioactivity that is chronically lacking in diseased heart tissue. It long-term suppresses the scavenging activities of the destructive ROS cascade, interferes with the pro-inflammatory signaling nexus, and enhances intrinsic anti-apoptotic defenses of the cardiomyocyte by imitating a family of endogenous antioxidant enzymes.

This integration of the green nanotechnology and the state-of-the-art material science provides an integrated approach. It also provides both biophysical (electrical and mechanical) and active biochemical (catalytic, anti-inflammatory, and anti-apoptotic) directly to the cellular front line. Directly addressing the interplay between oxidative stress, inflammation, and cell death cycles that lie at the heart of the conditions associated with myocardial infarction to chemotherapy-induced cardiomyopathy, this methodology addresses multiple conditions simultaneously.

Although preclinical validation and detailed pharmacokinetics, as well as protracted biosafety studies, are critical milestones on the translational pathway, the underlying science is sound. There is some positive but tentative early human safety data on engineered graphene materials which offer optimism in clinical development. The future studies are needed to maximize hybrid formulations to particular clinical indications, investigate scalable production, and combine enhanced targeting and imaging. To sum up, this pine-graphene hybrid system is a step forward in cardioprotective approach-a step towards multifunctional and intelligent nanomedicine that does not just shield the ailing heart but also gives it the energy to heal and regenerate.

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