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Pentagalloyl Glucose and Its Functional Role in Vascular Health: Biomechanics and Drug-Delivery Characteristics

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Abstract

Pentagalloyl glucose (PGG) is an elastin-stabilizing polyphenolic compound that has significant biomedical benefits, such as being a free radical sink, an anti-inflammatory agent, anti-diabetic agent, enzymatic resistant properties, *etc.* This review article focuses on the important benefits of PGG on vascular health, including its role in tissue mechanics, the different modes of pharmacological administration (e.g., oral, intravenous and endovascular route, intraperitoneal route, subcutaneous route, and nanoparticle based delivery and microbubble-based delivery), and its potential therapeutic role in vascular diseases such as abdominal aortic aneurysms (AAA). In particular, the use of PGG for AAA suppression and prevention has been demonstrated to be effective only in the calcium chloride rat AAA model. Therefore, in this critical review we address the challenges that lie ahead for the clinical translation of PGG as an AAA growth suppressor.

Keywords

Pentagalloyl glucose; Abdominal aortic aneurysms; Elastin; Collagen; Drug delivery

FUNCTIONALITY OF PENTAGALLOYL GLUCOSE

Pentagalloyl Glucose (PGG) is a polyphenolic compound, which is one of the most potent antioxidants in the tannins group and is known for its antimicrobial, anti-viral, anti-diabetic, anti-inflammatory, and anti-tumor properties (see Fig. 1).^{23,176,199} A critical role of PGG for

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ELECTRONIC SUPPLEMENTARY MATERIAL

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vascular pathologies is its inherent ability to stabilize elastin in the extracellular matrix (ECM) of blood vessels, especially the aorta. The application of PGG to aortic tissue specimens establishes a strong cohesive bond between the structural proteins that provide enhanced biomechanical stability and increased resistance to enzymatic degradation.^{68,70,172} Additionally, PGG was found to be less toxic to the cellular environment compared to tannic acid.⁶⁸ The topical application of PGG in rodent abdominal aortic aneurysms (AAA) maintained the aortic elastin architecture, tempered the aneurysm diameter expansion, and prevented aneurysm development (see Figs. 2a and 2b).^{70,88} The aforementioned advantages of PGG have paved the path for its use in tissue engineering studies of valves, development of vascular grafts, and numerous other potential therapeutic applications.^{32,33,35,39,47,88,119,120,129,154,156,167,168,170,171} In this review, we critically evaluate recent work relevant to drug-delivery and translation-related applications of PGG.

Biochemical Roles of PGG

The detailed chemical structure and functional roles of PGG have been thoroughly reported by others,^{23,176,199} as seen in Table 1. Some of the beneficial effects of hydrolyzable tannins (including those of PGG) on vascular health have been outlined in the review article by Larrosa *et al.*⁹² In this work, we focus primarily on the effect of PGG on vascular tissues from a therapeutic viewpoint (see Table 2 and 3). Tannins, like PGG, function primarily by utilizing their protein precipitation abilities *via* hydrophobic forces and hydrogen bonding,^{13,15,23,60} and have high affinity for proline-rich proteins such as collagens.^{13,15,22,64} PGG has the beneficial crosslinking properties of tannic acid (including elastin-stabilization, enzymatic resistance^{71,83} and prevention of calcification⁷²) when applied to cardiovascular tissues, compared to routine crosslinking agents. PGG, which is a polyphenolic derivative of tannic acid, had significant effect on preservation of the arterial elastic lamellae.⁶⁸ Binding of PGG with the structural proteins (primarily collagen and elastin) in the tissues (hydrophobic regions) provided superior compatibility, integration, and biomechanical stability to the cardiovascular grafts/scaffolds in several preclinical studies.^{33,35,71,150,170} The remedial benefits (non-vascular) of PGG are summarized in Appendix Tables I and II.

Radical Scavenging and Anti-inflammatory Properties of PGG

The balance between pro-inflammatory and anti-inflammatory molecules handle the delicate homeostatic process of tissue regeneration, growth, and cell death. Excess of reactive oxygen species (ROS) or nitric oxide could lead to deactivation of detoxifying enzymes such as superoxide dismutase (SOD) and glutathione (GSH), which has the potential to activate the inflammatory cascades at the cellular level. It is hypothesized that o-semiquinone radical intermediate, a product of PGG hydrolyzation,³⁰ is responsible for PGG's free radical scavenging ability.^{20,104,176} The latter allows PGG to have superior anti-inflammatory abilities and yield reduction of inflammatory cytokine expressions. The use of PGG has been suggested to lower the ROS and increase in SOD activity in rat pulmonary fibroblasts (10 μ g/mL PGG) and HBZY-1 cells, respectively. Correspondingly, the administration of PGG in lipopolysaccharide (LPS) induced mice and peripheral blood mononucleocyte cell culture was successful in reducing cytokine tumor necrosis factor- α (TNF- α) expressions by approximately 50 and 90%, respectively.⁴⁶ Likewise, the addition of PGG to LPS-activated murine macrophages induced a greater reduction of nuclear factor-kB (NF-kB) and nitric

oxide synthase levels (NOS), compared to other polyphenolic compounds.¹²³ A monocytic cell differential model (i.e., phorbol myristate acetate stimulated human monocytic U937 cells) exhibited increased interleukin-8 (IL-8) gene expression and nuclear factor- κ B (NF- κ B) activations, but addition of 20 mM PGG to the culture led to a reduction of IL-8 production and NF- κ B activation.¹²¹ Similarly, Jang *et al.* reported a reduction in TNF- α , IL-6, anti-IL-1 receptor-associated kinases, mitogen-activated protein kinases, and an increase in expression of IL-10 proteins in both LPS activated macrophage cells and experimentally induced mouse models of colitis.⁷⁵ This neuroprotective ability of PGG extends to the blood vessels in the brain as well.¹⁸³ A study by Viswanatha *et al.* showed that rodents pretreated with PGG were able to resist ischemia/reperfusion-induced brain injury and alleviate other physiological changes (neurological, morphological, *etc.*), compared to control subjects.¹⁸³ PGG attenuated the expression of IL-4 mediated ϵ germline transcript (ϵ GT) expression, which is key in immunoglobulin E (IgE) production and development of allergenic diseases.⁸⁴ Kanoh *et al.*⁸⁰ found that rat peritoneal mast cells activated by potassium superoxide (KO₂) release increased levels of histamine. Upon treatment with high molecular weight tannins such as PGG, the histamine release was inhibited and PGG molecules acted as both cell membrane stabilizers and free radical scavengers. Anti-oxidant characteristics of PGG were superior to vitamin E and gallic acid as reported by Westenberg *et al.*¹⁸⁸ and Abdelwahed *et al.*² respectively. In addition, PGG efficiently inhibited superoxide radical producer (XOD) compared to gallic acid.² PGG's ability to lower the cellular oxidation further inhibits inflammatory pathways by reducing the expressions of cytokines such as TNF- α ,^{50,121} TGF- β 1,¹⁸⁶ IL-6,^{50,186} IL-8,¹²¹ MCP-1,¹⁸⁶ MCP-5,¹⁰⁷ pro MMP-9;¹⁰⁷ and prevents mast cell infiltration.^{35,78,108}

Vascular Effects of PGG

PGG is typically extracted from plant sources and its yield typically varies according to the environmental conditions, seasonal changes, *etc.*^{65,103,118} Extraction of PGG from tannic acids has been standardized by the Hagerman group since 2002⁶⁶ and a HPLC grade extract of PGG is commercially available from Sigma-Aldrich Corp (St. Louis, MO). Evidently, for clinical usage, a more purified form of PGG will be necessary. For example, PGG extraction from more readily available sources such as *Mangifera indica* (mangoes) is ideal for clinical applications because the stem bark and the seeds have the same beneficial anti-oxidant traits as the fruit itself.^{1,77,111,176,180,183} A comprehensive list of more than 70 plants, which can be potential sources of PGG, has been reported by Ren *et al.*¹⁴⁰

At the tissue level, PGG treatment is non-cytotoxic,⁷⁰ lacks pro-oxidant activity,¹⁹⁹ promotes cellular infiltration by the host's fibroblasts,^{33,170} and reduces macrophage mediated inflammatory response and T-cell infiltration.³³ For arterial tissues, PGG exhibited *in vitro* endothelium-dependent vasodilatory effect⁵⁵ and dose-dependent (ranging from 1 to 30 μ M) vasodilatory effect⁷⁹ on prostaglandin F₂-pre-contracted and phenylephrine pre-contracted rat aortas, respectively. These effects were further attenuated by mediation from N^G-nitro-L-arginine methyl ester, which indicates potential involvement of PGG in the NO-cGMP pathway (Nitric Oxide (NO)-induced relaxation). As a tannin derivative from *Sapium sebiferum* leaves, the use of PGG for hypertension treatment has been patented by Cheng and co-authors,³¹ with vasodilatory effects at concentrations up to 10 mg/kg. Further, PGG

potently inhibited the enzymatic activity of 1-alkyl-2-acetyl-sn-glycero-3-phosphocholine (PAF) production in rabbit platelet-polymorphonuclear leukocyte (PMN) systems and/or PAF-stimulated platelet activations,¹⁶³ and was successful in preventing platelet aggregation (which is an initiating factor for intraluminal thrombus formation in AAA).^{117,142} In a similar fashion, PGG extracted from *Radix Paeoniae Rubra* assisted in downregulation of serum TXB2 levels (thromboxane B2) and upregulated serum 6-Keto-PGF1 α levels (6-keto-prostaglandin 1 α) in blood stasis rat models;¹⁹³ i.e., it successfully exhibited anticoagulant activity. In addition, PGG improved endothelial NO synthase levels, including hemodynamic metrics such as whole blood viscosity, plasma viscosity, etc.¹⁹³ PGG extracted from a lily, *Nymphaea tetragona* var. *angusta*,¹⁸ and from the tree *Elaeocarpus sylvestris* var. *ellipticus*,¹²⁷ exhibits radioprotective characteristics by increasing the proliferation of hematopoietic cells, and by decreasing reactive oxygen species (ROS) levels (which at higher levels can lead to ⁶⁰Co- γ rays radiation-induced apoptosis), respectively. Angiotensin-converting enzyme (ACE) [converts hormone angiotensin I to the active vasoconstrictor angiotensin II (AngII) and constricts the blood vessels to create a hypertensive condition in rodents¹⁹²] was effectively blocked by PGG in a direct chemical reaction.¹⁰⁰ In the same study, PGG infusion in hypertensive rodent models demonstrated a strong dose-dependent inhibition of ACE and a simultaneous reduction in blood pressure.¹⁰⁰ Similarly, PGG extracted from the whole plant of *Geum japonicum* was found to be a competitive inhibitor of *Factor Xa* and a non-competitive inhibitor of thrombin;⁴² both proteins that are highly expressed in arterial tissues of AngII AAA models.¹¹² Given that AngII infusion in apolipoprotein E-deficient mice develops a reliable atherosclerotic and aneurysm animal model,^{37,130} the stated vascular therapeutic properties of PGG can be applied to the aforementioned model and may assist in the development of potential pharmacological agents for AAA patients.

Role of PGG in Arterial ECM Stability

One of the envisioned roles of PGG in arterial stability would be the ability to deposit and/or preserve elastin lamellae,^{32,33,35,39,70,119,120,124,129,156,177} which is essential for the prolonged functioning of blood vessels and maintaining their biomechanical integrity. Sinha *et al.*¹⁵⁶ showed in an *in vitro* study with smooth muscle cell culture, that PGG treatment can enhance elastin fiber synthesis by upregulating lysyl oxidase (LOX) synthesis and downregulating matrix metalloproteinase 2 (MMP-2) activity. Chuang *et al.*³⁵ reported that PGG treated decellularized porcine carotid arteries devoid of collagen were not only able to resist elastase degradation, but also retained their biomechanical properties and exhibited substantial ECM remodeling. PGG exhibits higher affinity for proteins rich in proline (e.g., collagens) compared to BSA^{29,30,41,64} and hence, it could be beneficial for treating degenerated ECM *via* crosslinking in the diseased human abdominal aorta. This crucial trait of PGG translates into providing resistance to collagenase (or MMPs),^{62,91,107,119,120,124,156} which would assist in the suppression of MMP activity in human AAA to prevent both aneurysm expansion and rupture.

BIOMECHANICAL EFFECT OF PGG TREATMENT

The structural proteins of the abdominal aorta are primarily elastin and collagens (I, III, and V), with a higher collagen to elastin ratio compared to the thoracic aorta.^{144,189,190} Due to

its composition, the abdominal aorta is a stiffer vessel than the thoracic aorta as it has higher amounts of collagens and smooth muscle cells.¹⁸⁹ With aging, collagen deposition in the intimal and adventitial layers increases and elastin content decreases, resulting in a lower compliance. With the expansion of an AAA, the ECM throughout the aorta (in both aneurysmal and non-aneurysmal regions) undergoes varying degrees of modifications,^{12,148} leading to an aggravated biological response. The aorta would become less compliant concomitantly with time to accommodate the body's hemodynamic requirements.^{24,139} Inflammatory responses in conjunction with MMP infiltration results in the abnormal dilation of the infrarenal portion of this large blood vessel.^{52,53,139} As aneurysm geometry measures and wall thickness are known determinants of AAA pathology,^{28,105,125,139,153} PGG has the potential to both stabilize the vessel and prevent local biomechanical stress build up (see Figs. 2c and 2d).¹⁷² Potentially, this unique property of the polyphenol could be utilized to treat diseased arteries, as the role of PGG can be extended to (i) prevent infiltration of MMPs, (ii) stabilize elastin, and (iii) prevent arterial wall failure by reducing biomechanical stress. PGG-based stabilization of the ECM components, collagen and elastin, cohesively binds them closer and establishes a robust microarchitecture. This stabilized form of structural proteins has a direct effect on the mechanical behavior of PGG treated tissues.^{33,35,39,47,108,129,154,167,168,170,172,177} As most studies have utilized a pathological condition (e.g., AAA) or tissue-engineering based approach, PGG treatment has been focused on degenerated ECM tissues^{70,88,119,120,156} and decellularized tissue constructs,^{32,33,35,47,129,154,170,171} respectively. The application of PGG to native tissue (other than scaffolds) has been limited to the pericardium¹⁶⁸ and heart valves¹⁶⁷ for development of bioprosthetics only. PGG treated tissues exhibited excellent biaxial mechanical behavior,^{39,154,170} tear resistance,^{47,168,171} and diametrical compliance. However, it is important to note that most of this cross-linking makes the resulting tissue stiffer compared to the native one (e.g., TRI formation of PGG¹⁶⁷). The same increased stiffness was also exhibited by PGG-treated acellular elastin scaffolds implanted in diabetic mice vs. normal mice.³³ The work by Kloster *et al.*⁸⁸ briefly mentions the possibility of arterial stiffening by PGG in its pure form; however, there is no evidence or data supports this claim. PGG-treated vascular scaffolds (derived from porcine carotid arteries) has typically inhibited the tissue stiffening process compared to untreated scaffolds, when implanted in diabetic rats.³³ Hence, there is not enough evidence to suggest the possibility of stiffening of arteries due to PGG treatment. Further, the direct resultant effect of PGG on the biomechanics of pure elastin or pure collagen needs to be evaluated as well. Nevertheless, this favorable biomechanical characteristic resulting from PGG treatment could be critical for treatment of AAA patients and potentially prevent AAA rupture, since the primary cause of rupture is elevated wall stress and decreased wall strength.¹³⁹

PGG AS A POTENTIAL THERAPEUTIC OPTION FOR AAA PATIENTS

AAA is characterized by an abnormal dilation of the aorta of more than 50% its normal size. Aneurysms greater than 5–5.5 cm in diameter are usually repaired—either with open abdominal surgery or endovascular aneurysm repair (EVAR). Conversely, small aneurysms are mostly asymptomatic and more likely candidates for pharmacological intervention. These aneurysms may have an intraluminal thrombus (ILT), which further complicates the

arterial wall biology, vessel luminal morphology, blood flow dynamics, and its associated tissue mechanics.¹³⁹ AAA pathology is believed to be a result of medial lamellar degradation, due to a combined effect of vascular smooth muscle cell (VSMC) apoptosis, heightened inflammatory responses, increased oxidative stress, and disruption of tissue enzymatic homeostasis.^{57,109,139} Increased secretion of serine proteinases and MMP in AAA have resulted in a reduction in elastin content and elastin crosslinking, and an increase in collagen crosslinking.²⁴ Reduced elastin is associated with increasing AAA diameter, and the increased collagen content is correlated with high local wall stresses.¹⁶⁹ Because of this loss of load bearing fibrillar proteins, specifically elastin, the aortic wall undergoes progressive remodeling leading to increased level of collagen turnover along with high collagen content of the affected tissue.⁹⁹ This altered ECM is unable to withstand the resulting high wall stress and altered blood flow patterns.¹³⁹ The abnormally dilated abdominal aorta often ruptures if left untreated and this event is associated with a high mortality rate.¹²⁸ Therapeutic options for AAA patients are limited and no single drug or pharmacological therapy has been proven effective for preventing growth or rupture of AAA.¹⁶⁵

Current pharmacological strategies focus on suppression or inhibition of (i) proteases, (ii) oxidative stress, (iii) inflammatory responses, (iv) VSMC apoptosis, and (v) upregulation of matrix synthesis.^{53,54,109,113} Recently, a meta-analysis by Takagi *et al.* demonstrated that AAA patients are more likely to exhibit lower serum high-density lipoprotein (HDL) levels and higher low-density lipoprotein (LDL) levels.¹⁶⁶ With this observation, statins (hydroxymethylglutaryl-coenzyme A reductase inhibitors) and other lipid lowering drugs have been widely used for clinical studies, which have reported a decrease in AAA expansion rates.^{57,81,145} Yet, the effect of statins has been ambivalent for most AAA cases,^{48,82,149} and there is an undetermined possibility of cancer development¹⁷⁹ and adverse musculoskeletal and connective tissue disorders with statin use.⁵⁸ Doxycycline is one of the most studied drugs in AAA preclinical models⁵² with the potential to inhibit MMP-2 and -9¹⁷⁴ and decrease AAA growth.¹³⁴ In a short-term study with AAA patients, doxycycline reduced neutrophil infiltration and its associated proteases.³ However, the long-term results from clinical trials have not exhibited any extraordinarily beneficial effects.^{106,115} Currently, another clinical trial with a higher dosage of doxycycline is underway in the U.S. and its results are anticipated.¹¹ Further, AAA patients undergoing treatments with nonsteroidal anti-inflammatory drugs, diuretics, mast cell inhibitors, β blockers, calcium channel blockers, and ACE inhibitors have not exhibited any noteworthy accomplishments.^{17,57,155} Other concerns about oral medication therapy for AAA include limitations with respect to current AAA animal models, correct drug dosage, *etc.*⁵³ New clinical trials are focusing on the use of anti-angiogenic,¹⁸¹ anti-platelet,¹⁸⁷ cell-based immunomodulatory,¹¹⁶ and cyclosporine-based⁵ pathways as potential medical therapies for AAA patients.⁵³

With these shortcomings, a novel therapeutic option for AAA that will overcome the arterial tissue bio-chemical and biomechanical instabilities is needed. Therapeutic traits such as elastin stabilization, lipid lowering, protease resisting, anti-oxidant behavior, and improved ECM deposition make PGG an attractive option for pharmacological interventions in AAA patients. A reduction of aneurysm diameters up to 30% in the AAA rodent model has been reported by periaortic application.⁷⁰ This localized delivery of PGG for AAA treatment

was patented by Isenburg *et al.*⁷³ It uses a mixture of Pluronic™ block copolymers with PGG-loaded poly(lactic acid-co-glycolic) acid nanoparticles and hydrogel-based local delivery. Other therapeutic applications of PGG demonstrated a simultaneous reduction of aneurysm diameter and removal of calcification in rodent AAA aortas.^{119,120} Kloster and co-authors utilized a porcine AAA model to evaluate the therapeutic role of PGG; however, they did not observe any beneficial effects of the polyphenolic compound.⁸⁸ They further hypothesized that the porosity and permeability of the thrombus⁴ could facilitate easy uptake of PGG *via* the systemic circulation route.⁸⁸ Nevertheless, Kloster *et al.* suggest that a circulatory mode of PGG delivery may lead to stiffening of the entire arterial system and/or other organs in the body. Hence, a more targeted and site-specific approach for PGG delivery is needed for a potential future translational application.

CURRENT ISSUES WITH PGG ADMINISTRATION

Periadvential, intraluminal, and nanoparticle-mediated modes of delivery of PGG as potential therapies for AAA have been described previously.^{70,88,119,120,172} There are several limitations of the current approaches used for PGG administration. The PGG bioactivity value for various biomedical applications ranges from 0.05 IM (inhibition of fibrin hydrolysis⁴²) to 356.3 μ M (anti-viral activity¹) in *in vitro* studies (see Table 2) and up to 50 mg/kg in small animal models.^{36,46,94,98,137} (see Table 3) Much of published literature on PGG pharmacokinetics is based on the compound evaluated as a mixture or in combination with different chemical extracts sourced from plants and plant products; hence a full pharmacokinetic profile for PGG dosage is still undetermined. In the following sections, we provide insight into all the different modes of PGG administration for systemic delivery.

Oral Administration (Per os or PO)

The oral route of PGG administration is slightly problematic and an exact *in vivo* pharmacokinetics of the compound is not clearly established. Jiamboonsri *et al.* suggested that the elimination rate of PGG is about $0.023 \pm 0.012 \text{ h}^{-1}$ and it also has a long apparent elimination half-life [$t_{1/2} = (38.66 \pm 22.89)\text{h}$].⁷⁷ The toxicity of PGG was assessed by Cryan *et al.* with a dosage up to 20 mg/kg PO in mice with no severe side effects.³⁶ PO dosages of PGG formulations up to 30 mg/kg have been reported in anti-tumor studies.^{94,137} Mohan *et al.*¹¹¹ evaluated the toxic effect of PGG in oral doses of 10, 25, and 50 mg/kg to determine the therapeutic improvements of cardiovascular parameters in diabetic mice. They found that the dosages of PGG extracted from *Mangifera indica* did not produce any adverse events and helped lower blood pressure. Similarly, an oral dosage of 100 mg/kg PGG in hamsters was able to produce significant hypo-cholesterolemic effects (lower triglyceride levels).¹²⁶ Ren *et al.* found that beyond 1 hour after oral administration, PGG was found within detectable limits, although no additional details are provided.¹⁴¹ However, PGG levels in plasma were below the limit of detection (sub-micromolar) *via* oral gavage route (2 mg per C57BL/6 mice).⁹⁷ Due to the relatively symmetric structure of PGG, the measured octanol/water partition ratio of the polyphenolic derivative is close to 129 (which is high compared to other similar polyphenolic compounds),⁶⁰ indicating that PGG is a highly hydrophobic polyphenol. This hydrophobic nature of PGG affects its instability and *in vivo*

bioavailability. *In vitro* and *in vivo* pharmacokinetic studies of PGG extracted from mango seed kernels were found to be unstable in alkaline conditions, chemically degraded in the intestinal environment, and exhibited low absorptive permeability.⁷⁷ The latter may be the underlying factor in the low oral bioavailability of PGG. Additionally, PGG precipitates tannin-binding salivary proteins (mainly proline-rich proteins and histatins) by forming hydrogen bonds and hydrophobic forces and inhibiting its absorption in the alimentary canal.^{13,15} Skopec *et al.* reported that rats given a 3% PGG-containing diet exhibited formation of PGG protein complexes and lowered nitrogen digestibility, compared to the controls with normal diet.¹⁶¹ Further, in an *in vitro* experiment with human intestinal epithelial cells, it was shown that the majority of PGG is broken down into its constituents and only a small portion of the compound was transported across the cellular membrane.²² Histatin5 and 1B4 are the human salivary proline-rich proteins that preferentially bind to PGG, form insoluble protein-tannin complexes,¹⁹¹ and inhibit PGG transport across intestinal epithelial cells (Caco-2 cells) in culture.^{21,22} Remarkably, PGG has been reported to bind preferentially to human digestive enzymes such as α -amylases, pepsin, tripsin, and lipases. The hydrophobic binding nature of PGG is important to form amylase-PGG complexes and this effect is compounded by the presence of secondary binding sites (i.e., the aromatic rings) that provide increased stability to amylase-PGG bonds.⁵⁹ In addition, PGG is also known for its intestinal maltase inhibitory activity.¹⁷⁵

Drawbacks Although PGG has been shown to be stable at a pH of 5–6, it decomposes at pH close to neutral and alkaline conditions.^{77,90} Oxidization of PGG yields an o-semiquinone radical intermediate, which produces polymeric compounds in acidic conditions or produces o-quinones in alkaline conditions.^{20,30,199} However, in the presence of proteins, the PGG molecule favors the covalently linked bond formation, leading to PGG-protein conjugates.³⁰ Nevertheless, the type of tannin-binding salivary proteins in the animal model¹⁵² should be considered when formulating any oral pharmacokinetic studies with PGG to increase its bioavailability.

PGG has to overcome many physiological barriers prior to being systemically “available” in the body. The measure of PGG activity in the body or any other tissue would be a direct function of the unbound PGG concentration. Delivery of PGG to the target site will hence require the services of a carrier or external delivery system.¹³² An alternative approach for PGG delivery is the polymeric nanoencapsulation method utilized by Sanna and co-workers.¹⁴⁶ This method produces nanoparticles [poly(ϵ -caprolactone) and alginate] containing polyphenolic compounds with a release efficiency of 20% in gastric medium (low pH),¹⁴⁶ which is low compared to intravenous release methods. Nevertheless, modification of these delivery methods will improve the quantity of PGG release at the desired site and will further improve the anti-oxidant potential of the polyphenol *via* the oral route.

Intravenous (IV) and Endovascular Routes

Tail vein injection is the preferred drug delivery method in animal models as it bypasses the absorption step of traditional drug delivery methods and it is beneficial for low bioavailability chemical such as PGG. Studies utilizing delivery of nanoparticles loaded with PGG^{70,119,120,156,157} also utilize this IV method. Lin *et al.* reported that tannin doses up to

50 mg/kg, extracted from *Lumnitzera racemosa*, were able to suppress blood pressure in hypertensive rats.⁹⁸ Similarly, a PGG dosage (up to 50 mg/kg) has been reported by Feldman *et al.*⁴⁶ for suppression of immune response (IL-6 levels) in rats with high levels of tumor necrosis factor- α (TNF- α) output. Likewise, TNF- α suppression and endotoxin reducing ability of PGG was also exhibited in rats exposed to LPS and these rats exhibited dose-dependent response to PGG treatment (2–40 mg/kg).⁵⁰ However, Ma *et al.*¹⁰² reported that a single dose IV injection of 20 mg/kg PGG (dissolved in 0.9% saline) was not detected in the biofluids and the clearance routes were primarily through urine and fecal matter.

Drawbacks Endovascular routes, unlike IV routes, are not widely utilized for small animals. Kloster *et al.*⁸⁸ demonstrated that the endovascular delivery of PGG is feasible in porcine AAA models. However, clamping the aorta is not a clinically feasible technique during EVAR, unless conversion to open surgery is opted by the clinician. In addition, there is a theoretical risk of PGG binding to the undilated portions of the aorta, which could lead to local stiffening.⁸⁸ For aneurysm treatment, the localized endovascular delivery of PGG has been patented for the gel form of the compound using a nanoparticle-based systemic delivery method⁷³ and with drug-eluting stents.^{136,184} In addition, patents were issued for PGG delivery to blood vessels in combination with collagen stabilizing agents.⁶⁹ PGG is also known for its competitive inhibition of thrombin and fibrinogen.⁴² Nevertheless, changes in vascular hemodynamics due to PGG treatment are presently unknown.

One possible solution for improving the stability of PGG in slightly alkaline environments such as blood, is by liposome encapsulation, which tends to lower the anti-oxidant activity of polyphenols. This liposome encapsulation method has been utilized for epigallocatechin-3-gallate (EGCG)²⁰¹ (a polyphenolic compound similar to PGG⁸⁵) and IC₅₀ of PGG, which is almost half that of EGCG.¹⁶ This technique can be extended for improvement of PGG bioavailability. However, the visualization, targeting, and safe extraction of nanoparticles are common concerns. Recently, an ultrasound-mediated microbubble drug delivery approach was clinically tested and proven safe for IV routes,^{40,114,122,133,158,159,185} which could be used for clinical delivery of PGG to AAA.

Subcutaneous Route (SC)

SC route of drug delivery is used for small animals when the drug is non-irritant, near-neutral pH; hence, difficult to be translated towards a PGG-based application. Nevertheless, 5, 25, 125, and 625 mg/kg doses of PGG as a part of *Nymphaea lotus* extract were utilized for treating mice with anxiety issues.⁴⁴ Additionally, 625 mg/kg SC injection (or IP route) led to sedation and loss of paw grip in many animals.

Drawbacks Subcutaneous route of drug delivery is of interest in the clinical setting owing to its ease of administration and reduced treatment costs. However, it has been observed that the pharmacokinetics of subcutaneous drug delivery is greatly influenced by the body fat percentage or the obese nature of the subject.¹⁵¹ Further, targeting the largest artery in the body would mean the dependence of this approach on systemic circulation and/or lymphatic systems. Liquid jets, microneedles, microinjections, *etc.* have greatly improved the subcutaneous drug delivery approaches recently.⁶ However, the ability of PGG to reach the aneurysmal region *via* the subcutaneous route will depend on (i) a secondary carrier (e.g.,

nanoparticle, lipids, *etc.*), (ii) shielding of the hydrophobic portions of the drug to prevent it from interacting with other proteins, and (iii) site-specific targeted release mechanism for efficient delivery.

Intraperitoneal (IP) Route

IP drug delivery is a controversial method for clinical implementation.¹⁶⁴ It is widely applied in small animal models to avoid the risk of vascular injury. Recently, self-assembling type I collagen oligomers were successfully delivered in murine AAA models *via* ultrasound guided IP injection, resulting in minimal inflammatory response and cell invasion compared to the open-abdominal injections into the same region.¹⁹⁷ In a study by Li *et al.*,⁹⁷ IP delivery of PGG (5% ethanol/saline vehicle) was performed in a mouse model and liquid-liquid extraction of PGG was performed. PGG took longer to reach the blood stream than other polyphenolic compounds and eventually existed in free form; plasma concentration of PGG was 3–4 μM 2 hours post-injection. Similarly, PGG has been delivered in small animal models *via* IP routes for anxiolytic properties,⁴⁴ anti-viral treatment,^{14,178} anti-tumor studies,^{67,91} and anti-diabetic treatments.¹⁸⁶ Furthermore, PGG dosages up to 10 mg/kg have been used for the inhibition of capillary morphogenesis gene 2 in mice *via* the IP route.³⁶ Similarly, an IP dose of 10 mg/kg PGG was able to resolve both serum total cholesterol and triglyceride levels in hamster models, compared to similar PGG formulations administered at a higher oral dosage (100 mg/kg).¹²⁶

Drawbacks Even though PGG has been administered in small animal models *via* the intraperitoneal route for various therapeutic applications,^{25,36,67,94,126} there are still some translational limitations to this delivery method. One of the key issues with intraperitoneal drug delivery is the premature clearance of the drugs in the peritoneal cavity, inefficient permeation of the drug in the target area, cellular uptake, and limited residence time of the drug.⁹ In addition, there is another challenge to the retroperitoneal approach of the aorta and to administer PGG or any drug to the site of the aneurysm. To remedy these issues, one possible solution could be the use of hydrogels¹⁹⁶ or a viscous polymer¹¹⁰ that can a delivery system to delay the premature clearance of the drug in the peritoneal cavity. One of the primary advantages of delivering PGG retroperitoneally would be to minimize the compounds interaction with blood and its components and prevent rupture of the aneurysmal tissue periadventitially.

Nanoparticle-Based Delivery

Nanoparticle-based PGG delivery can be employed to quantify inflammatory events in vascular tissue pathologies such as AAA, atherosclerosis, *etc.*⁴³ Vyavahare *et al.* have used PGG-laden nanoparticle delivery extensively in small animal models.^{119,120,157} *In vitro* studies show that PGG nanoparticle formulations have more binding affinity toward the degraded elastin matrix, compared to healthy arterial tissue.¹⁵⁷ For the rat AAA CaCl_2 model, nanoparticles conjugated with PGG were able to reduce macrophage recruitment, elastin degradation, and aneurysm progression.¹²⁰ In addition, a dual EDTA and PGG nanoparticle combo acts as a pharmacological agent for calcium removal (calcification) and elastin stabilization (elastin cross-linking), respectively.¹¹⁹ However, the effectiveness of

AAA suppression in the presence of continuous blood flow and advanced elastin degradation still needs to be evaluated.

Drawbacks Nanoparticle based toxicity is one of the major issues in this mode of delivery. Issues such as degradation, cell death, endocytosis, and chemical toxicity are some of the chief concerns with drug delivery *via* nanoparticles.³⁸ Further, its surface characteristics can dictate the drug distribution properties and particle uptake abilities as well. Some of the improvements to the nanoparticle route could involve advances in drug entrapment techniques, development of efficient target-specific markers, and prevention of accumulation in the liver, spleen, and other organs in the body (which can potentially sieve these particles). With reference to PGG, it is metabolized by the liver and it easily forms insoluble precipitates. The goal of the nanoparticle-based delivery system carrying PGG molecules should be to bypass the liver and help reach its intended target (i.e. the abdominal aorta) with a greater efficiency compared to administering the compound by itself. Poly-(D,L-lactide-co-glycolide)-based nanosystems could potentially be used for PGG delivery as they have reported the least toxic effects while undergoing biodegradation to produce biocompatible metabolites like lactic acid and glycolic acid.^{8,146,147}

Proposed Microbubble-Based Delivery (MBD)

A detailed review of microbubble applications is presented elsewhere.^{89,122,133,158,159} In this work, we provide a brief introduction to MBD and its potential use for transporting PGG, as shown in the schematic in Fig. 3. MBD is an innovative extension of ultra-sound contrast agent (UCA) research efforts and more specifically of microbubbles, following the work of Gramiak and Shah in 1968.⁵⁶ Their use of agitated saline during ultrasound examination of aortic roots improved signal contrast, and hence, clinical visualization. However, due to high surface tension, these bubbles were not stable and quickly dissipated. Twenty years later, a more stabilized form of UCA (*e.g.*, albumin-coated air-filled microspheres) was developed by Feinstein *et al.*⁴⁵ and the product was FDA-approved and commercialized as Albunex. Since then, hard shelled-microbubbles, soft shelled-microbubbles, nanobubbles, and silica shells of sizes ranging from a few microns to nanometers have been developed for various ultrasound imaging and research applications.¹²² The subsequent generations of microbubbles were commercialized as Optison (1997), Definity (2001), Sonovue (2001), Luminity (2006), Sonazoid (2007), and Lumason (2014); the microbubbles Imagent/Imavist, Echovist, Levovist, and Albunex were withdrawn from clinical use. These new generations of microbubbles have been approved for use in North America and certain parts of the world for left ventricular opacification, endocardial border definition, and diagnostic assessment of blood vessels.⁷ This UCA application was extended for therapeutic options such as drug delivery and cancer cell ablation.

Microbubbles are *theranostic* agents (i.e., with both diagnostic and therapeutic functionalities) while the advantages of MBD are its real-time evaluation, safety over other molecular imaging modalities, low-dosage requirements, and lower costs.¹⁵⁸ Microbubbles are hollow spheres filled with gas encapsulated in a shell; gaseous contents and shell material determine their efficiency. They are highly efficient scatterers of ultra-sound energy due to the compressible gas core and resonate to ultrasound waves. The scattered energy can

be detected to assist in imaging of inflammation, thrombus, and tumors.^{87,182} The aforementioned commercially available microbubbles are made of an inert gas or biocompatible material such as octafluoropropane, perfluorohexane with nitrogen, sulfur hexafluoride, or perflubutane.^{7,122} The outer shell material is made up of either cross-linked albumin or phospholipids. The acoustic properties of the microbubbles can be altered by varying the shell material viscoelasticity and tailoring it to the preferred application.⁶³ Typically, circulating microbubbles are cleared in the reticuloendothelial system within the first ten minutes post-injection.¹⁹⁸ To prolong their circulation time, polyethylene glycol (PEG) is usually added to the microbubble shell, which also improves their biocompatibility.¹⁴³ In some cases, a coating of a polymer, liposome, or protein can be applied to stabilize the microbubbles.^{122,158} For MBD, microbubbles act as a vehicle to carry the drug, gene, or any other chemical. The drug can be within the microbubble shell or attached to its outer coating. The latter can be done with the help of streptavidin, biotin, or other chemicals. Further, these drug-loaded microbubbles can be juxtaposed to a targeting ligand for site-specific delivery of constituents *via* the blood stream. At the site of interest, the ligands on the microbubbles will attach to the receptors in the blood vessel lumen (e.g., VCAM on the endothelium, or elastin in the intima).

MBD relies on the mechanism of cavitation, i.e. application of mechanical forces that leads to the expansion and/or bursting of the microbubble, allowing for delivery of the drug at the target site. Application of ultrasonic forces lead to either (i) stable cavitation and/or (ii) transient cavitation. The released drug is transported through membrane pores, cellular junctions, or transient pore formation (mechanism of sonoporation).^{89,133} Some of our contributions to the field of MBD can be found in Refs. 61,162 and 194. Occasionally, the cavitation may produce smaller microbubbles that are either not released or flow downstream. Often, if these microbubbles attach to the lumen, they can be hyperpolarized and engulfed by cells (endocytosis). Microbubbles range in size from 0.1 to 10 μm ; larger bubbles may not pass through narrow vessels, which leads to extravasation and retention of macromolecules [termed the enhanced permeability and retention effect (EPR effect)],¹²² especially in tumors. Nonetheless, owing to the size and dilation of the abdominal aorta in AAA patients, we hypothesize that MBD applications would exhibit minimal EPR effects.

Drawbacks Microbubble enhanced ultrasound has been used for tracking endoleaks in repaired AAA with 99% accuracy, 97% sensitivity, and 100% specificity.⁵¹ While their applications in imaging have been well established, there are no current drug-formulated microbubble formulations that are available for clinical use, and there are no known studies reporting the use of microbubbles for on-site delivery of drugs to AAA. One of the major challenges with developing drug-loaded microbubbles is limited surface area available for drug loading on the lipid shell.¹⁵⁸ The bulk of the MB particle volume is gas surrounded by a thin shell. Non-gaseous therapeutic drugs must be loaded tethered to the surface of the bubble or embedded in the shell layer, thus drug loading capacity can be limited by constraints of allowable gas volume for injections. Strategies of improving drug-loading capacity by changing the shell material are being explored,^{49,74,96,160} but these strategies require further development and testing before they can be considered clinically viable. Another challenge with developing a drug-loaded-ultrasound vehicle is that encapsulations alters the pharmacodynamics and pharmacokinetics of drug, which may require lengthy

testing and evaluation for FDA approval¹⁰ compared to traditional microbubble sonoporation approaches that only permeabilize vasculature. However, once an effective drug-loaded formulation is fully developed, it would have the potential to significantly enhance patient outcomes by improving payload of drug delivered on-target and reducing off-target accumulation *in vivo* in a manner far more efficiently than traditional sonoporation.⁹⁶

For the present work, our interest in microbubbles is for their use in drug delivery applications and more specifically, for the delivery of PGG to the diseased aorta. Owing to the condition of the aorta in AAA patients, the delivery system must be minimally invasive, reliable, site-specific, efficient, biocompatible, and easy to operate. We hypothesize that a PGG MBD system with a targeting ligand, such as VCAM or elastin, could be used effectively for AAA pharmacotherapy. As clinical ultrasound is used routinely for detection and monitoring AAA, an MBD approach to PGG delivery could be performed with similar efficiency, low cost, and minimal discomfort to the patient. The proposed working mechanism of PGG MBD to the abdominal aorta is shown in Fig. 3. Presently, the only known therapeutic application of MBD is to deliver microRNA-126 to the AngII AAA mouse model,¹⁸⁵ however MBD delivery of PGG has the potential to significantly improve on therapeutic outcomes.

LIMITATIONS AND FUTURE WORK

Even with the vast volume of studies undertaken to understand AAA pathology and the potential treatment strategies being investigated, there are more unanswered questions than solutions for this vascular disease. Some of the accepted etiological theories of heterogeneous AAA pathophysiology include: (i) ECM remodeling, (ii) dysfunctional inflammatory signaling pathways, and (iii) metabolics related to ILT and the circulatory system.^{53,54,113} The risk factors for AAA are unique,¹⁹ owing to confounding factors such as diabetes mellitus, hypertension, *etc.* Conversely, diabetes has exhibited a somewhat cardioprotective role and is negatively associated with AAA^{19,93} and AAA growth rate.¹⁹⁵ Recent studies also suggest that diabetic AAA patients have a reduced mortality rate.¹⁰¹ This creates a challenge for clinicians when imagining an appropriate therapeutic strategy for AAA patients. Meanwhile, PGG has been successful in preventing calcification of vascular grafts,³³ exhibits vasodilation properties,^{55,79} reduces aneurysm growth,^{70,120} improves glucose tolerance in high fat diet-induced diabetic mice,¹¹¹ and inhibits cholesterol efflux across macrophage foam cells.^{135,200} Based on these prolific characteristics, PGG could be translated into clinical use for improving the vascular health of diabetic AAA patients. Even with these favorable anti-diabetic characteristics, the effect of PGG in complex scenarios, such as diabetic or hypertensive AAA patients, is unknown. Optimistically, a combinatorial benefit of these functional properties of PGG can be of clinical use in the future for treating AAA patients.

Cases of severe toxicity with polyphenols are rare; however, in large doses, these compounds can potentially cause adverse effects like nausea, abdominal pain, diarrhea, fatigue, and insomnia.¹⁷³ Nevertheless, a detailed pharmacokinetic analysis of PGG is yet to be completed. At present, studies focusing on the therapeutic effects of PGG are being designed

for a single AAA etiology, i.e. either proteolysis, inflammation, or thrombosis. The greater challenge will be to elucidate the role of PGG in AAA patients with the aforementioned confounding ailments. Some aspects of AAA disease are poorly understood, e.g. the role of ILT in AAA development, or predicting the risk and location of AAA rupture. Furthermore, current AAA animal models do not replicate the exact clinical pathology.¹³⁸ Hence, future animal studies should focus on the role of ILT in AAA, the effect of PGG on AAA (with ILT) suppression, and the effectiveness of PGG permeation to the aortic wall. Due to the heterogeneity of AAA pathology, there are no biomarkers that effectively indicate ILT presence, inflammation, and proteolysis simultaneously.¹¹³ Thus, the major hurdle for an AAA therapeutic approach is that it not only requires a novel minimally invasive treatment, but also the development/discovery of efficient disease biomarkers.

In summary, PGG is a versatile and promising compound in biomedical research. Its current benefits likely outweigh its disadvantages. From a biomechanical prospective, stabilization of the elastin lamellae not only gives support to the ECM, but also provides a cohesive integration of the residual elastin fibers. The degree or severity of elastin damage that can successfully be repaired by PGG remains undetermined. Nevertheless, this matrix-stabilizing polyphenol has remarkable potential and it is highly likely to be a multifaceted therapeutic drug.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

⁶⁰Co-γ rays	Cobalt-60 gamma rays
6-Keto-PGF1α	6-Keto-prostaglandin 1 α
ADP	Adenosine-5'-diphosphate
ALT	Alanine aminotransferase
AP-1	Activator protein-1
ArA	Arachidonic acid
B16F10	Metastatic mouse melanoma cells
BHK-21	cells Baby hamster kidney cell
BV-2	Transfected microglial cell line

CAT	Catalase
CC₅₀	50% cytotoxic concentration
C_{max}	Maximum serum concentration that a drug achieves in a test area of the body after the drug has been administrated and before the administration of a second dose
CML cell line K56	Human chronic myelogenous leukemia
DMSO	Dimethylsulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
EC 2.3.1.67	Acetyl-CoA:1-alkyl-sn-glycero-3-phosphocholine acetyltrans-ferase
EC₅₀	The concentration of a compound where 50% of its maximal effect is observed
EGF	Epidermal growth factor
FcεRI	High-affinity IgE receptors
GPIIb/IIIa	Glycoprotein IIb/IIIa inhibitors
GSH-Px	Glutathione peroxidase
HBZY-1 cells	Glomerular mesangial cell line
HPBMC	Human peripheral blood mononuclear cells
HUVECs	Human umbilical vein endothelial cells
IB5	Basic salivary protein
IC₅₀	Half maximal inhibitory concentration
ICAM-1	Intercellular adhesion molecule 1
IL-1	Interleukin-1
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
K_d	Dissociation constant—represents ligand-receptor affinity
mBMMCs	Mouse bone marrow-derived mast cells
MCP-1	Monocyte chemoattractant protein 1

NF-κB	Nuclear factor- κ B
NO-cGMP	pathway Nitric oxide/cyclic guanosine monophosphate signaling pathway
NOS	Nitric oxide synthase
NR	Not reported
NS3	Nonstructural protein 3
PAF	1-Alkyl-2-acetyl-sn-glycero-3-phosphocholine
PC-3	Human prostate cancer cell line
PMN	Polymorphonuclear leukocyte system
rhALR2	Recombinant human aldose reductase
ROS	Reactive oxygen species SCID Severe combined immunodeficiency
SK-MEL-28	Human skin melanoma cell line
SOD	Superoxide dismutase
SP-1	Specificity protein 1
TGF-β1	Transforming growth factor beta 1
T_{max}	Time at which the C _{max} is observed
TNF-α	Tumor necrosis factor alpha
TXB2	Thromboxane B2
U937	(Pro-) monocytic cell lines
V79-4	cells Chinese hamster lung fibroblasts
XOD	Xanthine oxidase

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FIGURE 1. PGG-mediated activation and suppression of molecular pathways with relevance to vascular health. The inset illustrates *in vitro* PGG-based tissue treatment for ECM stability. Adapted from Refs. 18,23,31,34,42,55,79,92,100,104,117,123,127,142,163,176,192,193,199, and 200.

FIGURE 2.

Suppression of AAA growth by PGG. (a) Isenburg *et al.*⁶¹ demonstrated that periadventitial application of PGG in the calcium chloride rat AAA model was successful in preventing further expansion of the abdominal aorta. Mean diameter reduction was seen in the PGG animal group and aneurysm formation was prevented in more than 80% of the animals. (b) Histological analysis reveal that calcium chloride induced fragmentation of the elastin fibers (black) and disruption of the ECM. PGG treatment crosslinks the elastin and preserves the elastin matrix of the arterial tissue, similar to the controls. (c) Thirugnanasambandam *et al.*¹⁴⁹ utilized a similar rat calcium chloride model and utilized PGG to suppress aneurysm growth. As shown, PGG treatment was also able to suppress MMP influx to the aorta, which led to a reduction of inflammation. (d) Concurrently, a reduction in Peak Wall Stress (PWS) was observed in pre- vs. post- AAA induction surgery in untreated [d(i) and (ii)] and PGG-treated [d(iii) and (iv)] specimens. These finite element studies indicate that a lower PWS yields more pronounced recovery of the aortic wall structure owing to PGG crosslinking of the ECM proteins. Adapted from Refs. 70 and 172.

FIGURE 3.

Concept of microbubble mediated systemic delivery of PGG at the aneurysm site for AAA patients. PGG would be delivered by two modes: (a) stable cavitation and/or (b) sonoporation. PGG particles embedded in the lipid-coated microbubbles are introduced in the blood stream *via* intravenous injection. Administration of ultrasonic energy to the desired target area can produce cavitation of the microbubbles. Cavitation can be either (a) stable—implosion of the microbubble leading to the release of PGG in the blood stream to be further absorbed *via* intracellular gap junctions, endocytosis, or membrane pores; or (b) transient—asymmetric collapse of microbubbles leading to a liquid jet that can pierce the endothelial lining and delivers the drug (PGG). Adapted from Refs. 89,133 and 159.

TABLE 1.

Biochemical characteristics of PGG.

Characteristic(s)	Value(s)	Citation
PubChem CID	65,238	NIH Pubmed
IUPAC name	2S,3R,4S,5R,6R)-2,3,5-Tris[(3,4,5-trihydroxybenzoyl)oxy]-6-[(3,4,5-trihydroxybenzoyl)oxymethyl]oxan-4-yl] 3,4,5-trihydroxybenzoate)	- Do -
Other names	- 1,2,3,4,6-Penta-O-galloyl- β -D-glucose; - 1,2,3,4,6-Pentakis-O-galloyl-beta-D-glucose; - Beta-Penta-O-galloyl-glucose.	- Do -
Dissociation constants (K_d)	1.7×10^{-5} M (with protein IB5) 3.2×10^{-6} M (with lipid A)	27, 50
Solubility	DMSO—10 mM DMSO—20%; pH 5.9	26
Oxidation products	pH < 4—predominantly polymers pH > 5—quinones	30

In vitro studies exhibiting beneficial effects of PGG to the vascular system (lowering of inflammatory responses).

Experiment	Dosage	Beneficial effects	IC ₅₀	Comments	Source
B16F10 cells	5–25 μ M PGG	Anti-tumor properties ↓ AP-1 ↓ SP-1 ↓ c-Jun protein	15 μ M for MMP-9	Expression of MMP-9 was greatly inhibited as compared to MMP-2; higher PGG dosage led to reduction of tumor cell viability to 50–60%	62
Rabbit platelet-PMN system	PGG as a part of black tea extract	Inhibition of platelet activation	28–58 μ M	EC 2.3.1.67 enzyme activity was inhibited	163
U937 cells	0–20 μ M PGG isolated from <i>P. suffruticosa</i> ANDREWS	Anti-inflammatory ↓ TNF- α ↓ IL-8	NR	NF- κ B inactivation; reduced degradation of I- κ B α	121
HPBMC	10–80 μ g/mL PGG—isolated from <i>Radix Paeoniae Rubras</i>	Inhibited TNF- α and IL-6 expression in a dose-dependent manner	K_d = 32 μ M for lipid A	80 μ g/mL of PGG was able to reduce 61.4% of TNF- α and 42.5% of IL-6 expression	50
HUVECs	1×10^{-4} mol/L PGG isolated from <i>P. suffruticosa</i> ANDREWS	↓ MCP-1 ↓ VCAM-1 ↓ ICAM-1	NR	1×10^{-6} or 1×10^{-5} mol/L PGG reduced the number of U937 cells adhering to HUVECs Maximal relaxation effect of PGG on pre-contracted aortic rings was observed at $77.2 \pm 2.2\%$ under the concentration of 3×10^{-5} mol/L	79
DPPH assay	1, 3, 10, 30 and 100 μ g/mL of PGG	Anti-oxidant potential—free radical scavenging assay	1 μ g/mL	PGG has better anti-oxidant property than Vit E and gallic acid	2
Primary rat aortic smooth muscle cells and rat skin fibroblasts	0.03, 0.06, 0.1, and 0.3% PGG	Cytotoxicity	NR	0.06% had minimal cytotoxic effects	70
rhALR2	2.0 μ M PGG isolated from the Bark of <i>R. verniciflua</i>	Anti-diabetic	> 2.0 μ M		95
PC-3 cells	5–40 μ M PGG isolated from the leaves of <i>Macaranga tanarins</i> (L.)	Suppression of EGFR/JNK pathway ↓ MMP-9 ↓ EGF	NR	20–70 μ M showed minimal cellular toxicity	91
Human neutrophils	5, 10, 20, and 50 μ M PGG	↓ ROS ↓ IL-8	NR	Dose-dependent reduction in ROS; no cytotoxic effect 75% inhibition in ROS at 5 μ M PGG	86
Rat aortic smooth muscle cells	10 μ g/mL PGG	↑ Elastin fibers synthesis ↑ Lysyl oxidase ↓ MMP-2	NR		156
BV-2 cells	6.25–200 μ M PGG for cell viability studies; 25 μ M PGG for cytokine arrays	↓ MCP-5 ↓ Pro MMP-9	NR	10-fold reduction in cytokine expression	107
DPPH Assay	PGG isolated from <i>C. coggygia</i>	Anti-oxidant potential—free radical scavenging assay	12.6 μ g/mL		188

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Experiment	Dosage	Beneficial effects	IC ₅₀	Comments	Source
90 μ L of whole blood	PGG (500 μ g/mL, final concentration of 0.53 mM)	↓ P-selectin ↓ GPIIb/IIIa	1.77×10^{-1} mM for ADP-induced aggregation 2.2×10^{-1} mM in ArA-induced aggregation 1.6×10^{-1} mM in collagen-induced aggregation	Inhibited the platelet induced aggregation, suppressed platelet membrane receptor expression and intracellular calcium mobilization	76
DPPH Assay	1, 10, and 50 μ g/mL PGG (isolated from <i>Elaeocarpus sylvestris</i> var. <i>elipticus</i>)	Anti-oxidant potential—free radical scavenging assay	17% at 1 μ g/mL 56% at 10 μ g/mL 75% at 50 μ g/mL	PGG exhibited similar anti-oxidation behavior as EGCG	131

in vivo studies exhibiting beneficial properties of PGG to the vascular system (with a focus on pharmacokinetics).

Experiment	Administration	Dosage	Beneficial effects	IC ₅₀	Comments	Source
Calcium chloride AAA rat model	Periadventitial application	0.03, 0.06, 0.1, and 0.3% PGG	Reduction in abdominal aorta diameter ↑ TIMP-2 ↓ MMP-2,9	NR	PGG limits AAA formation, inhibits elastin degeneration, and preserves the elastic lamellae; open angle measurements were smaller with increasing concentrations—indicating direct interaction of PGG with elastin fibers	70
BALB/c mice	PO	5 mg/kg	Reduction in mast cell infiltration	NR		78
Calcium chloride AAA rat model	Nanoparticle mediated delivery	10 mg/kg PGG	Reduction in abdominal aorta diameter ↑ Lysyl oxidase ↓ MMP-2,9	NR	PGG suppresses AAA expansion	120
Calcium chloride AAA rat model	Nanoparticle mediated delivery	10 mg/kg PGG + EDTA	Reduction in abdominal aorta diameter ↑ Lysyl oxidase ↓ MMP-2,9	NR	EDTA helps with chelation of calcium; circumferential strain was increased in PGG + EDTA treated animals	119
SCID mice	Single dose IP injection	PGG (50 mg/kg) dissolved in PBS containing 5% ethyl alcohol	Plasma PGG levels; ALT levels for liver toxicity	2–4 μ M after 2 h postinjection	PGG levels in plasma was almost diminished by 96 h in all the animals	14
BALB/c mice	Single dose IP injection	PGG (50 mg/kg) dissolved in PBS containing 5% ethyl alcohol	Plasma PGG levels; ALT levels for liver toxicity	NR	Increased levels of ALT for non-surviving animals (~40%); rest had moderately elevated level of ALT	14
C57BL/6 mice	Single IP injection	0.5 mg per mouse (~20 mg/kg) of PGG	Pharmacokinetics	$C_{max} = 3-4 \mu$ M at $T_{max} \sim 2$ h	PGG exists as free form in plasma and it is easily extractable; no gender differences found Takes longer to reach plasma than other compounds Absorption with 2% Tween 80-water vehicle is worse as compared to 5% ethanol/saline vehicle	97
C57BL/6 mice	Oral gavage or PO	2 mg PGG per mouse	Pharmacokinetics	NR	Not detected by UV detector and MS/MS ranges were sub-normal	97
Sprague-Dawley rats	IP injection	PGG as a part of Moutan Cortex 5 g/kg	Reduction in inflammatory cytokines ↓ ICAM-1 ↓ TGF- β 1 ↑ CAT ↑ GSH-Px	NR		186
Sprague-Dawley rats	Single dose IV injection	20 mg/kg body weight of PGG dissolved in 0.9% saline	Pharmacokinetics	NR	PGG not detected in biofluids; urine and fecal clearance were major excretion routes	102