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MINI-REVIEW

Biological and biomedical functions of Penta-*O*-galloyl-D-glucose and its derivatives

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Abstract Penta-*O*-galloyl-D-glucose (PGG) is a simple hydrolysable tannin in plants. PGG exists in two anomeric forms, α-PGG and β-PGG. While β-PGG can be found in a wide variety of plants, α-PGG is rather rare in nature. Numerous studies with β-PGG revealed a wide variety of biological activities, such as anti-microbial and anti-cancer functions. Until recently, studies with α-PGG were limited by the lack of its availability. Since the development of an efficient chemical synthesis of the compound, several investigations have revealed its anti-diabetic, anti-cancer, and anti-platelet-coagulation functions. Based on structure–activity-relationship (SAR) studies with α-PGG, a variety of α-PGG-related novel compounds were synthesized and some of them have been shown to possess promising therapeutic activities. In this review, the authors will survey and evaluate the biological functions of PGG with a focus on α-PGG and its derivatives.

Keywords Hydrolysable tannin · Diabetes · Cancer · Glucose transport · Insulin · Gallotannin

Introduction to PGG

Tannins are polyphenolic secondary metabolites in higher plants with a broad molecular weight distribution commonly ranging between 500 and 20,000 Da [1]. They are found in a wide variety of species and are considered to be part of the plant's natural defense system against environmental stressors [2]. The antinutritive and toxic effects of tannins are well-documented [2, 3]. The biological functions of tannins depend largely on their protein-precipitating properties mediated by hydrophobic forces and hydrogen bonds [2, 3]. In addition to the originally identified antinutritive and toxic effects, tannins possess

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multiple bioactivities that are beneficial to human health, such as immune modulatory activities [4], antioxidant activities [5], anticarcinogenic activities [4], and antimicrobial activities [4, 6]. For example, tannins in red wine have been shown to be related to the health beneficial effects in preventing heart-related diseases. The expression levels of endothelin-1, a major protein responsible for cardiovascular diseases, were found to be reduced in proportion with the tannin content of specific red wines [7].

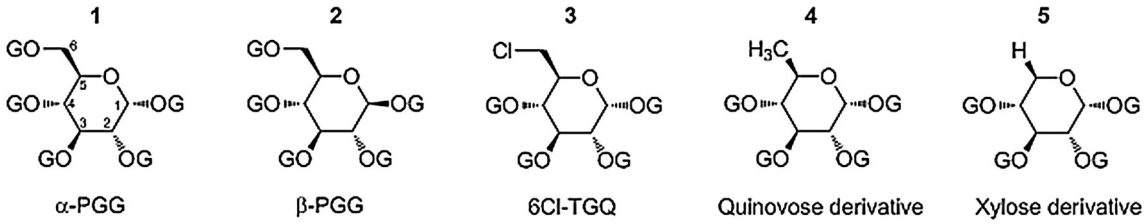
Tannins can be divided into gallotannins, ellagitannins, condensed tannins, and complex tannins [8]. The first two of these classes are often combined and referred to as hydrolysable tannins because of the presence of ester bonds that are easily hydrolyzed to yield carboxylic acids such as gallic and ellagic acid. Hydrolysable tannins are found in the human diet, including fruits and beverages. For example, ellagitannins are found in pomegranate [9] and whisky [10] while gallotannins are found in many plants such as Tara pods (*Caesalpinia spinosa*), gallnuts from *Rhus semialata* or *Quercus infectoria*, as well as oak and chestnut wood [11]. They are the primary reasons for the astringent taste of these fruits and beverages. Hydrolysable tannins have multiple beneficial effects. For example, hydrolysable tannins were shown to be effective in lowering blood glucose levels in diabetic patients [12].

The structure of gallotannins is usually simpler than the structure of other tannins. It consists of gallic acid molecules that are bound to a central carbohydrate core (usually D-glucose) via ester bonds [1]. Most of the isolated natural gallotannins are β-anomers. Penta-*O*-galloyl-D-glucose (PGG) constitutes a prominent example. The structures of the two PGG anomers are shown in Fig. 1.

β-PGG can be found in many plants such as *Rhus chinensis MILL*, *Paeonia suffruticosa* and *Pelargonium inquinans Ait* [13, 14], while α-PGG rarely occurs naturally [15, 16]. Both compounds are available via relatively simple chemical syntheses [17–19]. Highly purified material is available after crystallization.

β-PGG

β-PGG is one of the key intermediates in the biosynthesis of almost all hydrolysable tannins in plants. Functional studies have revealed multifunctional characteristics of β-PGG: (a) β-PGG interferes with lipid layers [20]; (b) β-PGG strongly inhibits the activity of a variety of enzymes including human placenta aldose reductase [21], Na(+),K(+)-ATPase [22], salivary α-amylase [23], metalloproteinase-9 [24], nitric oxide synthase [25], cyclooxygenase-2 [25], angiotensin-converting enzyme [26], β-oxoacyl-ACP reductase [27], endopeptidase [26], aminopeptidase N [26], elastase [28], hyaluronidase [28], and DNA polymerase [29]; (c) β-PGG alleviates oxidative stress [14, 30]; (d) β-PGG prevents nephrolithiasis and urolithiasis [31]; (e) β-PGG modulates immune reactions through, for instance, decreasing IL-8 expression [32], down-regulating mast cell surface FcepsilonRI expression [33], and suppressing chemokine production [34]; (f) β-PGG protects neuronal cells against ischemia, neurodegeneration and Alzheimer's amyloid β protein aggregation [35–37]; (g) β-PGG also protects animal hosts from infection by bacteria such as *Staphylococcus aureus* [38], and viruses such as influenza virus [39], herpes virus [40], HSV-1 [41], and HBV [42]; (h) β-PGG has anti-coagulant functions [43]; (i) β-PGG activates the insulin receptor signaling and stimulates glucose transport [12, 44]; (j) β-PGG inhibits adipogenesis, a process through which mature fat cells are generated from preadipocytes [16]; and (k) β-PGG has beneficial effects in the treatment of various cancers including, but not limited to, renal cancer [45], prostate cancer [46, 47], breast cancer [48–51], liver cancer [51, 52], and melanoma [24, 53]. It executes the anti-tumor effect by inducing apoptosis [53], preventing mutation, and inhibiting tumor proliferation [52], angiogenesis [54], and metastasis [24]. In several studies, it has been found that β-PGG inhibits growth of prostate [47] and breast cancer cells [50] by inducing cell cycle arrest. β-PGG also



Relative glucose stimulatory activity in adipocytes				
1	2	3	4	5
145	107	181	115	124

Fig. 1 α-PGG derivatives with their respective glucose uptake stimulatory activities

significantly reduced growth of triple-negative breast cancer in a mouse model [50].

A detailed review of β-PGG functions was prepared by Zhang et al. [55]. Although β-PGG has been extensively studied biochemically, biologically, and biomedically, the detailed mechanisms of action are far from fully elucidated.

α-PGG

Since there are no efficient ways to extract α-PGG from natural sources, studies of this compound have been rare and largely delayed compared to those on β-PGG. Until recently only little was known about the bioactivities of α-PGG. In an early report, it was shown that α-PGG increases the adhesion between opposing phosphatidylcholine bilayers [56]. Within a narrow concentration range, it collapses the inter-bilayer fluid space from about 15 to 5 Å [56].

The number of studies increased only after a recent report that described the chemical synthesis and purification of α-PGG [17, 18]. The procedure allows for the preparation of a 96:4 mixture of α- and β-PGG. Upon recrystallization, α-PGG with a purity of >99 % is obtained [17, 44]. Using a glucose uptake assay which monitors the total amount of glucose transported into adipocytes (3T3-L1 cells), it was shown that the chemically synthesized α-PGG possesses an insulin-like glucose transport stimulatory activity similar to β-PGG [44]. Strikingly, though, α-PGG demonstrated a 20–30 % consistently higher activity in stimulating glucose transport in adipocytes compared to β-PGG in vitro [17, 44]. Studies with high-fat diet-induced diabetic and obese mice models indicated that α-PGG is also effective in vivo. It reduced blood glucose levels and improved glucose tolerance while being well-tolerated by the animals [44]. Because α-PGG can induce glucose uptake like insulin, it was hypothesized that α-PGG may act on the insulin receptor signaling. A mechanistic study using 3T3-L1 adipocytes showed that inhibitors for the insulin receptor and for the PI3 kinase, both of which block the insulin receptor signaling and, thus, inhibit the insulin-mediated glucose transport, could completely stop the glucose transport induced by α-PGG [44]. Detailed cell studies about the effect of α-PGG on the insulin receptor signaling revealed that α-PGG induces tyrosine phosphorylation of the insulin receptor, followed by activation of PI3 kinase and Akt, and stimulation of the translocation of glucose transporter 4 (Glut4, an insulin responsive glucose transporter) from the cytosolic compartment to the cytoplasm membrane [44]. Therefore, it appears that α-PGG stimulates glucose transport by activating the insulin receptor signaling. In vitro receptor binding assays suggest that α-PGG binds directly to the α-subunit of the insulin receptor at a site different from the insulin binding site because the binding of α-PGG to the insulin receptor reduces maximal insulin binding without significantly altering the binding affinity of insulin to the insulin receptor [44]. Apparently, although the exact binding site on the receptor differs from insulin, α-PGG can still induce the insulin receptor to change to a conformation sufficient for the activation of the downstream signaling pathways in insulin responsive cells. The finding that both α-PGG and β-PGG activate the insulin receptor while β-PGG inhibits a series of proteins/enzymes studied by other groups [21–29] is striking and scientifically important. It is much more common for a natural compound to inhibit an enzyme rather than to activate it. The question arises as to how the activating interactions of α-PGG and β-PGG with the insulin receptor differ from their inhibiting effects on all other enzymes examined.

The potential beneficial effects of α-PGG in the treatment of diabetes are not only based on its ability to activate the insulin receptor signaling, but also on its capability to alleviate the weight gain problem in diabetes. In an animal study with high-fat diet-induced diabetes and obesity mice models, moderate weight loss caused by α-PGG was observed (Cao and Chen, unpublished observation). One of the explanations for this non-insulin-like weight reduction effect of α-PGG is that α-PGG is a tannin that can decrease nutrient absorbance at certain levels [57, 58]. Another explanation is that, like β-PGG, α-PGG may inhibit adipogenesis [16]. Insulin exerts its biological functions through two types of actions: a rapid insulin receptor activation resulting in Glut4 translocation and glucose uptake within minutes, and a much slower action promoting adipogenesis involving gene expressions that take days to complete [59]. The α-PGG's rapid action which leads to Glut4 translocation is insulin-like while its slower action which results in inhibition of adipogenesis is non-insulin-like or anti-insulin. It would be highly desirable to elucidate how α-PGG mediates these two types of activities at molecular and gene levels. Regardless of what the underlying mechanisms are, the non-insulin-like adipogenesis inhibitory activity of α-PGG could be beneficial for obese individuals. Because diabetes and obesity are highly associated, this weight reduction effect suggests that α-PGG may exert long-term benefits to diabetic subjects.

The α-PGG was initially intensively studied as an anti-diabetic compound. However, its biological function is not at all limited to being anti-diabetic. Since numerous studies have shown that β-PGG, the anomer of α-PGG, possesses anti-cancer cytotoxic activities, it was hypothesized that α-PGG could exhibit similar activities. Indeed, it was found that α-PGG induces apoptosis in multiple human cancer cell lines including colon cancer RKO cells, breast cancer MCF7 cells, cervical cancer Hela cells, and lung cancer

H1299 cells after 48-h treatments at a concentration of 25 μM [60]. It was also found in the cell studies that α-PGG targets cancer cells without significantly affecting their normal counterparts [60]. Using RKO as a model cell line for in vitro mechanistic studies, α-PGG was shown to induce apoptosis through increasing p53 levels and inducing the activation of p53, Bax, and caspase 3, three major players in the apoptosis pathway [60]. Surprisingly, α-PGG's ability to elevate p53 levels is diminished once the insulin receptor level or function was decreased by an siRNA or a specific inhibitor [60]. Further studies revealed that MEK, a downstream signaling factor of the insulin receptor, is activated by α-PGG in RKO cells [60]. Inhibition of MEK activity leads to the suppression of α-PGG-induced p53 and Bax elevation [60]. Therefore, the insulin receptor signaling pathway, particularly the insulin receptor-MEK pathway, which is traditionally considered as a survival or oncogenic pathway, mediates α-PGG-induced biological and biochemical changes in p53 levels and apoptosis in tumor cells [60]. This discovery of the connection between the activation of the insulin receptor signaling and the onset of p53 elevation and apoptosis was supported by a recent finding that the insulin receptor is a dependence receptor, functioning to either promote survival or induce apoptosis depending on the availability and characteristics of ligands [61]. Also, α-PGG was previously found to bind the insulin receptor at a site different from the insulin binding site, suggesting that it is possible that α-PGG may elicit untypical insulin receptor-mediated biological effects [44]. The two activities of α-PGG described above are likely to be extensions of the rapid and slow actions of α-PGG in fat cells, respectively. The uniqueness of α-PGG as both an insulin receptor signaling activator and an apoptosis inducer, may indicate a path to a new therapeutic strategy in the treatment of cancers. Patients with both diabetes and cancer may benefit from a treatment with α-PGG-like insulin mimetics. The elevated insulin receptor signaling results in more glucose transport in fat and muscle cells while simultaneously leading to apoptosis in cancer cells. The development and application of α-PGG-like insulin mimetics is promising based on the cell study results reported. On the other hand, the anti-cancer activity and mechanisms of α-PGG have to be further evaluated in animal models. Also, other possible anti-cancer mechanisms of α-PGG could be explored. For example, it would be desirable to learn more about the effects of α-PGG on glucose uptake in cancer cells. The α-PGG is known to induce glucose uptake in insulin-responsive cells [44]. However, the effect of α-PGG on cancer cell glucose uptake, which relies on mechanisms different from insulin-responsive cells, has not been fully studied. Preliminary results suggest that α-PGG inhibits cancer cell glucose uptake (Cao and Chen, unpublished observation), which could indicate the presence of another mechanism contributing to the anti-cancer activity of α-PGG.

In addition to the insulin-like anti-diabetic and non-insulin-like anti-cancer cytotoxic activities, α-PGG possesses insulin-like anti-platelet-coagulation properties in vitro and in vivo [62]. Incubation of human platelets in vitro with α-PGG induced the phosphorylation of the insulin receptor and the insulin receptor substrate-1 [62]. At least in part due to its action on the insulin receptor signaling, α-PGG blocks ADP, collagen, and thrombin-induced platelet aggregation [62]. Further in vitro and in vivo studies revealed that α-PGG inhibits agonist-stimulated platelet aggregation by preventing agonist-induced reduction of cyclic AMP levels. It increases cytosolic calcium levels and induces phosphorylation of Akt [62]. The α-PGG also prevents thrombin-induced release of P-selectin and secretion of ATP [62]. The insulin-like activities of α-PGG in platelets may lead to an effective treatment of patients with cardiovascular and/or platelet-related diseases.

6Cl-TGQ and other derivatives of α-PGG

The structure–activity-relationship (SAR) studies of α-PGG and some structurally related compounds have led to the synthesis and identification of novel compounds with stronger biological activities. The 6-chloro-1,2,3,4-tetra-*O*-galloyl-α-D-quinovopyranose (6Cl-TGQ) (Fig. 1) is remarkable for its more potent glucose uptake stimulatory activity than α-PGG [17, 63].

The results of a 60-min glucose uptake assay using 3T3-L1 adipocytes demonstrated recently that the glucose uptake induced by 6Cl-TGQ was much higher than the uptake induced by α-PGG, and almost as high as the one induced by insulin [17, 63]. Equally important, 6Cl-TGQ is stable, rapid-acting, long-lasting and orally deliverable. Oral administration of 6Cl-TGQ at 5–10 mg/kg activated insulin receptor signaling and lowered blood glucose levels in both type 1 and type 2 diabetic mice [63]. Furthermore, 6Cl-TGQ demonstrated low acute and chronic toxicity in vivo [63]. Strikingly, 6Cl-TGQ was shown to be one of the few agents that can differentiate insulin receptors from IGF1 receptors. It activates the former without activating the latter in cell studies [63]. The insulin receptor is highly homologous with the IGF1 receptor. Insulin receptor signaling and IGF1 receptor signaling share many similarities. However, IGF1 receptor activation is much more mitogenic than insulin receptor activation [64], and IGF1 receptor signaling activation is intimately associated with the development of various cancers [65–68]. Therefore, insulin receptor agonists that are not affecting IGF1 are highly desirable [69–71]. The ability of 6Cl-TGQ to

differentiate insulin receptor from IGF1 receptor is consistent with the finding that α-PGG induced MEK and p53 activation through the insulin receptor but not the IGF1 receptor [60]. Overall, 6Cl-TGQ was shown to be a selective and more potent anti-diabetic agent than α-PGG with some moderate anticancer activity [63]. It is also worth mentioning that 6Cl-TGQ was observed to possess mild anti-adipogenesis activity (Cao and Chen, unpublished observation).

The same study that led to the isolation of 6Cl-TGQ also identified other compounds with significant, but lower biological activity (Fig. 1). Glucose uptake in adipocytes was found to be stimulated by α-PGG derivatives that have modified substituents on carbon 5 of the glucose core. The removal of galloyl groups in any other position than carbon 6 led to inactive compounds. Likewise, derivatives in which one or two of the hydroxyl functions on the galloyl groups were removed did not stimulate glucose uptake.

An extended SAR study focusing on the anti-cancer function of α-PGG has resulted in the synthesis of a group of anti-cancer compounds possessing glucose transporter 1 (GLUT1) and basal glucose uptake inhibitory activities [72, 73]. These compounds have been shown to induce cell cycle arrest, senescence and necrosis in cancer cells by reducing glucose transport and glycolysis [74]. Furthermore, one of the leading GLUT1 inhibitors that emerged from the study, WZB117 (Fig. 2), is effective in inhibiting tumor growth in a nude mouse model with grafted human lung cancer cells without significant side effects [74]. The SAR study indicated that the PGG-lead structure can be significantly simplified for the glucose transport inhibitory activity. It was shown that the glucose core could be replaced by an aromatic ring. In addition, high activity was induced even when only two monohydroxylated benzoyl groups were connected to the core via ester bonds [72]. Furthermore, a replacement of the ester bonds with more stable and rigid amide linkages led to compounds with a considerably lower activity (Qian and Chen, unpublished observation).

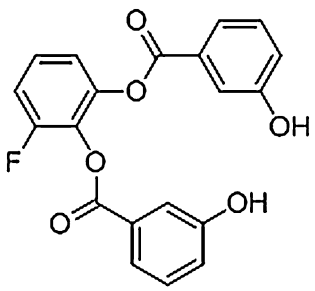


Fig. 2 Chemical structure of anticancer glucose transport inhibitor WZB117

Considering the success of the two SAR studies mentioned above, it seems likely that the ongoing research in α-PGG and related compounds will lead to the identification of more promising therapeutic agents.

Summary

The PGG anomers and their derivatives are potentially beneficial to human health [75–77]. Table 1 summarizes the major anti-diabetic-related and anti-cancer-related biological activities of α-PGG, β-PGG and their derivative 6Cl-TGQ in comparison with those of insulin. All three gallotannins are insulin mimetics since they share the primary function of insulin, the binding and activation of the insulin receptor. On the other hand, these compounds are different from insulin in that they do not induce

Table 1 Major anti-diabetic-related and anti-cancer-related activities of α-PGG, β-PGG, and 6Cl-TGQ in comparison with insulin

Compound	Insulin receptor activation	Adipogenic activity	IGF1 receptor activation	mitogenic activity (cancer growth-promoting)
β-PGG	+	− inhibitory	ND	− anti-cancer
α-PGG	++	− inhibitory	−/+	− anti-cancer
6Cl-TGQ	+++	− mildly inhibitory	−/+	− mildly anti-cancer
Insulin	+++++	+++	+++	+ (possible)

"+" for insulin receptor inducing activity using insulin's activity as the highest, "−" for mitogenic inhibitory activity. The more negative, the stronger is the mitogenic inhibitory (anticancer cytotoxic) activity

ND not determined

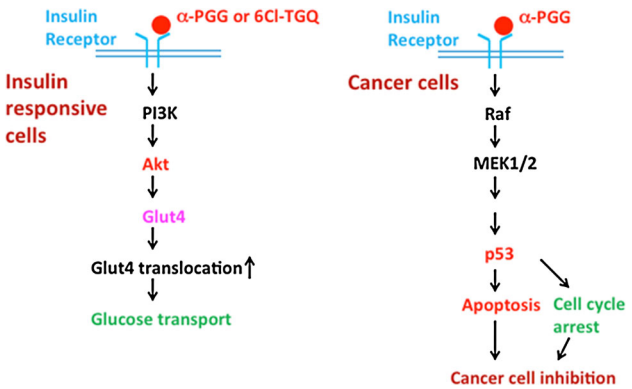


Fig. 3 Schematic presentation of anti-diabetic and anti-cancer mechanisms of α-PGG or 6Cl-TGQ

adipogenesis, a major undesirable "side effect" of insulin in the era of the obesity epidemic. Instead, they inhibit adipogenesis. Furthermore, unlike insulin, at least two of the compounds do not activate the IGF1 receptor or its signaling pathway, preventing the promotion of cancer development [68–72]. Even more strikingly, all three gallotannins exhibit anti-cancer activities [60, 63]. The activation of the insulin receptor without activating the IGF1 receptor constitutes a major advantage of PGG and 6Cl-TGQ over insulin. The anti-diabetes and anti-cancer mechanisms of α-PGG and/or 6Cl-TGQ are schematically presented in Fig. 3. It clearly illustrates that the two mechanisms are mediated by totally different signaling pathways.

Future directions

The α-PGG was demonstrated to be a very good model compound for the study of the pharmacological activities of gallotannins and for the development of more effective therapeutics with lower side effects. The α-PGG and 6Cl-TGQ were determined to possess roles in insulin and IGF1 receptor signaling. However, the evaluation of the biological functions of α-PGG is still at an early stage. Only the effects on lipid interactions, diabetes and cancer development, and platelet functions have been studied more thoroughly. Since it has been found that some of the most important biological functions of both PGG anomers and their derivatives are associated with insulin receptor binding and insulin receptor-mediated signaling, future studies should continue to focus on these areas. The following directions may be particularly interesting and productive: (a) In diabetes-related research, the use of genetic methods to alter the sequence and structure of the insulin receptor could be adopted in PGG binding studies to determine in more detail where and how PGG and its derivatives bind to the insulin receptor and subsequently activate it. The completion of this study could lead to the development of small molecules with higher insulin receptor binding affinity and activating capability. (b) In cancer-related research, it would be most valuable to identify the detailed mechanism by which α-PGG induces insulin receptor-mediated apoptosis in cancer cells. The success of this study would provide valuable information on how α-PGG can mediate glucose transport and apoptosis, two apparently incompatible activities, through the same receptor. (c) It is equally important to determine how α-PGG and 6Cl-TGQ differentiate the insulin receptor from the IGF1 receptor. The completion of this study should significantly enhance our understanding of how these compounds recognize and bind to the insulin receptor, as well as activate the insulin receptor-mediated signaling pathway without inducing IGF1 receptor-mediated signaling. This could contribute to the development of anti-diabetic therapeutics with low carcinogenic potential as well as anticancer agents. (d) Studies on the adipogenesis inhibitory activity of PGG anomers and derivatives should explore the anti-obesity activity of the compounds. (e) Last but not least, synthesis and SAR studies of new PGG derivatives should continue in order to identify and develop novel agents and therapies in the treatment of diabetes and cancer.

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