Review

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A systematic review on anti-diabetic action of 7-*O*-galloyl-D-sedoheptulose, a polyphenol from Corni Fructus, in type 2 diabetic mice with hepatic and pancreatic damage

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SUMMARY Traditional medicines are recently being focused on to treat diabetes and its complications because of their lack of toxic and/or side effects. This report describes the effects of 7-*O*-galloyl-D-sedoheptulose (GS), a polyphenolic compound isolated from Corni Fructus, on type 2 diabetic *db/db* mice with hepatic and pancreatic damage. We examined several biochemical factors and oxidative stress- and inflammation-related markers. In the serum, levels of glucose, leptin, insulin, C-peptide, resistin, tumor necrosis factor-α, and interleukin-6 were down-regulated, while adiponectin was augmented by GS treatment. In addition, GS suppressed the reactive oxygen species and lipid peroxidation in the serum, liver, and pancreas, but increased the pancreatic insulin and pancreatic C-peptide contents. These results were derived from attenuating the expression of nicotinamide adenine dinucleotide phosphate oxidase subunit proteins, Nox-4 and $p22^{phox}$. Augmented nuclear factor (NF)-E2-related factor 2 and heme oxygenase-1 were reduced with a decrease in oxidative stress during GS treatment. NF-κB-related pro-inflammatory factors were also alleviated in hepatic tissue. Moreover, GS modulated the protein expressions of pro-inflammatory NF-κB, cyclooxygenase-2, inducible nitric oxide synthase, c-Jun N-terminal kinase (JNK), phosphor-JNK, activator protein-1, transforming growth factor-β_1, and fibronectin. Based on these results, we demonstrated that the anti-diabetic action of GS may be due to its anti-oxidative stress property and anti-inflammatory action.

Keywords 7-*O*-galloyl-D-sedoheptulose, type 2 diabetes, liver, pancreas, oxidative stress, inflammation, fibrosis

1. Introduction

Changes in lifestyle and diet have resulted in increasing rates of obesity, and obesity has been considered as a causative factor for several diseases, such as type 2 diabetes, hypertension, cardiovascular disease, various infectious diseases, and cancer. Among these problems related to obesity, the most devastating may be type 2 diabetes. Type 2 diabetes, a complex metabolic disorder, is a major health problem associated with high morbidity, mortality, and health-care costs (*1*). Therefore, prevention and the implementation of intervention for people with type 2 diabetes should become a public health priority worldwide.

Type 2 diabetes is a systematic multi-organ dysfunction caused by dynamic interplay among different organs (*2*). It is characterized by reduced responsiveness to normal circulating concentrations of insulin through a long period of insulin resistance (*3*). In particular, hepatic insulin resistance is a principal component of type 2 diabetes. Decreased insulin sensitivity in the liver leads to elevated hepatic glucose production, hyperinsulinemia, β-cell stress, and hyperglycemia (*4*). Additionally, insulin resistance is accompanied by the intracellular production of free radicals, consequently causing elevated oxidative stress in the tissues of various organs (*5*). This indicates that there is a strong association between the degree of oxidative stress and risk of developing insulin resistance.

Increased oxidative stress induced by hyperglycemia is associated with type 2 diabetes. Reactive oxygen species (ROS) activate stress-sensitive intracellular signaling pathways, such as the transcription of nuclear factor-kappa B (NF-κB), which plays a central role in inflammation-related disease (*6*), and mitogen-activated

protein kinase (MAPK), which mediates the induction of NF-E2-related factor 2 (Nrf2) (*7,8*). Several researchers have demonstrated that ROS generation induced by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the mitochondrial electron transport chain occurs in an early stage of diabetic development (*9,10*). In addition, oxidative stress activates different processes involving protein kinase C, cytokines, and others (*6*). Therefore, novel approaches are necessary to identify therapeutic agents that can act with a pleiotropic effect, including antioxidant properties, to prevent and treat diabetic development.

Marked effort has been made to identify safe and effective therapeutic agents from natural sources for metabolic disorders such as obesity and diabetes mellitus. Traditional medicines have been touted for their potential therapeutic actions in diabetes and its complications due to their lack of toxicity and side effects. Accordingly, previous studies from our group have reported that Corni Fructus (*Cornus officinalis* SIEB. *et* ZUCC.), which is used as a traditional medicine, exhibited antidiabetic effects by ameliorating glucose-mediated metabolic disorders as well as aminoguanidine, an inhibitor of advanced glycation endproduct (AGE) formation, in streptozotocin-induced diabetic rats (*11*). Furthermore, we screened out an iridoid glycoside fraction containing morroniside, loganin, mevaloside, loganic acid, and 5-hydroxymethyl-2-furfural, and a low-molecular-weight polyphenol fraction containing 7-*O*-galloyl-D-sedoheptulose (GS) from Corni Fructus. These components may be important contributors to prevent or delay the onset of diabetic kidney disease (*12*). In particular, GS has only been isolated from Corni Fructus as far as we know (*13*), and the biological activity of GS has been poorly understood until now. For these reasons, we decided to clarify the mechanisms of GS in type 2 diabetes using *db/db* mice as a model, especially in the liver and pancreas.

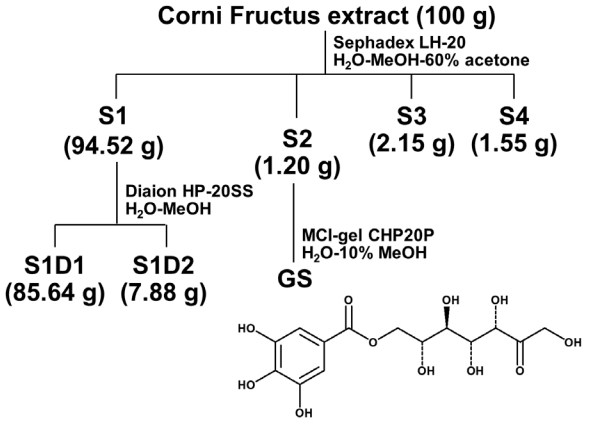

Figure 1. Fractionation of Corni Fructus.

2. Purification of GS from Corni Fructus

As shown in Figure 1, a water extract of Corni Fructus (100 g) was fractionated by Sephadex™ LH-20 column chromatography (32 × 5 cm) with water containing increasing proportions of methanol (0-100%, 10% stepwise gradient elution) and finally with 60% acetone to obtain four fractions: S1 (94.52 g), S2 (1.20 g), S3 (2.15 g), and S4 (1.55 g). The fraction S1 was further separated by Diaion™ HP-20SS column chromatography (28 × 5 cm) with water-methanol (0-100%, 10% stepwise gradient elution) to obtain S1D1 (85.64 g) and S1D2 (7.88 g). TLC and HPLC analyses showed that S1D1 and S1D2 mainly contained sugars and iridoid glycosides, and S2, S3, and S4 contained phenolic substances. A portion of S2 (150 mg) was further purified by MCI-gel CHP20P column chromatography (28 × 2 cm) with 0-10% methanol to obtain GS (98 mg). A white amorphous powder was analyzed by HR-FAB-MS; *m/z*: 363.0903, $C_{14}H_{19}O_{11}$ [M+H] requires 363.0927. ^{1}H-NMR (acetone-d_6 + D_2O) of major anomer δ: 7.13 (s, galloyl-H), 4.36 (m, H-4, H-7a), 4.23 (dd, J = 6.6, 11.7 Hz, H-7b), 4.09 (d, J = 6.4 Hz, H-3), 4.05 (m, H-6), 3.88 (t, J = 5.5 Hz, H-5), 3.5 (2H, br s, H-1), ^{1}H-NMR (acetone-d_6 + D_2O) of major anomer δ: 167.0 (galloyl C-7), 145.9 (galloyl C-3,5), 138.7 (galloyl C-4), 121.5 (galloyl C-1), 109.8 (galloyl C-2,6), 103.7 (C-2), 83.3 (C-5), 78.0 (C-3), 77.1 (C-4), 71.1 (C-6), 66.2 (C-7), 64.4 (C-1). Other anomeric carbon signals were observed at δ 98.2, 103.7, and 109.0. Assignments of the signals were achieved by COSY, HSQC, and HMBC spectral analysis. The structure was further confirmed by the formation of an osazone derivative: a mixture of the compound (10 mg), phenylhydrazine hydrochloride (20 mg), and sodium acetate (30 mg) in water (0.5 mL) was heated at 80°C for 25 min, and the resulting precipitates were collected by filtration. The ^{1}H-NMR spectral data (in DMSO-d_6) and $[\alpha]_D$ value coincided with the data for the osazone derivative of GS (*14,15*).

3. General characteristics

Compared with the vehicle-treated *db/db* mice, the body weights were not changed by GS treatment throughout the experimental periods. However, the administration of GS led to a significant decrease of food intake in a dose-dependent manner. The water intake showed a tendency toward a slight decrease (without significance) by 20 and 100 mg of GS treatment for 6 weeks (*14*). Type 2 diabetes causes characteristics such as hyperglycemia, hyperleptinemia and hyperinsulinemia, in *db/db* mice compared with *m/m* mice. GS administration significantly reduced the serum leptin and insulin levels at a dose of 100 mg/kg, and the C-peptide level at doses of 20 and 100 mg/kg, while the serum glucose level was slightly decreased without significance (*16,17*). Thus, GS administration can prevent diabetes in *db/db* mice, as evidenced by improved insulin sensitivity

through the maintenance of insulin and glucose levels and preservation of insulin and C-peptide levels in the pancreas, revealing that GS can ameliorate impaired glucose and insulin tolerance in *db/db* mice. In addition, the resistin, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) levels in serum were increased in the *db/db* control group compared with *m/m* group, and reduced by GS administration (*17*). Regarding the adiponectin level, the oral administration of GS at a dose of 100 mg/kg to *db/db* mice significantly enhanced the reduction. Moreover, oxidative stress-related biomarkers, such as ROS and thiobarbituric acid-reactive substance (TBARS), in the serum of *db/db* mice were higher than those in *m/m* mice. However, ROS and TBARS in the serum of GS-treated *db/db* mice were markedly reduced in a dose-dependent manner (*17*). Concerning hepatic functional parameters, the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were increased compared with *m/m* mice, and these augmented levels showed a significant decrease at a dose of 100 mg/kg (*16*).

4. GS attenuates diabetes-induced hepatic damage through regulation of oxidative stress and inflammation

4.1. Oxidative stress-related protein expressions in the liver

As a major source of ROS generation, the Nox family of NADPH oxidase strongly contributes to the initial step and development of oxidative stress. Nox-derived ROS play a physiological role in stimulating various growth factors, cytokines, and hormones, including insulin (*18*), and have pathophysiological roles in endothelial dysfunction, inflammation, apoptosis, fibrosis, and angiogenesis, and important processes underlying diabetes and tissue injury (*19*). Structurally, NADPH oxidase comprises a membrane-associated cytochrome, *b*558, composed of one $p22^{phox}$ and one $gp91^{phox}$ subunit and at least four cytosolic subunits ($p47^{phox}$, $p67^{phox}$, $p40^{phox}$, and the small GTP_{ase} *rac*1 or *rac*2) (*20*). Especially, Nox-4 and $p22^{phox}$ were found to be major sources of ROS production and play roles in pathological conditions (*21-23*). Therefore, we performed immunoblotting analyses of Nox-4 and $p22^{phox}$ in hepatic tissue of *db/db* mice. GS administration to *db/db* mice significantly attenuated oxidative stress by reducing ROS and TBARS levels in hepatic tissue, showing similar levels as those of normal *m/m* mice (*16*). These results suggest that the effect of GS involved the control of oxidative stress-induced hepatic injury, without serum glucose adjustment. Additionally, the increased expressions of hepatic Nox-4 and $p22^{phox}$ were significantly reduced by the administration of GS, which is also related to the reduction of hepatic ROS and TBARS levels (*16*). Therefore, the efficacy of GS may be related to the suppression of ROS-generating NADPH oxidase triggered by hyperglycemia, which is a potential source of oxidative stress in diabetes.

Oxidative stress also induces alterations in the Nrf2 complex, and its gene transcription, such as that of heme-oxygenase-1 (HO-1), is enhanced (*24*). Under physiological conditions, Nrf2 is sequestered in the cytoplasm by Keap1, which facilitates its ubiquitination and proteasomic degradation (*25*). Upon exposure to oxidative stress, the sequestration complex breaks down and dissociated Nrf2 translocates into the nucleus, where it binds to cis-acting antioxidant response elements and promotes the transcription of numerous cytoprotective genes (*26,27*). NADPH oxidase-derived superoxide and the consequently induced activation of intracellular protein kinase cascades, such as mitogen-activated protein kinase, can mediate the induction of Nrf2 and HO-1 expression (*7,8*). Therefore, increased Nrf2-HO-1 pathway activation may be a biomarker of oxidative stress and an adaptive response under pathological conditions. In our results, type 2 diabetic *db/db* mice showed enhanced expressions of Nrf2 and HO-1 in the liver compared with normal *m/m* mice; however, GS treatment significantly reduced these expressions (*16*). These results suggest that GS administration effectively alleviates oxidative stress and results in the down-regulation of Nrf2 and HO-1.

4.2. Inflammation-related protein expression in the liver

Chronic hyperglycemia also favors the increased expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) mediated by the activation of NF-κB, which is also involved in ROS generation and inflammatory responses (*28*). Following inflammatory stimuli, both COX-2 and iNOS have been reported to induce deleterious effects on the liver (*29*). Among them, iNOS inhibitor improved hepatic insulin signaling at the levels of insulin receptor substrate-1 and -2 and protein kinase B in the liver of genetically obese diabetic mice (*30*). Excess nitric oxide (NO) generation, most of which is attributable to iNOS expression, often occurs under pathogenic conditions. High NO production by iNOS in macrophages and other cells is an inflammatory mediator (*31*). In *db/db* mice, NADPH oxidase-derived ROS and iNOS-produced NO were augmented together, suggesting that the type 2 diabetic condition augmented oxidative and nitrosative stress in the liver. In the present study, GS significantly suppressed hepatic NF-κB, COX-2, and iNOS protein expressions in a type 2 diabetic *db/db* mouse model, which was probably the result of reduced ROS and TBARS in the hepatic tissue. Additionally, these results suggest that GS can effectively prevent oxidative and nitrosative stress and their related inflammatory responses by attenuating the expression of NADPH oxidase subunits and NF-κB-related protein (*16*).

5. The role of GS in ameliorating hyperglycemia-mediated oxidative damage to the pancreas

The pancreas is a complex of exocrine and endocrine glands that controls many homeostatic functions. In the development of diabetes, chronic hyperglycemia can exert deleterious effects on β-cell function (*32,33*), and the mechanisms of glucotoxicity involve several transcriptional factors and are, at least in part, mediated by the generation of chronic oxidative stress (*34,35*). Furthermore, β-cell dysfunction caused by glucotoxicity has been reported to be potentially reversible with the restoration of metabolic control (*36*). Thus, an effective remedy to attenuate the decline in pancreatic function by suppressing oxidative stress with the restoration of glucose metabolism may help to prevent the development of diabetic complications, whereas attempts to stimulate insulin secretion and improve insulin action with drug therapies are temporarily helpful but are ultimately unable to prevent progressive β-cell dysfunction.

The destruction of β-cells and disorder of insulin secretion in the diabetic state generally causes physico-metabolic abnormalities such as a decrease in body weight gain and an increase in the pancreatic weight, food intake, and water intake. The diabetic mice in this study also showed these changes. However, the administration of GS slightly, but not significantly, decreased these diabetes-induced physiological changes and led to a decrease in the pancreatic weight (*17*).

A number of mechanisms contribute to the development of pancreatic disorders such as glucotoxicity, oxidative stress, AGE accumulation, fibrogenesis, and cytokine production (*37*). ROS play an important role in insulin resistance and pancreatic β-cell dysfunction, a highly prevalent condition implicated in the development of diabetes (*38,39*). Under diabetic conditions, hyperglycemia may induce large amounts of ROS that are responsible for the progressive dysfunction of β-cells, worsening insulin resistance and further promoting relative insulin deficiency (*40*). In particular, β-cells are sensitive to ROS because they are low in free radical quenching (anti-oxidant) enzymes (*41*). The excess ROS may also indirectly damage cells by activating a variety of stress-sensitive intracellular signaling pathways, including NF-κB and MAPK. In the present study, GS administration suppressed pancreatic ROS and TBARS in addition to c-Jun N-terminal kinase (JNK), p-JNK, and activator protein-1 (AP-1) oxidative stress-related proteins (*17*).

Since inflammation is considered a major factor contributing to type 2 diabetes (*42*), we examined the pro-inflammatory markers TNF-α and IL-6 in serum, and found that GS treatment inhibited serum TNF-α and IL-6 (*17*), showing that the anti-diabetic action occurred due to an inhibition of inflammation. We further examined pro-inflammatory NF-κBp65, COX-2, and iNOS protein levels in the pancreas of *db/db* mice, and found that GS treatment down-regulated these levels (*17*).

6. Hepatic and pancreatic histological examination

The present study showed that in the results of histological examination using HE staining, which detects hepatocellular damage. The level of

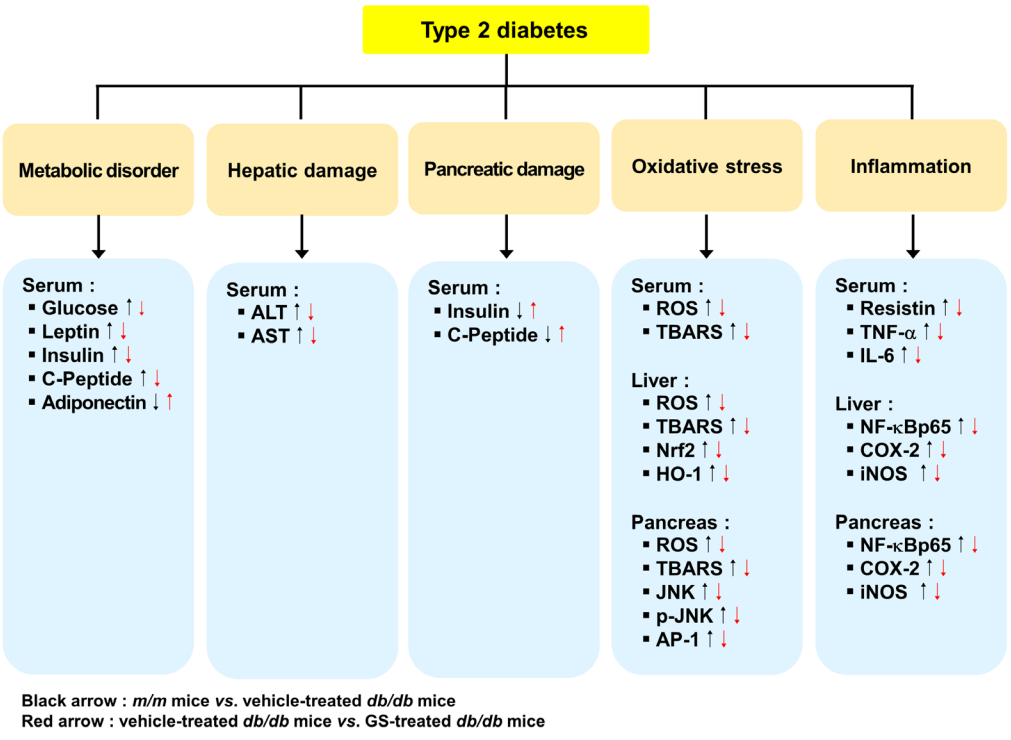

Figure 2. The effect of 7-*O*-galloyl-D-sedoheptulose against *db/db* mice.

hepatocellular damage was higher in the liver of *db/db* mice compared with *m/m* mice. However, GS-treated *db/db* mice clearly showed decreased hepatocellular damage (*16*). To evaluate pancreatic fibrosis, sections of pancreatic tissue obtained from *m/m* and *db/db* mice were stained with Azan, along with representative blue-stained fibrotic tissue sections from vehicle-treated *db/db* and GS-treated mice. The administration of GS showed a reduction of the blue-stained section (*17*).

7. Conclusion

Traditional medicine has been used widely in the treatment of diabetic mellitus in East Asia, including Japan, China, and Korea. In traditional medicine, Corni Fructus is the main ingredient for the treatment and prevention of diabetes. In our previous study, we analyzed the bioactive compounds of Corni Fructus, and morroniside, GS, and loganin were isolated (*12*). Notably, GS has only been found in Corni Fructus as far as we know, and the biological activity of GS has been poorly understood until now. The present study showed that GS treatment protected mice against type 2 diabetes due to its ameliorating effects on oxidative stress, inflammation, and fibrosis, as summarized in Figure 2. We provided experimental evidence of GS as an anti-diabetic agent, which warrants further clinical investigation.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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