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Heat-processed *Panax ginseng* and diabetic renal damage: active components and action mechanism

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Diabetic nephropathy is one of the serious complications in patients with either type 1 or 2 diabetes mellitus but current treatments remain unsatisfactory. Results of clinical research studies demonstrate that *Panax ginseng* can help adjust blood pressure and reduce blood sugar and may be advantageous in the treatment of tuberculosis and kidney damage in people with diabetes. The heat-processing method to strengthen the efficacy of *P. ginseng* has been well-defined based on a long history of ethnopharmacological evidence. The protective effects of *P. ginseng* on pathological conditions and renal damage associated with diabetic nephropathy in the animal models were markedly improved by heat-processing. The concentrations of less-polar ginsenosides (20(*S*)-Rg3, 20(*R*)-Rg3, Rg5, and Rk1) and maltol in *P. ginseng* were significantly increased in a heat-processing temperature-dependent manner. Based on researches in animal models of diabetes, ginsenoside 20(*S*)-Rg3 and maltol were evaluated to have therapeutic potential against diabetic renal damage. These effects were achieved through the inhibition of inflammatory pathway activated by oxidative stress and advanced glycation endproducts. These findings indicate that ginsenoside 20(*S*)-Rg3 and maltol are important bioactive constituents of heat-processed ginseng in the control of pathological conditions associated with diabetic nephropathy.

Keywords: *Panax ginseng*, Heat-processing, 20(*S*)-Rg3, Advanced glycation endproducts, Free radical

INTRODUCTION

The kidney is an excretory organ that plays a vital role in excretion of waste through urine in the human body. Diabetic nephropathy is an important cause of end-stage renal disease and is clinically defined as progressively increasing proteinuria accompanied by hypertension and impairment of glomerular filtration [1,2]. The onset of renal disease is multifactorial, involving oxidative stress, hypertension, hyperglycemia and hyperlipidemia [3-6]. The pathophysiological mechanisms that lead to nephropathy and the morphological features of diabetic renal damage are similar in type 1 and type 2 diabetes mellitus [2,7].

Under hyperglycemic condition, glucose and other reactive carbonyl compounds react non-enzymatically with proteins, lipids, or nucleic acids to form Schiff bases and Amadori products. Additional rearrangement and modification lead to the generation of diverse advanced glycation endproducts (AGEs), which can alter the structure and function of intra- and extracellular molecules, increase oxidative stress, and modulate cell activation,

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signal transduction, and the expression of cytokines and growth factors through receptor-dependent and receptor-independent pathways [8-11]. In people with diabetes and/or chronic renal failure, AGEs that accumulate in the kidney are responsible for the pathological changes, including increased kidney weight, glomerular hypertrophy, glomerular basement membrane thickening, and progressive albuminuria [12].

Moreover, AGEs stimulate free radical mechanisms and induce membrane peroxidation, which in turn increase membrane permeability [11]. Therefore, AGE accumulation in the kidney has been regarded as an index of progressive renal damage in diabetic nephropathy. Reciprocally, oxidative stress is known to induce AGEs. Protein kinase C and mitogen-activated protein kinase-extracellular signal regulated kinases 1, 2 can be activated by reactive oxygen species (ROS) and signal profibrotic responses in kidney cells [13-15]. Several researchers have demonstrated that ROS generation induced by nicotinamide adenine dinucleotide phosphate oxidase and the mitochondrial electron-transport chain is an early event in the development of diabetic renal disease [1,16,17]. Therefore, a variety of synthetic antioxidants for reducing oxidative damage from generating free radicals and improving oxidative stress via improvement of the antioxidant activating system in the body in order to prevent or treat renal diseases have been proposed [10,13].

Clinical evidence has suggested that an appropriate use of traditional medicines in combination with modern Western medicine, or mainstream anti-diabetic drugs, can prevent or ameliorate the development of diabetic complications. Many diabetic patients choose alternative therapeutic approaches, such as herbal or traditional Chinese medicine along with the mainstream anti-diabetic drugs; thus, making alternative therapy for diabetes a popular remedy option [18]. Based on a large number of chemical and pharmacological research work, numerous bioactive compounds have been found in medicinal plants for diabetes [19]. Among the frequently mentioned herbal medicines that help manage blood glucose, ginseng extracts made from the root, rootlet, berry and leaf of *Panax ginseng* (Korean ginseng) and *P. quinquefolius* (American ginseng), have been proven effective for anti-hyperglycemia, insulin sensitization, islet protection, anti-obesity and anti-oxidation in many model systems [20].

EFFICACY OF CONVENTIONAL GINSENG AND GINSENOSIDES ON RENAL DAMAGE

P. ginseng is a perennial plant that belongs to the *Panax* species, Araliaceae family. Examples of *Panax* species plants having similar efficacy to *P. ginseng* include *P. quinquefolius*, *P. notoginseng*, *P. japonica*, *P. trifolia*, *P. pseudoginseng*, and *P. vietnamensis*. These *Panax* species plants contain dammarane-based saponin in common with 1 to 4 saccharide(s) combined with a dammarane backbone, unlike the other plants [21-23].

Table 1. Potential approaches of conventional ginsenosides to prevent chemical, surgical and/or genetic-induced renal damage

Ginsenoside	Animal model	Mechanism	Reference
Rg1	Spontaneously hypertensive rat	Repair of glomerular structure	26
	UUO	Renal interstitial fibrosis↓ Repair of peritubular capillary Thrombospondin-1↓, VEGF↑	25
Re	STZ-induced diabetic rat	Oxidative stress↓	27
Rb1	Glycerol-induced acute renal failure	Renal function↑ Oxidative stress↓ Repair of renal morphology	28
	UUO	Oxidative damage↓ Renal TGF-β1↓ Renal interstitial fibrosis↓	30
	Intestinal ischemia reperfusion-induced renal injury	Renal function↑ Oxidative stress↓ Nrf2/ARE pathway↑	29
Rd	Cisplatin-induced acute renal failure Cephaloridine-induced renal failure Renal ischemia-reperfusion	Renal function↑ Oxidative stress↓	31-33

UUO, unilateral ureteral obstruction; VEGF, vascular endothelial growth factor, STZ, streptozotocin; Nrf2, nucuear factor erythroid 2-related factor 2; ARE, antioxidant response element.

In particular, ginseng that contains high concentration of saponins includes ginsenosides Rb1, Rb2, Rc, Rd, Rg1, and Re. These saponins have a variety of pharmaceutical effects that greatly differ in types and intensities, depending on the structures [21].

Alcoholic extract of *P. quinquefolius*, which shows presence of the major ginsenoside Rg1, Re, Rb1, Rc, Rb2, and Rd with predominance of the ginsenoside Rb1 and Re, was effective in the prevention of diabetic nephropathy through a combination of mechanisms, such as anti-hyperglycemic and antioxidant effects [24]. Table 1 shows potential approaches of conventional ginsenosides to prevent chemical, surgical and/or genetic-induced renal damage. Ginsenoside Rg1 (20 to 50 mg/kg) attenuated kidney damage with improvement on glomerular structure in spontaneously hypertensive rats and inhibited renal interstitial fibrosis in rats with unilateral ureteral obstruction, via suppressing oxidative stress [25,26]. Treatment of ginsenoside Re (20 mg/kg) restored the levels of both glutathione and malondialdehyde in the kidney of streptozotocin (STZ)-induced diabetic rats [27]. Ginsenoside Rb1 (25 to 60 mg/kg) ameliorated renal dysfunction in glycerol-induced acute renal failure in rats [28] and attenuated acute renal injury induced by ischemia reperfusion by activating the Nrf2/ARE pathway [29]. Ginsenoside Rb1 (12.5 to 50 mg/kg) also inhibited renal interstitial fibrosis in rats with unilateral ureteral obstruction by modulating thrombospondin-1 and vascular endothelial growth factor expression [30]. Ginsenoside Rd (5 mg/kg) attenuated renal dysfunction by preventing oxidative stress in cisplatin or cephaloridine-induced acute renal failure and ischemic-reperfused rats [31-33]. Although the efficacy on nephropathy are poorly understood, total saponins of *P. notoginseng* has been tested on chronic renal failure (non-uremic) patients and showed good therapeutic results as improving the renal function and lowering urinary protein [34]. In addition, *P. ginseng* supplementation maintained good glycemic control and improved plasma glucose and insulin regulation safely beyond usual therapy in well-controlled type 2 diabetes [35].

EFFICACY OF LESS-POLAR GINSENOSIDES ON FREE RADICAL AND RENAL DAMAGE

Research in efforts to develop methods for increasing the pharmaceutical effect of ginseng by conversion of the dammarane-based saponin by high temperature and high pressure thermal processing has been conducted. The heat-processing method to strengthen the efficacy of ginseng has been well defined in Korea, based on the long history of ethnopharmacological evidence [21,23]. *P. ginseng* cultivated in Korea is harvested after 4 to 6 years of cultivation, and it is classified into three types depending on how it is processed. Fresh ginseng can be consumed in an unprocessed state. White ginseng (harvested when 4 to 6 years old) is dried ginseng root. Red ginseng is ginseng root steamed at 98°C to 100°C after peeling (Fig. 1) [22]. Red ginseng is more widely used than white ginseng in Asian countries, because steaming induces changes in the chemical constituents and enhances the biological activities of ginseng [22,36,37]. A novel heat-processing method of autoclaving ginseng at a higher temperature than red ginseng was recently developed to achieve an even stronger activity than that of red ginseng; this ginseng product was termed sun ginseng (SG) (Fig. 1) [38].

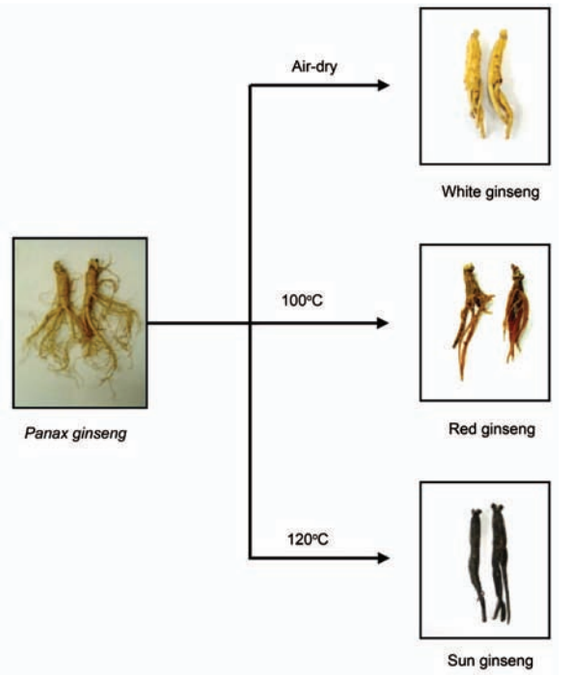

Fig. 1. Classification of *Panax ginseng* products by heat-processing methods.

In vivo evidence for the roles of free radicals and AGEs in diabetic kidney disease comes mainly from studies in STZ-induced type 1 diabetic rats [11]. We have previously showed that the protective effects of both *P. ginseng* and *P. quinquefolius* on renal damages in STZ-induced diabetic rats were significantly improved by heat-processing [39,40]. The kidney protecting active components of heat-processed *P. ginseng* were identified by investigating further the changes in the constituents of *P. ginseng* by heat-processing and its antioxidant activity

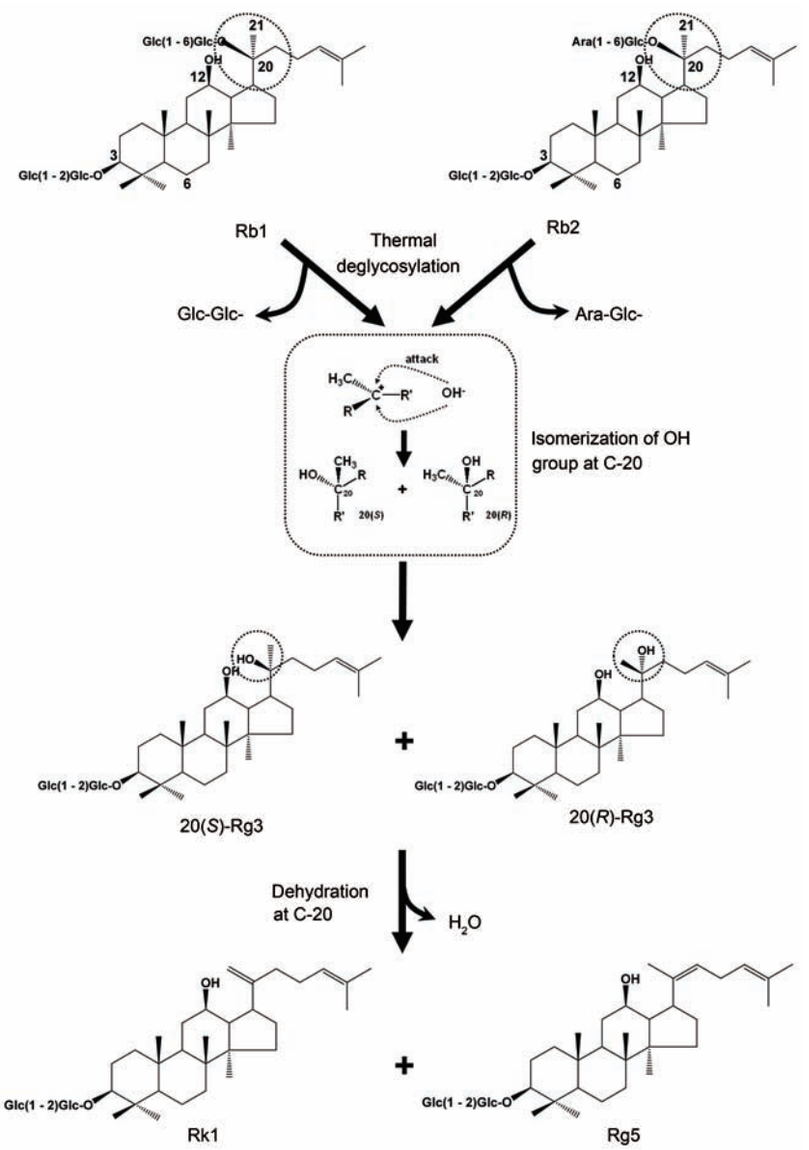

Fig. 2. Structural changes of ginsenoside Rb1 and Rb2 brought about by heat-processing.

[23,41-53]. As a representative example, protopanaxadiol-type ginsenoside Rb1 and Rb2 are known to produce stereoisomers 20(*S*)-Rg3 and 20(*R*)-Rg3 by dissociation of a glycosyl residue located at carbon 20 by thermal processing, as illustrated in Fig. 2; followed by a dehydration reaction at carbon 20 to produce ginsenoside Rg5 and Rk1 [45,52]. Among them, 20(*S*)-Rg3 showed the strongest hydroxyl radical (•OH)-scavenging activity, and the following were shown in decreasing order; Rg5, 20(*R*)-Rg3, and Rk1 at a concentration of 0.5% [45].

According to the studies in STZ diabetic rats, the elevated serum glucose, glycosylated protein, and thiobarbituric acid-reactive substance levels in diabetic rats were significantly reduced by the 20(*S*)-Rg3 administrations (20 mg/kg) in STZ-induced diabetic rats [49]. In addition, the renal dysfunction of diabetic rats was significantly ameliorated by the 20(*S*)-Rg3 administrations in a dose-dependent manner. A growing body of evidence supports the important roles of renal *N*-methyl-d-aspartate (NMDA) receptors, originally identified in the central nervous system, in renal blood flow and nephrotoxicity. Moreover, the nephrotoxicity and renal vasoconstriction were attenuated by treatment with an NMDA receptor antagonist [54,55]. The elevated NMDA-NR1 levels of

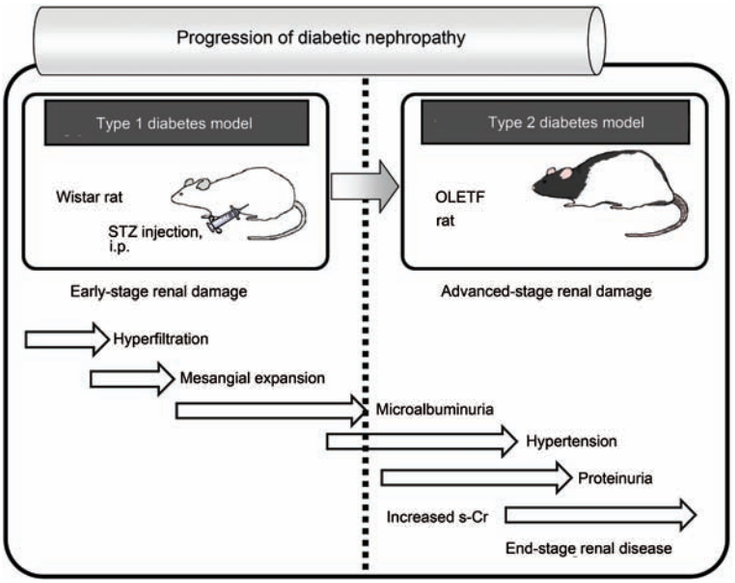

Fig. 3. Schematic description for the progression of diabetic nephropathy in the type 1 and 2 diabetes animal models. STZ, streptozotocin; i.p., intraperitoneal; OLETF, Otsuka Long-Evans Tokushima Fatty.

diabetic rats were significantly decreased in the groups administered 20(*S*)-Rg3 or aminoguanidine (20 mg/kg body weight/d). These beneficial effects on diabetic renal damage were related to the inhibitory effect of 20(*S*)-Rg3 against NMDA receptor-mediated nephrotoxicity [49].

The sign of early diabetic nephropathy is an increased urinary albumin level, and advanced diabetic nephropathy is characterized by proteinuria and decreasing CCr levels [11]. The Otsuka Long-Evans Tokushima Fatty (OLETF) rat is an animal model of spontaneously obese type 2 diabetes characterized by hyperglycemia, insulin resistance, hyperinsulinemia, hypertriglyceridemia, and hypercholesterolemia, and with complications such as nonalcoholic fatty liver and renal disorders; in addition, these typical characteristics of OLETF rats are known to be useful for analyzing the complex forms of human diabetes (Fig. 3) [56,57]. In our previous study to identify the effect of 20(*S*)-Rg3 at advanced-stage of diabetic renal damage in OLETF rats, the elevation of pro-inflammatory protein expressions, such as inducible nitric oxide synthase and 3-nitrotyrosine were significantly reduced by the administrations of 20(*S*)-Rg3. N^{ε}-(-(carboxymethyl)lysine (CML) is known as a marker of cumulative oxidative stress and is involved in the development of diabetic nephropathy [14,58,59]. In addition, the activation of receptor for AGEs by CML results in an activation of NF-κB and production of proinflammatory cytokines [60,61]. The elevation of CML levels in diabetic control rats were prevented by the 20(*S*)-Rg3 administration. These findings imply that the 20(*S*)-Rg3 prevents the progression of renal damage and dysfunction in type 2 diabetic rats via inhibiting oxidative stress and AGE formation [62]. Based upon chemical and biological activity tests, 20(*S*)-Rg3 was found to prevent the progression of renal damage and dysfunction in type 1 and 2 diabetic rats, via inhibiting oxidative stress and inflammation [23].

EFFICACY OF MALTOL ON AGES, FREE RADICLAS AND RENAL DAMAGE

Although the main pharmacologically active constituents of ginseng are believed to be ginsenosides, researchers also have paid attention to the other components. It is well known that Maillard reaction products (MRPs) produced in both heat-treated food systems and in sugar-amino acid model systems have antioxidant activity [63-65]. MRPs in ginseng were reported to increase by heat-processing; these compounds are arginyl-fructosyl-glucose, arginyl-fructose, maltol, maltol-3-O-β-D-glucoside, and so on [66,67]. Maltol is formed by sucrose pyrolysis or thermal degradation of starch [68,69], and is extensively used in food, beverage, tobacco, brewery, cosmetics and pharmaceuticals industries [70]. When ginseng extracts were analyzed with GC-MS, content of maltol in red ginseng and SG was about 4 and 36 times higher, respectively, than in white ginseng [41,50]. There are several lines of evidence regarding the antioxidant

Table 2. Effect and mechanism action of heat-processed components in *Panax ginseng* on renal damage

Ginsenoside	Animal model	Mechanism	Reference
20(*S*)-Rg3	STZ-induced diabetic rat	Renal function↑ NMDA-mediated nephrotoxicity↓	49
	Otsuka Long-Evans Tokushima Fatty rat	Renal function↑ Oxidative stress↓ Advanced glycation endproduct↓	62
	Lipopolysaccharide-induced renal injury	Renal function↑ Oxidative stress↓ Renal inflammation↓	48
Maltol	STZ-induced diabetic rat	Advanced glycation endproduct↓ Oxidative stress↓	78

STZ, streptozotocin; NMDA, *N*-methyl-d-aspartate receptor.

activities of maltol, and antioxidants are known to protect against glycation-derived free radicals and may have a therapeutic potential [8,61]. Maltol with hydroxypyrone structure acts as a potent metal-chelating agent [71], and complexes of maltol with metals are now applied to the treatment for some diseases [72-74].

Numerous AGE inhibitors have been investigated by *in vitro* AGE-inhibitory activity tests, but some classes of AGEs inhibition is primarily mediated by their transition metal-chelating or antioxidant activities [75,76]. In our previous *in vitro* study, maltol exhibited a stronger inhibitory effect against glucose-induced AGE generation than aminoguanidine, a well-known AGE inhibitor. In addition, the •OH scavenging activity of maltol was slightly stronger than that of aminoguanidine, and this effect was interpreted to be important because •OH scavenging activity in electron spin resonance spectrometer is mediated by the transition metal-chelating and free radical scavenging activities of the compounds [77].

In STZ-diabetic rats, maltol (50 mg/kg body weight/d) significantly decreased the renal fluorescent AGE level, suggesting that it would inhibit oxidative damage and irreversible renal damage caused by protein glycation reaction under diabetes [78]. In addition, the elevated CML expression, a major AGE in human tissues, and receptor for AGE levels in diabetic control rats were significantly reduced by the 50 mg/kg body weight/d of maltol administration. These findings imply that the beneficial effect of maltol in type 1 diabetic rats was mainly mediated by the inhibition of AGE generation (Table 2) [78].

CONCLUSION AND PERSPECTIVES

Diabetic nephropathy has been the major cause of patients needing chronic haemodialysis since 1998 [79,80]. Prevention of the occurrence and progression of diabetic nephropathy has become a very important issue. Results of clinical research studies demonstrate that *P. ginseng* can help adjust blood pressure and reduce blood sugar and may be advantageous in the treatment of tuberculosis and kidney damage in people with type 2 diabetes [34,35]. In this mini-review, we have summarized that the contents of free radical-scavenging active components, such as 20(*S*)-Rg3 and maltol in *P. ginseng* were significantly increased, depending on the temperature of heat-processing. Based on the observations on the roles of 20(*S*)-Rg3 and maltol in AGEs and free radicals *in vitro* and *in vivo* studies (type 1 and/or 2 diabetes models), 20(*S*)-Rg3 and maltol were evaluated to have therapeutic potential against diabetic renal damage in the early-stage. The identification and management of diabetic kidney disease in the early-stage is important because the majority of people have no symptoms until the disease is very advanced [81]. Therefore, the beneficial effects of ginsenoside 20(*S*)-Rg3 and maltol in the early-stage have important implication by preventing the advancement of diabetic renal damage to advanced-stages. Considering the relevant use and individual daily consumption of ginseng, it is clear that 20(*S*)-Rg3 and maltol are important bioactive constituents of heat-processed ginseng, especially in the control of diabetic renal complication. This investigation of bioactive constituents of heat-processed *P. ginseng* is important for the scientific elucidation of improved efficacies of ginseng by traditional and modern heat-processing methods, and may contribute to the development of ginseng-derived novel drugs.

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