

## Neuroprotective Potential of 20(S)-Ginsenoside Rg3 Against the Progression of Diabetic Neuropathy: Experiments on Rat Sciatic Nerve

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### ABSTRACT

**Objective:** This study aims to experimentally evaluate the impact of 20(S)-ginsenoside Rg3 on the progression of neuropathy induced by streptozotocin (STZ)-induced diabetes.

**Materials and Methods:** Adult male Wistar rats were randomly divided into three groups: control, untreated diabetic, and 20(S)-ginsenoside Rg3-treated diabetic groups (n=6 each). The rats were intraperitoneally injected with a single dose of STZ (50 mg/kg) to induce diabetes, which was verified by the presence of hyperglycemia (>300 mg/dl). Treatment involved administering a daily dose of 20(S)-ginsenoside Rg3 at 5 mg/kg/day through oral gavage for five weeks. Control rats received an equivalent volume of saline phosphate buffer (pH 7.4). Nociceptive alterations were assessed using tail flick and hot plate tests in the fourth week. Distal latency and nerve conduction velocity were measured in vivo from the exposed sciatic nerve in the fifth week.

**Results:** While STZ-induced diabetes led to a significant decline in body weight, an increase in blood glucose levels, and delays in both sensory and motor responses, 20(S)-ginsenoside Rg3 treatment favorably corrected these adverse effects. This treatment effectively alleviated weight loss, lowered blood glucose levels, protected the sciatic nerve, and thus clearly demonstrated a protective role against the progression of neuropathy.

**Conclusion:** Treatment with 20(S)-ginsenoside Rg3 holds the potential to be used as a neuroprotective agent for diabetic neuropathy. It may also exert preventive actions against post-diabetic events at the molecular level, and the mechanisms underlying these actions need further exploration.

**Keywords:** 20(S)-ginsenoside Rg3, diabetic peripheral neuropathy, nerve conduction velocity, hot plate test, tail flick test.



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### INTRODUCTION

Diabetes mellitus (DM) is a significant disease with high morbidity and mortality, affecting 2.5-3% of the world's population.<sup>1</sup> It represents a heterogeneous metabolic disorder with chronic implications due to prolonged hyperglycemia associated with impaired insulin secretion (Type 1), impaired insulin action (Type 2), or a combination of both.<sup>2</sup> Diabetic neuropathy (DNP) is a complication of



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diabetes that emerges during the course of the disease in both types. It affects peripheral nerves, including unmyelinated small fibers, motor and sensory neurons, and the autonomic nervous system.<sup>3,4</sup> DNP is often misdiagnosed or diagnosed at a later stage of the complication, resulting in irreversible nerve damage. Furthermore, it is frequently inadequately treated, as there is currently no known effective treatment for DNP, with good blood glucose control being the only approved method to reduce its development risk. Consequently, ongoing research is concentrated on developing preventive or protective measures against DNP, with exploration of the potential of plant extracts or pharmaceutical agents in experimental studies.<sup>5,6</sup>

Ginseng, a natural plant and herbal agent, has been used in folk medicine in far-eastern countries. The pharmacological effects of ginseng are attributed to its constituents called ginsenosides, triterpenoid saponins linked with sugar chains. Depending on the positioning of the sugar chain, ginsenosides can be categorized into various types.<sup>7,8</sup> These compounds have been associated with benefits in treating obesity, chronic kidney disease, non-small-cell lung cancer, atherosclerosis, hypertension, ischemic heart disease, and stroke.<sup>7,9–11</sup> In the context of diabetes and metabolic syndrome, the antihyperglycemic action of ginsenosides provides a potential treatment option, which may explain the common use of ginseng in Chinese Medicine.<sup>7,9,12</sup> Ginsenosides exist in various forms in nature. Among those, ginsenoside F1, Rg1, and Rb1 have previously been reported to possess neuroprotective properties.<sup>8,13</sup> However, the neuroprotective potential for 20(S)-ginsenoside Rg3 remains unexplored, making it the focus of this current study. Hence, this study builds upon ongoing efforts and employs an experimental rat diabetes model to investigate the impact of 20(S)-ginsenoside Rg3 administration on the progression of DNP. It reports the observed changes during the course of the disease. The extent of DNP was characterized through *in vivo* nociceptive tests and electrophysiological measurements taken from the sciatic nerve.

## MATERIALS AND METHODS

The study was conducted following the protocol with the identification number 64583101-2013/062, which was approved by the the Experimental Animal Ethics Committee of Adnan Menderes University. The experiments were carried out longitudinally using a total of 18 male Wistar rats initial weighing between 200 g and 250 g upon acquisition. The study was designed in a cross-sectional manner. The animals were randomly allocated into three groups (each with n=6):

Group 1: Sham (non-diabetic),

Group 2: Diabetic control,

Group 3: Treatment (diabetic + administration of 5 mg/kg 20(S)-ginsenoside Rg3).

The rats were housed under semi-climatized laboratory conditions for approximately six weeks, with controlled relative humidity (40–50%) and ventilation. The room temperature was maintained at (22±1 °C), and a 12-hour light-dark cycle was implemented.

Diabetes was induced by a single intraperitoneal (i.p.) dose of streptozotocin (STZ) injection at 50 mg/kg dissolved in 0.05 M citrate buffer (pH=4.5). The sham group received a single i.p. dose of 0.05 M citrate buffer solution. To prevent rats from experiencing hypoglycemic shock, a 5% dextrose solution was administered six hours after the STZ injection. On the third day, blood glucose levels were measured, and rats with levels exceeding 300 mg/dL were categorized as diabetic. Following this confirmation, a daily dose of 5 mg/kg 20(S)-ginsenoside Rg3 (Sigma-Aldrich, USA) was administered as treatment via oral gavage for a period of five weeks. Throughout the 5-week treatment period, rats in the sham and diabetic groups received injections of phosphate buffer.

The weights of all rats were recorded weekly, while blood glucose levels were measured only twice – at the beginning and end of the 5-week treatment – using a glucometer (IME-DC GmbH, Germany). At the conclusion of the fourth week of treatment, neuropathy was assessed using nociceptive tests, specifically the tail flick and hot plate tests.<sup>14–16</sup> After the fifth week, the rats were anesthetized, and the left sciatic nerve was exposed for *in vivo* electrophysiological measurements.<sup>14,17,18</sup>

### Evaluation of Nociceptive Pain Perception

Nociceptive pain perception was assessed through tail flick and hot plate tests. The hot plate test was conducted using a pre-heated (55±0.3 °C) metal surface device (May Tic., Türkiye). After placing each rat on the heated plate, the latency time for the response to thermal stimuli, such as hind leg movement or leaping, was recorded. The cut-off time for this test was set at 15 seconds.<sup>14</sup>

For the tail-flick test, a semi-automatic tail-flick device (May Tic., Türkiye) with an 8V/50W radiant heat source was utilized. Rats were allowed to rest in their cages for at least five minutes prior to the test. The lower 1/3 of the tail was positioned on the heat source, and the device automatically detected tail movement. The time taken for tail withdrawal was noted as the tail-flick latency, providing another measure of response to thermal stimulation. To prevent potential thermal damage to the tail, the stimulation was capped at ten seconds.<sup>14</sup>

### Electrophysiological Measurements with *In Vivo* Electromyography

Upon completion of the treatment period, the rats were anesthetized with ketamine (50 mg/kg, Alfamine 10%, Alfasan,

Netherlands) and xylazine (10 mg/kg, Alfazyme 2%, Alfasan, Netherlands). Subsequently, a 3 cm incision was made at the mid-thigh to expose the left sciatic nerve. The liberated nerve was carefully positioned on *in vivo* electrodes, spaced at a fixed distance of 1.1 cm underneath the nerve. These electrodes were then connected to a stimulator (Biopac Systems Inc, USA). Two supramaximal electrical stimulations (0.1 ms, 1 Hz, 7 mV) were administered to the sciatic nerve through the distal and proximal electrodes. The resulting compound muscle action potentials were recorded, amplified, and transferred to a computer using AcqKnowledge data acquisition and analysis software (Biopac Systems Inc., USA). The data were examined, and values of proximal and distal latencies were measured. To determine motor nerve conduction velocity (MNCV), the fixed distance between the distal and proximal electrodes (1.1 cm) was divided by the difference between proximal and distal latencies.

### Statistical Analysis

The collected data included body weights, blood glucose levels, latency values from nociceptive tests, and MNCV values from electrophysiological tests for all rats. The measurements were organized in columns corresponding to each group. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software (IBM, USA). Initially, the Anderson-Darling normal distribution test was employed to determine the normal distribution of the data in the columns distributed and to validate the application of parametric statistics. The significance level was set at  $\alpha=0.05$ , and the critical value was established at 0.752. Accordingly, data were deemed normally distributed if  $A^2>0.752$ . The test statistics confirmed that the data exhibited a normal distribution. Where applicable, cross-sectional and cross-over statistical analyses were conducted between groups using Analysis of Variance (ANOVA) and paired t-test. Intergroup comparisons were executed for each measurement through one-way ANOVA analysis to identify differences in variances among groups. Subsequently, Tukey's test was applied as a post-hoc test to ascertain the significance level, particularly when variances demonstrated significant differences among groups. A statistical difference was recognized as significant when  $p<0.05$ . The outcome of Tukey's test was indicated with an asterisk (\*) for comparisons between the control group and the diabetic and treatment groups. Additionally, a dagger (†) was used for comparisons between the diabetic group and the treatment group.

## RESULTS

There were no instances of rat loss, yet diabetic rats displayed clinical symptoms of diabetes, including increased urination and weight loss.

**Table 1.** Weekly changes in body weight in experimental groups

Weeks	Body weight (g)			p
	Control	Diabetic	Treatment	
1	278.60±14.40	274.00±6.17	247.50±12.88	0.116
2	304.33±24.67	269.00±27.92	268.83±20.36	0.061
3	323.67±26.43	258.20±24.15*	285.00±23.76*†	0.001
4	326.40±31.04	253.67±10.88*	294.50±31.38*†	0.002
5	330.17±31.16	252.60±12.00*	300.00±16.02*†	0.001

Data are represented as arithmetic mean±standard deviation (n=6). P values equal to or less than 0.05 were considered statistically significant. The p values presented in the table are the result of the comparison of variances between the groups. The symbols indicated represent the result of the post-hoc test. \* denotes significant differences between the control and either diabetic or treatment groups, † denotes significant differences between the diabetic and treatment groups.

### Body Weight

The pertinent data are presented in Table 1, starting from the seventh day of treatment. Control rats consistently gained weight, whereas diabetic rats exhibited weight loss in comparison to their prediabetic values over the study period. In contrast, rats treated with ginsenoside Rg3 demonstrated weight gain relative to their pre-diabetic state, although the gain was not as substantial as that observed in the control group. These findings indicated that the administration of 5 mg/kg ginsenoside Rg3 had a supportive effect on physical growth in the context of diabetes.

### Blood Glucose

As depicted in Table 2, the STZ injection led to the onset of diabetes, evident through a significant increase in blood glucose levels at the start of treatment. Early on, both diabetic and treatment groups exhibited notably higher blood glucose levels than the control group. By the end of the treatment period, blood glucose levels remained elevated in diabetic rats but were lower in rats administered with ginsenoside Rg3, approaching levels closer to those observed in the control group. These results demonstrated the regulatory capacity of ginsenoside Rg3, as reflected by the reduction in blood glucose levels in the context of diabetes.

### Nociceptive Pain Perception

Diabetes caused a delay in the neuronal response to thermal stimuli, as demonstrated in Table 3. Both hind-limb licking/upholding and tail-flicking upon exposure to heat took longer times in diabetic rats, likely due to neuropathy affecting the function of their sensory neurons. In contrast, the treatment shortened the response time and induced an intensified perception of pain, indicating the neuronal protective activity of ginsenoside Rg3 against neuropathy.

**Table 2.** Blood glucose levels measured at the beginning and the end of the treatment

Blood glucose (mg/dl)	Control	Diabetic	Treatment	p
Treatment onset	130.67±11.54	455.80±42.74*	416.50±148.81*	<0.001
End of treatment	118.17±38.80	529.00±78.58*	131.00±32.24†	0.002
P value	ns	<0.050	<0.001	

Data are represented as arithmetic mean±standard deviation (n=6). P values equal to or less than 0.05 were considered statistically significant. The p values represented in the left panel of the table are the result of the comparison of variances between the groups. The p values in the lower panel represent changes over time compared by paired t-test. “ns” denotes non-significant. The symbols indicated represent the result of the post-hoc test. \* denotes significant differences between the control and either diabetic or treatment groups, † denotes significant differences between the diabetic and treatment groups.

**Table 3.** Latencies measured from nociceptive tests at the fourth week

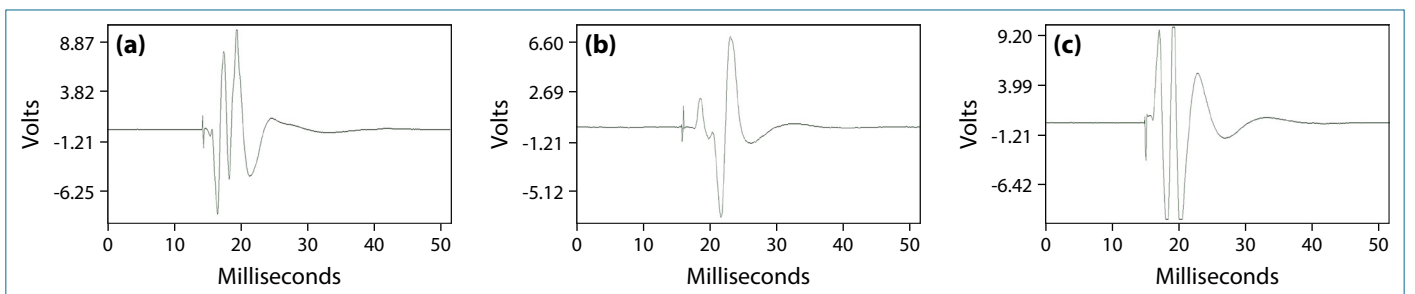
Latency (s)	Control	Diabetic	Treatment	p
Hot plate	3.98±0.61	5.91±0.64*	4.59±0.61*†	0.010
Tail-flick	4.38±1.27	8.25±1.69*	6.62±2.33*†	0.009

Data are represented as arithmetic mean±standard deviation (n=6). P values equal to or less than 0.05 were considered statistically significant. The p values presented in the table are the result of the comparison of variances between the groups. The symbols indicated represent the result of the post-hoc test. \* denotes significant differences between the control and either diabetic or treatment groups, † denotes significant differences between the diabetic and treatment groups.

**Table 4.** Electrophysiological measurements from the left sciatic nerve

	Control	Diabetic	Treatment	p
Motor nerve conduction velocity (MNCV) (m/s)	58.58±16.34	19.44±2.79*	38.84±4.92*†	p<0.001

Data are represented as arithmetic mean±standard deviation (n=6). P values equal to or less than 0.05 were considered statistically significant. The p values presented in the table are the result of the comparison of variances between the groups. The symbols indicated represent the result of the post-hoc test. \* denotes significant differences between the control and either diabetic or treatment groups, † denotes significant differences between the diabetic and treatment groups.



**Figure 1.** Representative recordings of CMAPs from (a) control, (b) diabetic, and (c) treatment groups.

### Electrophysiological Measurements

*In vivo* measurements obtained from the exposed left sciatic nerves are presented in Table 4, and the representative Compound Muscle Action Potential (CMAP) recordings can be seen in Figure 1. The data exhibited a similar trend: diabetes led to a decrease in MNCV, indicating nerve degeneration resulting from neuropathy. The treatment significantly improved MNCVs, providing convincing evidence that ginsenoside Rg3 administration protected the motor neurons from neuropathy.

### DISCUSSION

Ginsenosides, the active components of ginseng, have been suggested to have therapeutic benefits for various disorders, including metabolic syndrome, diabetes, and hyperglycemia.<sup>7</sup> Several reports have indicated the neuroprotective potential of ginsenosides, such as F1, Rg1, and Rb1. For instance, (S)-ginsenoside F1 was observed to protect Schwann cells against peripheral nerve degeneration,<sup>13</sup> ginsenoside Rb1 was found to prevent high glucose-induced Schwann cell injury by coun-

teracting oxidative stress and the activation of the mitochondrial apoptotic pathway,<sup>19</sup> and ginsenoside Rg1 was noted for its antiaging and antineurodegenerative effects.<sup>8</sup> However, the neuroprotective potential of 20(S)-ginsenoside Rg3 remains to be determined. This study was therefore conducted to assess this aspect of 20(S)-ginsenoside Rg3 using an experimental rat model of STZ-induced diabetes. The administration of 20(S)-ginsenoside Rg3 at a dose of 5 mg/kg/day via oral gavage was chosen based on its previously reported effectiveness in ameliorating diabetes-induced alterations in rat retinas and kidneys.<sup>20,21</sup>

20(S)-ginsenoside Rg3 has been demonstrated to possess hypoglycemic and antidiabetic effects in animal models,<sup>7,22</sup> stimulate insulin secretion in HIT-T15 pancreatic cells,<sup>22</sup> INS-1 insulinoma cells,<sup>23</sup> and protect against INS-1 cell apoptosis.<sup>23</sup> Additionally, ginsenoside Rg3 was observed to enhance glucose uptake and insulin signaling by upregulating the expression of insulin receptor substrate-1 transcripts in rat L6 myoblasts.<sup>24</sup> In alignment with these findings, the current study demonstrated that the administration of 20(S)-ginsenoside Rg3 at a dose of 5 mg/kg significantly reduced blood glucose levels in diabetic rats, restoring them to levels comparable to the control group (Table 2). Specifically, the blood glucose value of the Rg3-treated group decreased by 75% compared to the diabetic group (Table 2). In the treatment of diabetes, the primary objective is to maintain blood glucose levels closer to normal values; therefore, 20(S)-ginsenoside Rg3 could be considered a potential adjunct for managing diabetes-related complications. Furthermore, treatment with 20(S)-ginsenoside Rg3 also mitigated diabetes-induced weight loss, with the body weights of the treated rats approaching those of the control group (Table 1).

In addition to its impact on blood glucose levels, the results revealed a significant reduction in sciatic MNCV due to diabetes compared to the control group ( $p < 0.05$ ). Notably, administration of 20(S)-ginsenoside Rg3 led to a 51% increase in sciatic MNCV when compared to the diabetic group ( $p < 0.05$ ) (Table 4), indicating that 20(S)-ginsenoside Rg3 has a neuroprotective effect on motor nerve conduction in DNP. Additionally, nociceptive pain perception was significantly diminished in the diabetic group, with increased hot-plate and tail-flick latencies compared to the control group ( $p < 0.05$ ). The decrease in nociceptive latencies compared to the diabetic group ( $p < 0.05$ ) upon administration of 20(S)-ginsenoside Rg3 highlights the protective role of ginsenoside Rg3 in mitigating nociceptive pain perception in DNP (Table 3). Consistent with our findings, Rhim et al.<sup>25</sup> observed that ginseng saponins, including ginsenoside Rg3 as a prominent active component, suppressed  $Ca^{+2}$  currents in rat dorsal root ganglia, suggesting a role for ginsenosides in pain perception. In our experimental diabetes model, diabetes led to a loss of pain perception due

to nerve damage, resulting in slowed nerve conduction and the induction of peripheral neuropathy. Our findings indicated that the administration of 20(S)-ginsenoside Rg3 attenuated the deceleration in nerve conduction caused by DNP, thus demonstrating a neuroprotective effect.

One of the proposed mechanisms underlying nerve damage in DNP is mitochondrial dysfunction related to increased reactive oxygen species and inflammation. 20(S)-ginsenoside Rg3 was reported to inhibit  $Ca^{+2}$ -induced reactive oxygen species production in isolated rat brain mitochondria and attenuate  $Ca^{+2}$  and hydrogen peroxide-induced mitochondrial swelling, thereby enhancing mitochondrial function.<sup>26</sup> Previous studies also indicated that administration of 20(S)-ginsenoside Rg3 decreased diabetes-induced inflammation and kidney damage in diabetic rats.<sup>20,27</sup> Based on these findings in the literature, the observed neuroprotective effect of 20(S)-ginsenoside Rg3 may be attributed to improved mitochondrial function, reduced inflammation and oxidative stress, ultimately leading to improved nerve conduction velocities and nociceptive pain perception.

In summary, the preventive and therapeutic effects observed following the treatment of DNP with 20(S)-ginsenoside Rg3 are likely associated with the preservation of myelination and neuronal integrity, delaying the progression of neuropathy as elucidated above. Our results hold significance in shedding light on the beneficial effects of ginsenoside Rg3 in ameliorating diabetes-induced dysfunction in the sciatic nerve and nociceptive pain perception. This contribution is essential in further explicating the mechanisms of action of this drug in nerve conduction. Nevertheless, certain limitations in our study must be acknowledged. The sample size employed in this pilot study was relatively small, and therefore the results may not be sufficient to fully characterize the comprehensive aspects of the neuroprotective potential of 20(S)-ginsenoside Rg3. We solely utilized electrophysiological measurements and nociceptive tests, without evaluating the effects of 20(S)-ginsenoside Rg3 administration on oxidative stress levels, inflammation, and myelination. These aspects should be further investigated. Additionally, this study considered only one dose (5 mg/kg) of 20(S)-ginsenoside Rg3. The potential effects of different doses should also be assessed in future research. It is important to note that this study aimed to assess the neuroprotective role of 20(S)-ginsenoside Rg3 on DPN; thus, the agent was administered for five weeks following the induction of diabetes, aligning with previous reports that revealed the protective effects of agents in DPN.<sup>28</sup> DPN outcomes can be observed in rat models over a wide range of periods, spanning from 4 weeks up to 24 weeks from the onset of diabetes, with more pronounced alterations often becoming apparent after eight weeks. As a result, the impact of 20(S)-ginsenoside Rg3 on different stages of DPN remains an area to explore in future assessments.

## CONCLUSION

In experiments with STZ-induced diabetic rats, the administration of 20(S)-ginsenoside Rg3 via oral gavage at a dose of 5 mg/kg/day for five weeks effectively lowered blood glucose levels and alleviated weight loss. This treatment preserved sciatic nerve conduction velocity and prevented further damage to both motor and sensory neurons caused by diabetes. Thus, this natural adjunct could be regarded as a potential neuroprotective agent against the progression of DNP.

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**Ethics Committee Approval:** The Adnan Menderes University Experimental Animal Ethics Committee granted approval for this study (date: 02.09.2013, number: 64583101-2013/062).

**Author Contributions:** Concept – SO, MDB; Design – SO, MDB; Supervision – MDB; Resource – MDB; Materials – SO, MDB; Data Collection and/or Processing – SO, OBG, MB; Analysis and/or Interpretation – SO, OBG, MB, MDB; Literature Search – SO, MDB; Writing – SO; Critical Reviews – OBG, MB, MDB.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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