Research in Vestibular Science Vol. 19, No. 3, September 2020
pISSN 2092-8882, eISSN 2093-5501 https://doi.org/10.21790/rvs.2020.19.3.79

**Original Article**

# 한국 홍삼이 일측 미로 절제술 후 전정기능 조기 회복에 미치는 영향

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# Effect of Korean Red Ginseng on Early Vestibular Function Restoration after Unilateral Labyrinthectomy

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· Received May 22, 2020
Revised Jun 8, 2020
Accepted Jul 31, 2020

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**Objectives:** Vertigo is a common condition. Definitive treatment is to induce vestibular compensation. Currently, no medications have been discovered that enhance vestibular functional restoration. The current study was conducted to evaluate the ability of ordinary Korean red ginseng (KRG) to induce vestibular compensation.
**Methods:** Twelve Sprague-Dawley rats were divided into two groups. Five rats (KRG group) were fed KRG extract (100 mg/kg) for 2 weeks before undergoing unilateral labyrinthectomy (ULx). The remaining seven rats (control group) were untreated before ULx. After surgery, all animals were housed in the same environment without being fed additional extract. To evaluate vestibular function, gain of the horizontal nystagmus to 0.2 Hz with a peak velocity of 100°/second sinusoidal rotation was compared and analyzed before ULx as well as 3 and 7 days after surgery.
**Results:** Before the operation, gain of the control and KRG group were 0.81±0.05 and 0.88±0.08, respectively, with 0.2-Hz stimulation. This value decreased to 0.43±0.08 and 0.53±0.08, respectively on 3 days after operation ($p$=0.047), and it was 0.40±0.06 and 0.68±0.11, respectively on 7 days after surgery. The difference of gain between the two groups was statistically significant at each 3 and 7 days ($p<0.05$). By confirming c-Fos protein expression in medial vestibular nuclei, the functional effect of KRG causing vestibular modulation was confirmed.
**Conclusions:** Rats treated with KRG showed more rapid and complete recovery after acute vestibular loss compared to untreated animals. Therefore, KRG could be one of candidate for the useful medication of vestibular diseases.

**Res Vestib Sci 2020;19(3):79-88**

**Keywords:** Compensation; Ginseng; Vertigo; Vestibule

## INTRODUCTION

Vertigo is experienced by 30% of all people more than once during their lifetime [1]. Morbidity associated with this condition tends to increase among the elderly [2]. Pathologic vertigo is caused by complex factors such as degenerative disorders, viral infection, or ischemic brain injury [3]. The degeneration of vestibular hair cells, one cause of vertigo, cannot

be reversed in mammals but can be in birds [4]. Therefore, for function recovery, the definitive treatment tool is to induce vestibular compensation with exercise for early adaptation [5]. Early vestibular compensation after unilateral vestibular loss is induced by decreased efficacy of postsynaptic *N*-methyl-D-aspartate (NMDA) receptor responses of vestibular nucleus neurons to *gamma*-aminobutyric acid (GABA) agonists [6]. If the total compensation courses are unsuitable, chronic vertigo occurs and the return to daily activities is also delayed [7]. Vertigo tends to arise in the elderly, a population with decreased cognitive abilities and diminished locomotion [8]. Thus, it is not easy for these individuals to effectively complete the vestibular rehabilitation exercises [9]. In cases of certain diseases such as depression or anxiety disorders, treatment with anti-depressants and vestibular suppressants delay the recovery of vestibular function because vestibular compensation is disturbed [10]. Nevertheless, studies evaluating possible pharmacological methods for reinforcing vestibular homeostasis or preventing vestibular imbalance have been rare until now [11].

Korean red ginseng (KRG) may possibly serve as a medication for treating or preventing vestibular disorders. This plant has been used as a traditional medicine in Asia for more than 2,000 years and recently been proven to enhance memory while increasing plasticity and boost cognitive functions [12]. Especially, saponin, a compound found in KRG, is a complex material that contains different types of ginsenosides. Saponin is known to have beneficial activities such as antioxidative [13,14], anti-apoptotic [15], and immune regulatory functions [16,17]. All of these properties could influence neuromodulation and vestibular compensation after acute vestibular loss. Additionally, ginsenoside-Rb1 is believed to exert antivertigo effects primarily on the peripheral vestibular system through the inhibition of calcium influx into vestibular hair cells, thereby regulating hair-cell afferent vestibular transmission [10,18,19].

The main purpose of the current study was to evaluate the useful effect of KRG on vestibular compensation. This investigation is the first to assess protection against and recovery from vestibular function following acute vestibular loss induced by unilateral labyrinthectomy (ULx) in an animal model.

## MATERIALS AND METHODS

### 1. Animals

All animal experiments were conducted according to the guidelines of the Institutional Animal Care and Use Committee of Gachon University, Incheon, Korea (GIACUCR-009). Twelve- to 16-weeks-old Sprague-Dawley rats (Koatec, Seoul, Korea) weighing up to 250 to 350 g were used for this study. Five of the 12 rats were in the KRG group and seven were the control group (Fig. 1). All animals were housed with 100 lx of light with a 12-hour light/dark cycle at 23℃, 50% humidity, and a noise level below 50 dB.

### 2. Ginseng Administration

KRG extract was provided by Korea Ginseng Corporation (Daejeon, Korea). The extract contained Rb1 (0.83%), Rb2

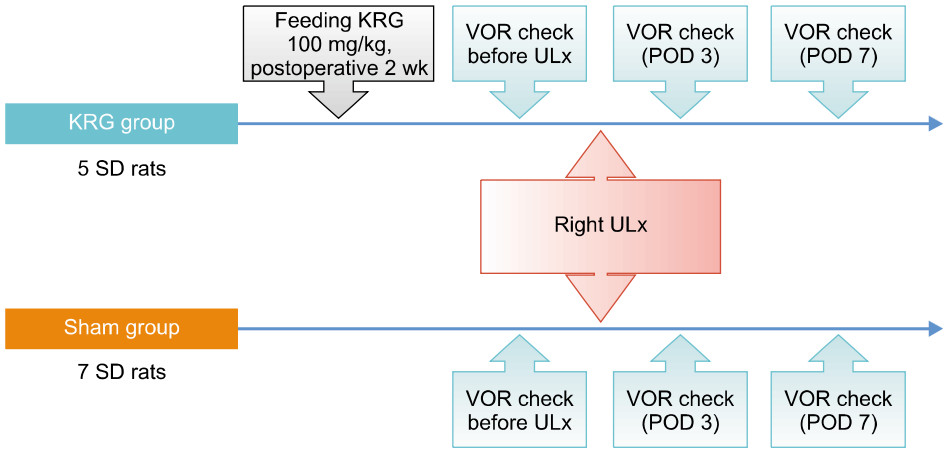


**Fig. 1.** Diagram of the experimental protocol. Sprague-Dawley (SD) rats were divided into two groups. The Korean red ginseng (KRG) group (n=5) was treated with 100 mg/kg oral doses of KRG extract for 2 weeks. Saline was given to the control rats (n=7) in place of the KRG extract. Vestibulo-ocular reflex (VOR) was recorded immediately before the unilateral labyrinthectomy (ULx) as well as 3 and 7 days after surgery. POD, postoperative day.

(0.32%), Rc (0.39%), Rd (0.11%), Re (0.26%), Rf (0.16%), Rg1 (0.20%), Rg2 (0.14%), Rg3 (0.01%), and Rh1 (0.10%), and other minor ginsenosides. The KRG group was treated with 100 mg/kg of KRG extract orally once a day for 2 weeks. The control group was under the same condition and these animals were treated with the same volume of saline at the same times as the KRG group. After the treatment period, all rats underwent ULx.

### 3. Unilateral Labyrinthectomy

Surgery was performed with the animals under gas anesthesia. The rats were placed in a prone position and inhaled isoflurane (Aerane; Ilsung Pharm Corp., Seoul, Korea). To maintain a constant physiological state during anesthesia, the following conditions were carefully monitored: body temperature, pulse, electrocardiogram signals (THM 100; Indus Instruments, Webster, TX, USA), and $O_2$ saturation (Ohmeda Biox 3760; Datex-Ohmeda, Madison, WI, USA). A vertical incision almost 1 cm in length was made following the right retroauricular sulcus and the eardrum was exposed. A small perforation was made in the middle ear space using a 23-gauge needle (Shingchang Medical Corp., Gumi, Korea) on the vestibular lateral wall positioned at the upside of the fallopian canal to later identify the pterygopalatine artery and stapes (Fig. 2). After observing perilymph leakage, the small perforation was extended and the vestibular lateral wall was completely opened. Next, suction was applied until there was no more leakage of lymphatic fluid. To maintain the opening, the hole was filled with collagen (Helitene; Intergra Life Sciences Corp., Plainsboro, NJ, USA). ULx completeness was verified by a tail hanging test and the appearance of spontaneous nystagmus, skew, and head tilting. Furthermore, auditory brainstem responses (ABR) were double-checked the constant ULx by the ABR workstation (Tucker-Davis Technologies, Alachua, FL, USA) objectively.

### 4. Head Fixation and Sinusoidal Rotation Stimulation

While under anesthesia, a 3-cm-long flat head bolt (30-mm tab screw; Junghwa Metal Corp., Hanam, Korea) was fixed on the skull of the rats with six tiny brass Phillips head screws (#1106; SM Medical, Seoul, Korea) and glue (Loctite 401, 20 g; Henkel, Dublin, Ireland) using a stereotaxic alignment system (Model 900 with a #1929B rat anesthesia mask; KOPF, Tujunga, CA, USA). For permanent fixation, dental cement (Vertex Self-Curing; Vertex-Dental BV, Zeist, the Netherlands) was placed overhead bolt. After bolt implantation, we waited 1 week for the animals to stabilize. The rat was then placed in a restrainer (S44-RR; Plas Labs Inc., Lansing, MI, USA) in a prone position and a bolt placed on the top of skull was inserted into the holder of the sinusoidal animal rotator (M-YS4080FN001; NSK, Ukiha, Japan) for complete fixation. A restrainer was also attached to the rotator stage with a machine screw to limit the movement of the body and head. A micro-control x-, y-, z-linear trans-

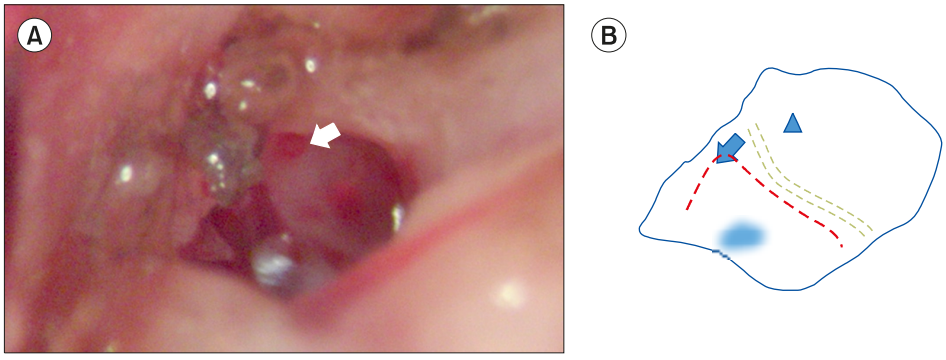


**Fig. 2.** (A) Unilateral labyrinthectomy of the right; the tympanic membrane was removed using a retroauricular approach. A hole (arrow) was made with a needle 1 mm anterior and superior to the head of the stapes and the pterygopalatine artery. Perilymphatic fluid was completely removed through that hole. (B) A diagram illustrating the position of the hole in the middle ear. The red and green dotted lines represent the pterygopalatine artery and the facial nerve, respectively. The arrow and the arrowhead indicate the head of the stapes and the position of the hole made on the labyrinth respectively.

lation stage was installed on the head holder device and an animal within restrainer was moved up, down, left, and right to bring the camera (GRAS-03K2M-C; Point Grey Research Inc., Richmond, BC, Canada) into final focus (Fig. 3A-C). Rotational stimulation was performed in a vertical plane at 0.2 Hz with a peak velocity of 100°/second. Stimulus duration was long enough to include at least 10 cycles at this frequency.

## 5. Eye Movement Measurement

For our experiments, the reference coordinate system was aligned with the animal's head (specifically, with the plane through the animal's horizontal semicircular canals, the midsagittal plane, and the coronal plane orthogonal to these). The head was in turn aligned by virtue of a rigid head mount in the Fick gimbal superstructure device (Hyunjin Precision, Seoul, Korea) holding the animal. To ensure correct angular orientation of the camera with respect to the gimbal (and thus the animal's head), the camera was mounted on a rotating turntable to adjust the azimuth and elevation alone.

Drops of proparacaine HCl (Alkaine 0.5% eye drops; S.A. Alcon-Couvreur N.V., Purrs, Belgium) were applied to the pupil of the rats under a microscope (GL-99B-V7; Daemyung Optical, Seoul, Korea). A glue (Gel-10; Daejin Chemical Corp., Siheung, Korea) was applied to the center of the pupil to fix the 200-μm diameter marker. Next, the upper and lower eyelids were held open (Fig. 3D) with sutures (D-7308M2, Deknatel; Teleflex Medical, Research Triangle Park, NC, USA) to prevent blinking during the experiment.

Eye movement was recorded in a dark room with 10-lx illumination and 120 frames per second (GRAS-03K2M-C) using a telecentric lens (TCL1.0×-40-ST; SPO Inc., Daejeon, Korea) with Y2 filter (Hoya 25 mm Y2; Tokia Co., Tokyo, Japan) and six extension tubes (ML-EXR5; Point Grey Research Inc.). Video recordings were saved as *.avi files. The images in the videos were 640×480 pixels in size and acquired with a special capturing board (HP NK653AA; Hewett-Packard Development Company, Palo Alto, CA, USA) using Flycapture software (Point Grey Research Inc.) with an IBM-compatible computer (I7; Intel, Santa Clara, CA, USA). To produce fluorescent reflection from the marker on the eyeball, a 385-nm light bulb (VAOL-3EUV8Y4; VCC Optoelectronics, San Marcos, CA, USA) was attached to the front line of the camera lens facing the eye. The intensity of the light was kept constant by using a 3.3 V battery (LiFePO4 rechargeable battery; Shenzhen Grenergy Tech, Guandong, China).

## 6. Immunohistochemical Staining

To investigate the vestibular compensated effect of KRG extract feeding before ULx, we stained for c-Fos like protein (FLP) in the medial vestibular nucleus (MVN) using coronal sections. We sacrificed the experimental animals (KRG group and control group) with an overdose of urethane (Sigma-Aldrich, St. Louis, MO, USA) after ULx 2, 6, and 12 hours and perfused transcardially with 250 mL of 0.1-M phosphate buffer (PB). The rats were then perfused with 500-mL 4% paraformaldehyde dissolved in 0.1 M PB (pH 7.4). We removed the brains from

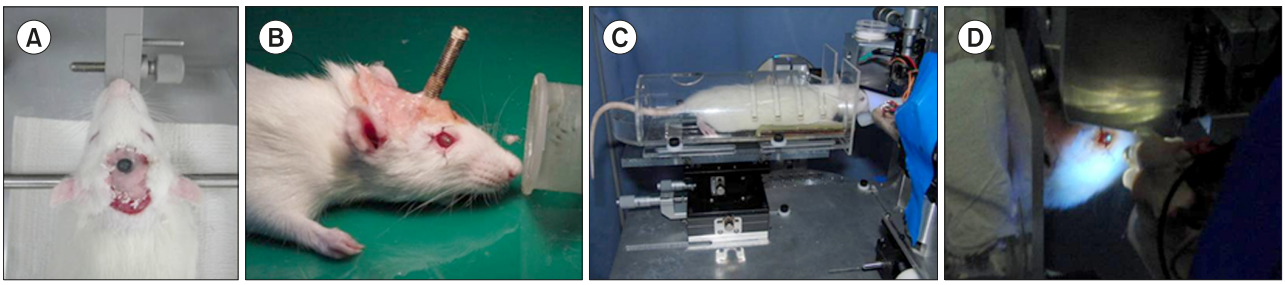


**Fig. 3.** The set-up used for nystagmus recording. After the permanent implantation of a head bolt on the skull (A, B), the rats were placed in a prone position in a restrainer with the neck and head fixed on an animal rotator to prevent movement of the body and head (C). (D) A marker was attached on the right pupil with glue under a microscope, and the upper and lower eyelids were sutured open to prevent blinking (D).

the skulls and postfixed them with the same solution used for initial fixation for 4 hours at room temperature (RT). We immersed the fixed brains in a 30% sucrose/phosphate-buffered solution (PBS) for 2 days at 4℃ for cryoprotection. We then cut sections at a thickness of 35 μm with a freezing microtome (Leica, Wetzlar, Germany), incubated them for 20 minutes at RT with 3% hydrogen peroxide ($H_2O_2$), rinsed them three times for 5 minutes with 10-mM PBS, incubated them for 20 minutes with 0.5% Triton X-100 dissolved in 10-mM PBS and incubated them for 1 hour at RT with 5% skim milk. We then washed the sections in 10-mM PBS plus 0.05% Triton X-100 (PBST) and incubated them overnight at 4℃ with rabbit polyclonal anti-c-Fos antibody (1:3,000; Oncogene Research Products, San Diego, CA, USA) in antibody diluent solution (Invitrogen, Carlsbad, CA, USA). The following day, we rinsed the tissue sections with PBST, incubated them with biotinylated goat anti-rabbit secondary antibody (1:1,000; DAKO, Glostrup, Denmark) for 1 hour at RT and incubated them for 1 hour at RT with avidin-biotin complex (Vector Laboratories, Burlingame, CA, USA). We visualized the neurons that were positive for FLP by incubating the sections with 0.05% diaminobenzidine (DAB; Invitrogen) plus 0.003% $H_2O_2$. After the DAB reaction was completed, we rinsed the sections with 0.1-M PB and mounted them on gelatin-coated slides. The slides were then air-dried, dehydrated, xylene-cleared, and mounted on coverslips with Permount (Fisher Chemical, Fairlawn, NJ, USA). We examined the brain tissue sections using bright-field microscopy (Olympus BX50; Olympus, Tokyo, Japan) to identify FLP-positive neurons. We captured and digitalized images of the dark-brown, FLP-positive neurons using a microscope-mounted digital camera (Olympus DP70, Olympus) and image-capture software (Image-Pro Plus; MediaCybernetics Inc., Rockville, MD, USA).

### 7. Data Analysis

A nystagmus analysis program was developed with LabVIEW (National Instruments, Austin, TX, USA). The x-axis represented time (second) and the y-axis represented the distance the eyeball moved (°). Basically, this program calculated gain, phase, and symmetry of three axes to monitor nystagmus. With horizontal nystagmus about sinusoidal rotational stimulation of KRG group and control group, the amount of gain was evaluated with descriptive statistics (mean±standard deviation). Data are presented as a box and whisker plot. Normality of the data was assessed with a Kolmogorov-Smirnov test before performing repeated-measures (RM) ANOVA. No variables were rejected, indicating that they maintained a normal distribution. We also used a one-way RM ANOVA to identify mean differences between the two groups for three replicate experiments. The Greenhouse-Geisser method was used to correct the violation of sphericity of the covariance. The *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics ver. 21.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

Before surgery, gain of the control and KRG groups were 0.81±0.05 and 0.88±0.08, respectively, with 0.2-Hz stimulation. The difference between the two groups was not significant. Gain of both groups observed 3 days after surgery was 0.43±0.08 for the control group and 0.53±0.08 for the KRG group. Seven days after surgery, gain was recovered more rapidly in the KRG group than in control animals; gain was 0.40±0.06 for control group and 0.68±0.11 for the KRG group (Fig. 4). RM ANOVA analysis of between-subjects effects showed that the gain was significantly higher for the KRG group than the control group ($F[1,10]=19.91$, $p<0.001$). Analysis of the within-subjects effects demonstrated that the linear and quadratic trends among replication measurements were statistically significant (linear: $F[1,10]=217.13$, $p<0.001$; quadratic: $F[1,10]=67.71$, $p<0.001$). The interaction effect between group and replication measurements (Fig. 5) was also significant ($F[2,20]=9.61$, $p<0.001$).

Immunohistochemical staining of FLP expression in bilateral MVN in coronal midbrain sections on 2, 6, and 12 hours after right side ULx in control group (Fig. 6B-D), and in KRG group (Fig. 6E-G) showed that KRG group did not express any FLP (Fig. 6A is negative control).

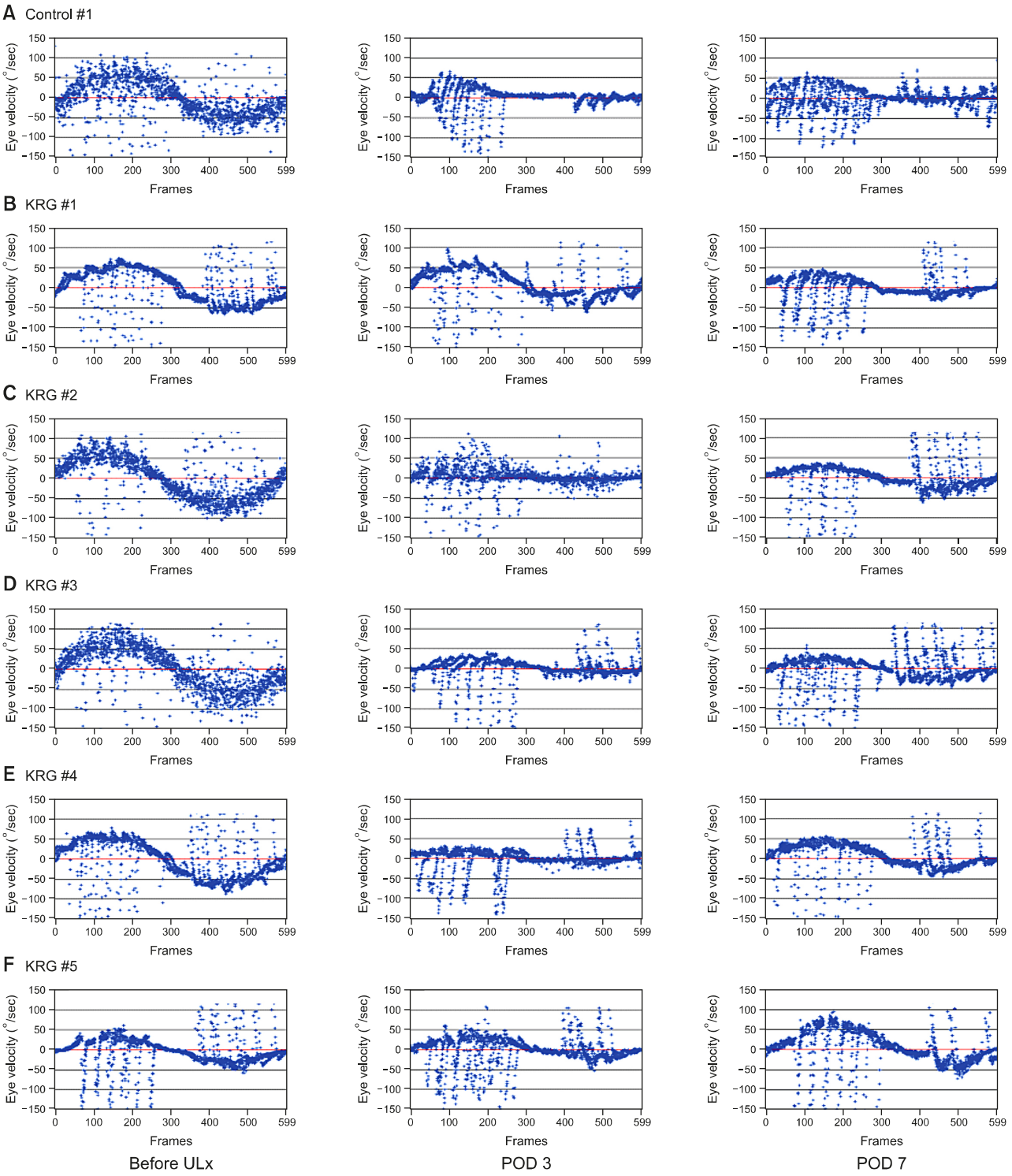


**Fig. 4.** Vestibule ocular reflex summation graphs of raw data of one animal in the control group (A) and five animals (B–F) in Korean red ginseng (KRG) group for sinusoidal rotation stimulation. Graphs in the left column present the data acquired immediately before unilateral labyrinthectomy (ULx) while graphs in the middle column present the data acquired 3 days after ULx and the graphs in the right column present the results obtained 7 days after surgery. No spiking nystagmus at one side was observed in the control animal 3 or 7 days after ULx. However, a nystagmus spiking on same side was seen 3 days after ULx in the KRG group. In each graph, the X-axis represents the frames. POD, postoperative day.

## DISCUSSION

In the present study, consumption of KRG extract significantly attenuated nystagmus induced by ULx. Gain in the vestibular system after ULx was also restored more rapidly. This study is the first to investigate the protection and recovery of vestibular function against acute vestibular loss induced by ULx in an animal model.

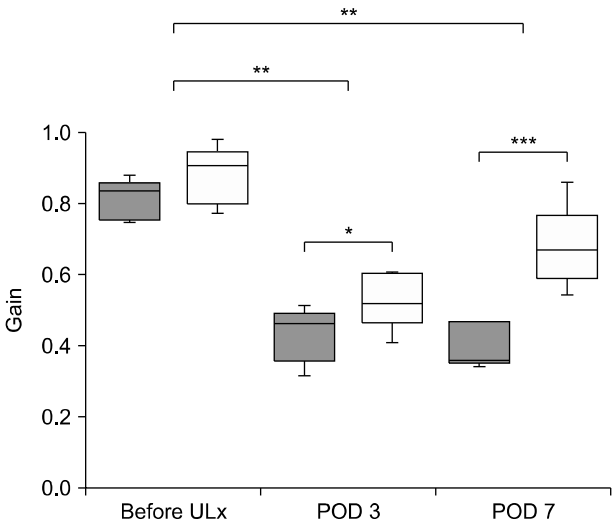


**Fig. 5.** Comparison of gain between the control and Korean red ginseng (KRG) groups for the sinusoidal rotation stimulation. The hatched boxes correspond to the control group while the white columns correspond to the KRG administration group. The gains of the KRG group 3 and 7 days after unilateral labyrinthectomy (ULx) were significantly better than those of the control group. *$p<0.05$, **$p<0.001$, and ***$p<0.0001$. POD, postoperative day.

In our pilot study, we found that animals treated with KRG recovered more rapidly from ULx than the untreated group. No spiking nystagmus was observed at one side oscillation in the control group 3 and 7 days after ULx while this spiking on same oscillation was observed 3 days after ULx in the KRG group (Fig. 7). This phenomenon was observed in all KRG-treated rats (Fig. 4).

KRG is a complex material that contains numerous types of ginsenosides. The effect, mechanisms of action, and characteristics of each ginsenoside were not clearly demonstrated in this study. Nevertheless, the authors speculate that KRG exerts beneficial effect on the vestibular system through several different mechanisms. The vestibular system has a distinctive compensation mechanism for repairing defective balance functions. Vestibular compensation consists of two stages: inhibition of the contralesional MVN (contra-MVN) activities during the acute stage after unilateral vestibular loss, and recovery and maintenance of spontaneous ipsilesional MVN (ipsi-MVN) activities during the chronic stage. In this overall vestibular compensation process, activated neurons in the ipsi-MVN project their axons into the flocculus to inhibit contra-MVN neurons via NMDA

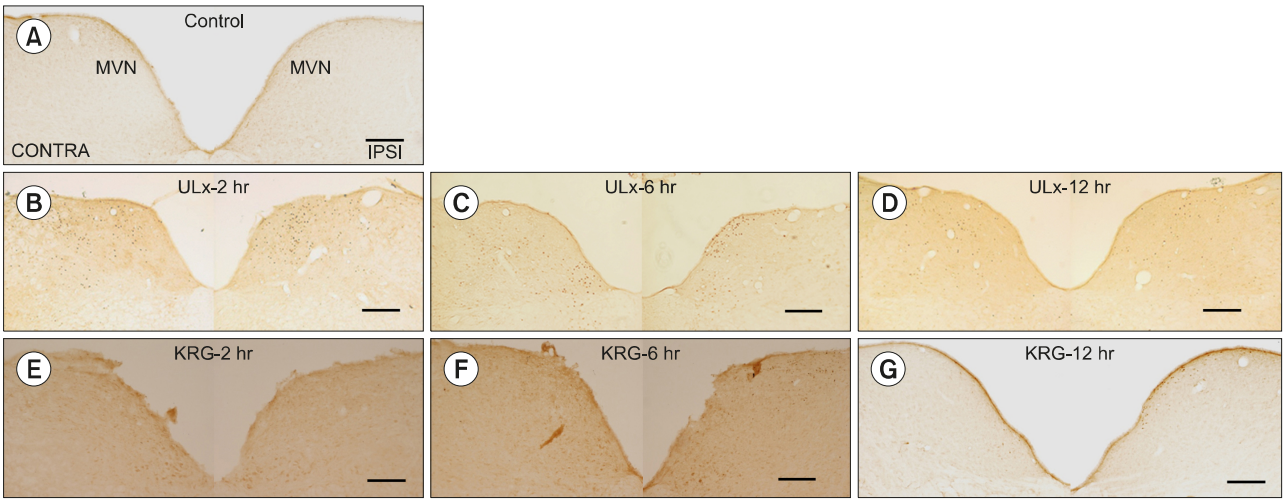


**Fig. 6.** Immunohistochemical staining of c-Fos like protein (FLP) expression in bilateral medial vestibular nucleus (MVN) in coronal midbrain sections of normal Sprague-Dawley rat (A), and on 2, 6, and 12 hours after right side unilateral labyrinthectomy (ULx) in control group (B–D) and in Korean red ginseng (KRG) group (E–G). The induction of FLP expression in the bilateral MVN caused by ULx was not detected in KRG group on 2, 6, 12 hours. Fig. 6A is negative control. CONTRA, contralateral to ULx; IPSI, ipsilateral to ULx. Scale bars, 400 μm.

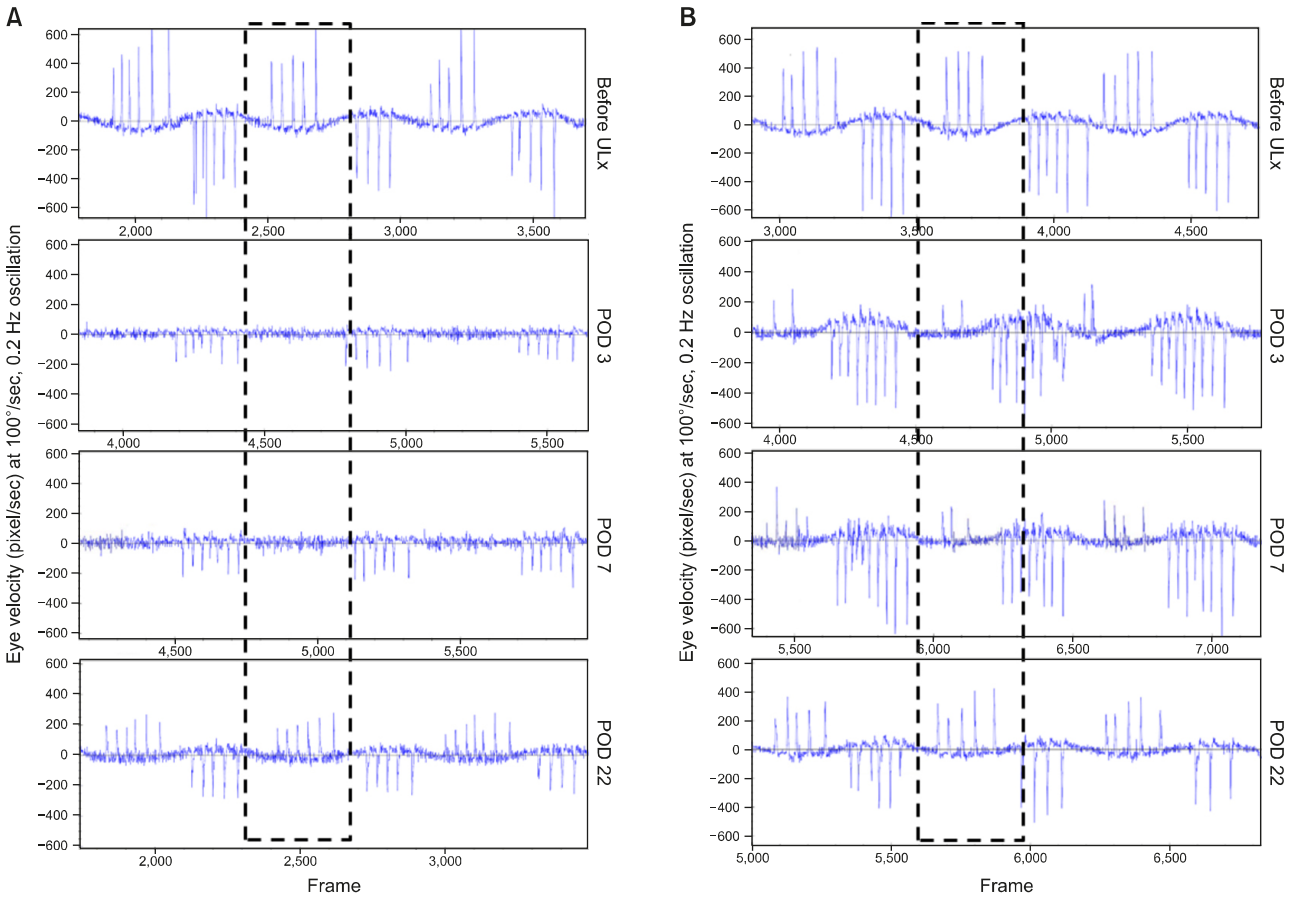


**Fig. 7.** The timely serial changes of nystagmus for the sinusoidal rotation stimulation in control (A) and Korean red ginseng (KRG) treated animal (B) for 22 days after unilateral labyrinthectomy (ULx). In the dotted box, no spiking at one side was observed in the control group 3 and 7 days after ULx. However, spiking at same side was seen 3 days after ULx in the KRG group. In each graph, the x-axis represents the frames. PO, postoperative.

receptor, nitric oxide, and/or GABA-mediated signaling, thereby restoring intervestibular nuclear activities. During the chronic stage after unilateral vestibular loss, the flocculus suppresses the inhibition of the ipsi-MVN neurons via protein phosphatase, protein kinase C, and glutamate receptors to promote the recovery and maintenance of ipsi-MVN activities [20].

An ideal medication for enhancing vestibular compensation should decrease the efficacy of postsynaptic NMDA receptor responses of vestibular nucleus neurons in the contra-MVN. Alternatively, neuronal activity could be augmented through increased glutamate release at the ipsi-MVN, and induce the decreasing sensitivity of GABA agonists at ipsi-MVN. Non-competitive antagonists of the NMDA receptor such as MK-801 have been shown to induce vestibular compensation. However, use of these reagents is limited due to psychotomimetic side effects and acute neurotoxicity both *in vitro* and *in vivo* [21]. It has been demonstrated that KRG modulates glutamate release through GABAergic receptor antagonists in mice [22]. Additionally, the administration of KRG significantly increases the expression of proteins that influence plasticity including phospho-NMDA receptor 1, phospho-calcium-calmodulin-dependent kinase II, phospho-PKA catalytic beta subunit, phospho-cAMP response element binding protein, and brain-derived neurotrophic factor in the hippocampus [12,23,24]. This neuromodulatory effect of KRG could improve the vestibular tonic imbalance. During this process, antioxidant [13,14], antiapoptotic [15], and immune regulatory [16,17] mechanisms could influence the outcomes. Another well-known benefit of KRG extract is the ability to

block calcium channels in the central nervous system of patients with ischemic disease [18,25]. Reagents that block calcium channels are a representative class of medications that alleviate acute vertigo symptoms.

Although the neuroregulation system is different, the cochlear and vestibular have similar mechanoelectrical transduction systems and communicate with each other. Several trials evaluating the effect of KRG on inner ear diseases such as noise-induced [26] or sudden hearing loss [27] have been performed and proposed several action mechanisms [25]. Nevertheless, it is nothing to study about medicine for strongly induced vestibular compensation preventively.

In the present study, we documented some evidence for unknown beneficial effect. Additional investigations should be performed to further investigate this topic. For determining preventive effects of KRG on vertigo, there was no sufficient information about period, number, and concentration of KRG. In this study, through the review of literatures [12,28,29], the amount of KRG is determined to be taken once each day for 2 weeks by 100 mg/kg concentration, used frequently in the study of nervous system.

In conclusion, oral administration of KRG in rats led to better and faster recovery after acute vestibular loss compared to untreated control animals. Our findings indicated that KRG can promote early vestibular compensation after acute vestibular loss. Therefore, KRG could be one of candidate for the useful medication of vestibular diseases.

중심 단어: 보상, 홍삼, 어지럼, 전정

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGMENTS

This work was supported by a 2011 grant from the Korean Society of Ginseng funded by the Korea Ginseng Corporation.

## REFERENCES

1. **Nazareth I, Yardley L, Owen N, Luxon L.** Outcome of symptoms of dizziness in a general practice community sample. Fam Pract 1999;16:616-8.
2. **Jahn K, Zwergal A, Schniepp R.** Gait disturbances in old age: classification, diagnosis, and treatment from a neurological perspective. Dtsch Arztebl Int 2010;107:306-15.
3. **Kim MJ, Kim KS, Joo YH, Park SY, Han GC.** The dizziness handicap inventory and its relationship with vestibular diseases. J Int Adv Otol 2012;8:69-77.
4. **Walshe P, Walsh M, McConn Walsh R.** Hair cell regeneration in the inner ear: a review. Clin Otolaryngol Allied Sci 2003; 28:5-13.
5. **Lacour M.** Restoration of vestibular function: basic aspects and practical advances for rehabilitation. Curr Med Res Opin 2006;22:1651-9.
6. **Yamanaka T, Him A, Cameron SA, Dutia MB.** Rapid compensatory changes in GABA receptor efficacy in rat vestibular neurones after unilateral labyrinthectomy. J Physiol 2000;523 (Pt 2):413-24.
7. **Bronstein AM, Lempert T.** Management of the patient with chronic dizziness. Restor Neurol Neurosci 2010;28:83-90.
8. **Krampe RT, Rapp MA, Bondar A, Baltes PB.** Allocation of cognitive resources during the simultaneous performance of cognitive and sensorimotor tasks. Nervenarzt 2003;74:211-8.
9. **Vaz Garcia F.** Disequilibrium and its management in elderly patients. Int Tinnitus J 2009;15:83-90.
10. **Rascol O, Hain TC, Brefel C, Benazet M, Clanet M, Montastruc JL.** Antivertigo medications and drug-induced vertigo: a pharmacological review. Drugs 1995;50:777-91.
11. **Smith PF, Darlington CL.** Can vestibular compensation be enhanced by drug treatment?: a review of recent evidence. J Vestib Res 1994;4:169-79.
12. **Zhao H, Li Q, Pei X, Zhang Z, Yang R, Wang J, et al.** Long-term ginsenoside administration prevents memory impairment in aged C57BL/6J mice by up-regulating the synaptic plasticity-related proteins in hippocampus. Behav Brain Res 2009;201: 311-7.
13. **Rausch WD, Liu S, Gille G, Radad K.** Neuroprotective effects of ginsenosides. Acta Neurobiol Exp (Wars) 2006;66:369-75.
14. **Konishi T.** Brain oxidative stress as basic target of antioxidant traditional oriental medicines. Neurochem Res 2009;34:711-6.
15. **Li H, Deng CQ, Chen BY, Zhang SP, Liang Y, Luo XG.** Total saponins of Panax notoginseng modulate the expression of caspases and attenuate apoptosis in rats following focal cerebral ischemia-reperfusion. J Ethnopharmacol 2009;121: 412-8.
16. **Block KI, Mead MN.** Immune system effects of echinacea, ginseng, and astragalus: a review. Integr Cancer Ther 2003;2: 247-67.
17. **Kaneko H, Nakanishi K.** Proof of the mysterious efficacy of ginseng: basic and clinical trials: clinical effects of medical ginseng, Korean red ginseng: specifically, its anti-stress action for prevention of disease. J Pharmacol Sci 2004;95:158-62.

18. **Rhim HW.** The effects of ginsenoside Rg 3 as a potent inhibitor of Ca 2+ channels and NMDA-gated channels in the peripheral and central nervous systems. J Ginseng Res 2003;27:120-8.
19. **Choung YH, Kim SW, Tian C, Min JY, Lee HK, Park SN, et al.** Korean red ginseng prevents gentamicin-induced hearing loss in rats. Laryngoscope 2011;121:1294-302.
20. **Kitahara T, Takeda N, Kiyama H, Kubo T.** Molecular mechanisms of vestibular compensation in the central vestibular system: review. Acta Otolaryngol Suppl 1998;539:19-27.
21. **Kornhuber J, Weller M.** Psychotogenicity and N-methyl-D-aspartate receptor antagonism: implications for neuroprotective pharmacotherapy. Biol Psychiatry 1997;41:135-44.
22. **Wang ZJ, Sun L, Peng W, Ma S, Zhu C, Fu F, et al.** Ginseng derivative ocotillol enhances neuronal activity through increased glutamate release: a possible mechanism underlying increased spontaneous locomotor activity of mice. Neuroscience 2011;195:1-8.
23. **Kim JH, Cho SY, Lee JH, Jeong SM, Yoon IS, Lee BH, et al.** Neuroprotective effects of ginsenoside Rg3 against homocysteine-induced excitotoxicity in rat hippocampus. Brain Res 2007;1136:190-9.
24. **Jesky R, Hailong C.** Are herbal compounds the next frontier for alleviating learning and memory impairments?: an integrative look at memory, dementia and the promising therapeutics of traditional Chinese medicines. Phytother Res 2011; 25:1105-18.
25. **Fujita K, Hakuba N, Hata R, Morizane I, Yoshida T, Shudou M, et al.** Ginsenoside Rb1 protects against damage to the spiral ganglion cells after cochlear ischemia. Neurosci Lett 2007;415: 113-7.
26. **Ahn JH, Kim TS, Chung H, Lee NY, Chung JW.** The protective effect of orally ingested Korean red ginseng on the noise induced hearing loss in mice. J Ginseng Res 2009;33:104-10.
27. **Im GJ, Cinn YG, Chang JW, Choi J, Chae SW, Jung HH.** Beneficial effect of ginseng extract on sudden sensorineural hearing loss. J Ginseng Res 2009;33:155-9.
28. **Kim SK, Lee SR, Park CG.** Effect of total ginseng saponin on the opioid receptor binding in mouse brain. J Ginseng Res 1995;19:219-24.
29. **Kim HS, Hwang SL, Seong YH, Jung MW, Lee MK.** Effects of ginseng total saponin on caffeine-induced stimulation of locomotor activity and the related brain catecholamine contents. Korean J Ginseng Sci 1990;14:399-403.