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# 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

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**Abstract.** We are exposed to many external and internal stresses in this day and age. Stress weakens the function of immune systems in living organisms and disturbs homeostasis. As a result, stress induces various psychosomatic diseases. Thus, ways of reducing stress and thus protecting humans from disease must be developed. One such method is called "the prevention of *Mibyou*" in *Kampo*, the Chinese traditional medicine. Many studies have reported the direct effects of medical ginseng on damaged target organs and recovery from disease. It also increases immune potential and may maintain homeostasis of living organisms through the autonomic-endocrine systems. It is also thought to prevent the development of disease. We studied and considered the action of medical ginseng on living organisms that were exposed to various stresses such as cold environment and industrial work. Furthermore, we confirmed the preventive effects of medical ginseng on the common cold symptom complex, including flu, by clinical observation. Here, we report our experiences.

***Keywords***: red ginseng, stress, ice water tolerance time, industrial fatigue, common cold symptom complex

## Introduction

The present time is called the stress age. Stress reduces physical and mental tolerances (immune potential) of humans and it induces progression of existing illness or causes latent disorders to become active. Thus, the control and suppression of stress is very important in the improvement of quality of life and prevention of diseases.

Many researchers have investigated the mechanisms of medical ginseng as a therapeutic medicine, and the findings from these studies are currently in clinical application.

Based on the consideration of ancient oriental medicine (*Kampo*), the most important way to prevent disease is to protect it in the undeveloped stage (*Mibyou*), but unfortunately, there has been no report of systemic research in this field. We have performed several clinical studies on the human stress model and have reported that red ginseng (RG) has clear anti-stress action. In this report, as part of these studies, we outline the effects of medical ginseng on environmental cold stress, prevention of industrial (occupational) fatigue, and a disease model. The medical ginseng we used in these studies was the Seikansho brand of powdered RG root aged for 6 years.

## Cold stress and RG

In an environmental stress model, we observed the reaction of human organisms that were exposed to cold stress (1). We aimed to determine whether RG can prevent disorders that occur in cold environments. So, we examined the effect of RG on changes in blood pressure, heart rate, and tolerability to cold stress.

Ninety healthy male and female volunteers joined our study. We divided them into three random groups. One group received RG, one received placebo (PL), and one received nifedipine (NP). A cold stress test was then

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performed as follows. Each subject's right hand was immersed up to the wrist in ice water kept at 4°C. Subjects feel a cold sensation at first, which gradually changes to pain. We measured the time until interruption of the test, which was when the pain became intolerable. We obtained interesting results by observing the physical reactions during the test.

Figs. 1 – 3 show various physiological parameters. 1) Cold stress had little effect on systolic blood pressure (SBP) in subjects that took RG and PL. 2) After added cold stress, SBP in subjects that took NP dropped significantly (Fig. 1). 3) Similarly, in comparison with the other groups, diastolic blood pressure (DBP) in subjects that took NP dropped significantly before load and just after, with added stress (Fig. 2). If each remedy has a different ice water tolerance time (IWTT), it would be suggested that subjects with faster heart rates may have longer IWTT. However, we can solve this problem by comparing average heart rates (AHR) during added stress by operating AHR ÷ IWTT (AHR/IWTT). A comparison of mean heart rate during added stress after medication showed significant differences, and the order was NP>PL>RG (Fig. 3).

The coefficient of variance of heart rate (CV) is thought to reflect the function of the parasympathetic nerve. So, a larger CV is thought to be a reflection of a more parasympathicotonic state. CV order was NP>PL>RG.

Figure 4 shows a comparison of the IWTT of each drugs. We set the exponent value before medication of

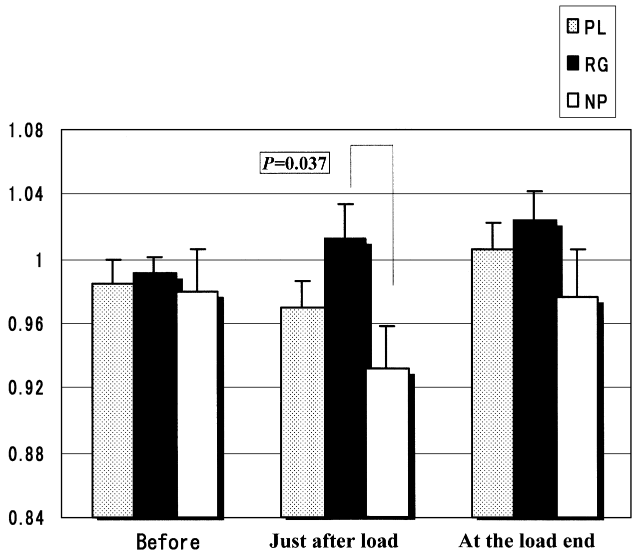


**Fig. 1.** Exponent comparison of SBP. The value before medication is 1. (Scheffe's multiple comparison tests). Modified and reproduced from Ref. 1.

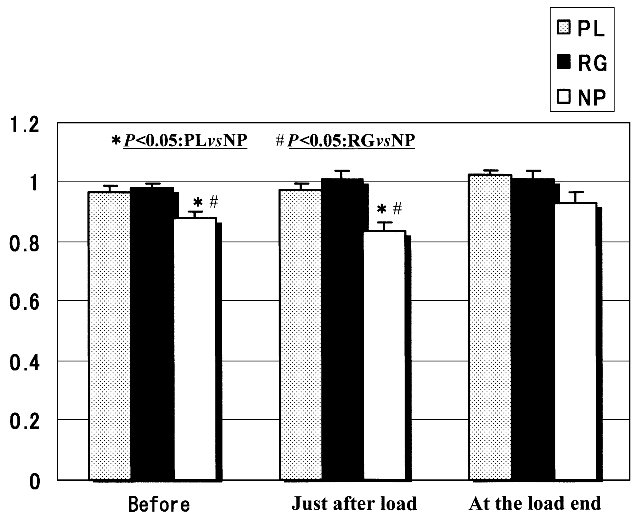


**Fig. 2.** Exponent comparison of DBP. The value before medication is 1. (Scheffe's multiple comparison tests). Modified and reproduced from Ref. 1.

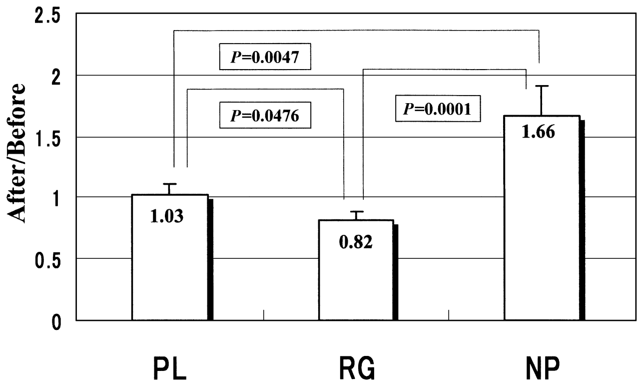


**Fig. 3.** Comparison of average heart rate after medication (Scheffe's test). Modified and reproduced from Ref. 1.

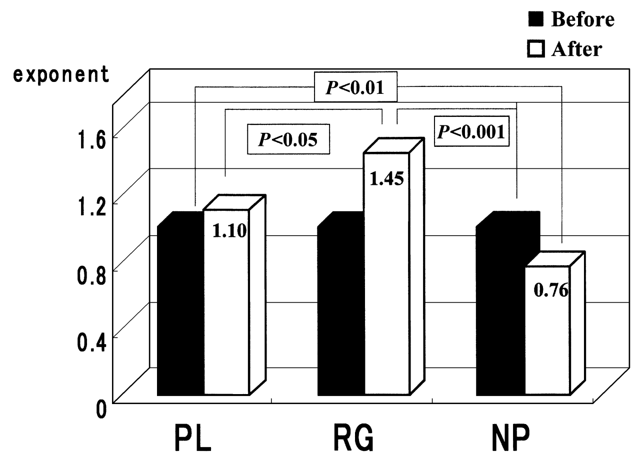


**Fig. 4.** Comparison of IWTT change after medication. Modified and reproduced from Ref. 1.

each drugs at 1. The exponent of IWTT for each drug after medication was changed to RG = 1.45, PL = 1.10, and NP = 0.76. The IWTT for RG showed significant prolongation, but the IWTT for NP showed significant shortening. This suggests that tolerance to cold stress significantly increased after administration of RG.

In the past, we proved that RG and components of RG (ginsenoside) have a vasodilating action on peripheral vessels through clinical physiology and animal experiments (2, 3). From this experience, we believe that RG dilates blood vessels, increases blood flow under cold stress, decreases the pain from ischemia, protects local tissue, which may be connected to prolongation of IWTT. We thought that NP, a well-known vasodilator, had the same action. RG showed the expected action, but NP unexpectedly showed opposite action. It significantly shortened IWTT. The action mechanism of NP can be explained as follows. NP may disturb the normal sympathicotonic reaction of skin, which is called cold-induced vasodilatation (COVD). As a result, the skin temperatures are adversely lowered due to heat dissipation from continuously dilated vessels, which induces a lowering of the pain threshold. An increase in CV that presents a parasympathetic dominant state and a reflex tachycardia following the reduction in blood pressure are proof of this fact. On the other hand, COVD was not affected by administration of RG, which may stimulate sympathetic nerves a little and perhaps constrict peripheral blood vessels adequately. It contributes to the redistribution of local blood flow to every corner of capillary vessels and prevents degradation of skin temperature; finally, it increases tolerance of cold stress. A weak, but significant, positive correlation ($r = 0.489$, $P = 0.003$) between prolongation of IWTT and increasing DBP, was considered as a proof of the above-mentioned fact. Thus, it is estimated that the vasodilating effect of "RG" is revealed via the regulation of the autonomic-endocrine system rather than the simple direct action of blood vessels.

## Work stress (industrial fatigue) and RG

Generally, industrial fatigue (occupational fatigue) includes both mental and physical fatigue. Simple physical fatigue is easily remedied by rest, but mental stress or complicated mental and physical fatigue is more difficult to be cured. Immune potential is weakened and consequently, illness is triggered. We chose taxi driver as suitable occupational model for this investigation (4).

Figure 5 shows a comparison of flicker values (F values) of 23 male taxi drivers (43 – 65-year-old, mean age: 51.2 ± 5.9) who were treated with RG or PL, before

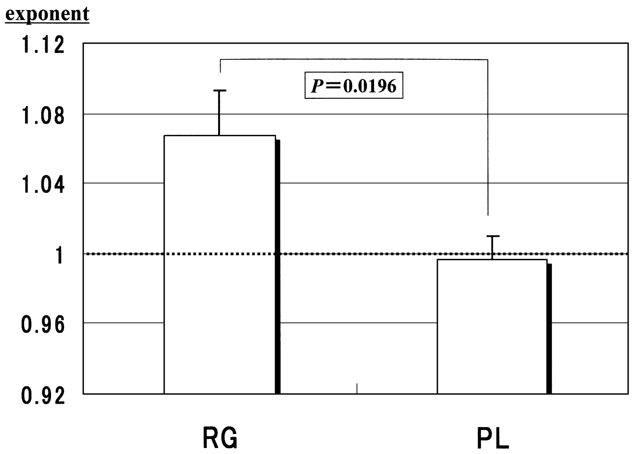


**Fig. 5.** Comparison of F value (after/before). Modified from Ref. 4.

and after their work. When compared with the exponent of F value (we set the value of the untreated exponent at 1) between RG and PL, the exponent that was treated with PL was almost unchanged. However, the exponent of the individuals that were treated with RG was significantly increased.

When we watched the relationship between mileage (quantity of work) and the F value, F value decreased in proportion to prolongation of mileage in the PL phase. The correlation coefficient was $r = 0.447$ and probability was $P = 0.032$. On the other hand, the F value in the RG phase showed no relationship to mileage. The F value was constant and was improved in most of the RG phases.

Generally, the F value decreases in proportion to the degree of mental fatigue. Also, a researcher reported that the F value is maybe a suitable parameter used to detect fatigue of mental workers (5). The F value showing the reaction of the brain to visual irritation decreases in proportion to aging. Based on these reasons, the taxi driver was thought to be a sort of "neuro-mental occupation".

Thus we determined that RG increases the F value and improves many neuro-mental symptoms.

## The protective effects of RG against the common-cold-symptom complex and the flu

We reported the effects of red ginseng on various stress models. Based on previous studies, in this section, we introduced several verification results of epidemiology that showed that RG is effective in the prevention of certain diseases.

Between autumn 1998 and spring 1999, we performed a study of long-term use of RG in the staff of a geriatric hospital. In the winter of that year, during a nationwide flu outbreak, many staff members were infected with the flu. After the examination period ended, many subjects talked to us about their experiences that a man who was treated with RG during the examination period was not easily infected with the flu. We performed a retrospective investigation by listening comprehension and tried to prove whether it had been true. We decided on the following definition of the common cold symptom complex (CCSC) including flu: 1) Fever more than 37.5°C, 2) General malaise (headache, chill, pain in the joints or muscles etc.), 3) Inflammatory symptoms in the respiratory tracts (nasal discharge, nasal obstruction, sore throat, cough, sputum, etc.). We defined as common cold cases that satisfied more than two of the above-mentioned three cardinal symptoms. When the whole staff of the hospital was the population for a comparison of the incidence of CCSC, no significant differences in the incidence of CCSC were found between the mother population and the PL group. On the other hand, the incidence of CCSC in the group treated with RG was significantly lower than that in the mother population and the PL group ($P = 0.032$ *vs* mother population, $P = 0.018$ *vs* PL).

Next, we performed a prospective investigation from 2000 to 2001 to prove these results. We added numbers of total patients that visited the Kaneko Heart Clinic during this period and called that the total mother population of this investigation. In the mother population, we selected certain patients who had visited the clinic regularly but were not treated with RG. Next, we calculated populations that were infected with CCSC in the group not treated with RG and defined it as the rate of incidence in the untreated group. In the same way, we defined the rate of incidence of CCSC from the RG group, as follows. The incidence of CCSC in the RG group was the rate of patients who caught cold, although they frequently visited the clinic and were given long-term (more than 3 months) RG treatment. RG group patients were having chronic cardiovascular disease, and were given 3.0 g of RG per day in addition to a standard treatment.

Figure 6 shows the incidence of CCSC during a 2-year accumulation investigation. Each denominator shows the number of the patients, and the numerator is the number of patients with CCSC. The incidence of CCSC in the mother population and the non-RG treated group was around 5%. On the other hand, it was proved that the incidence of CCSC from the RG group was significantly low compared to the other groups (1.38%).

We believe that the activation of immune potential is a very important mechanism of the preventive effect of RG against CCSC and especially its ability to prevent

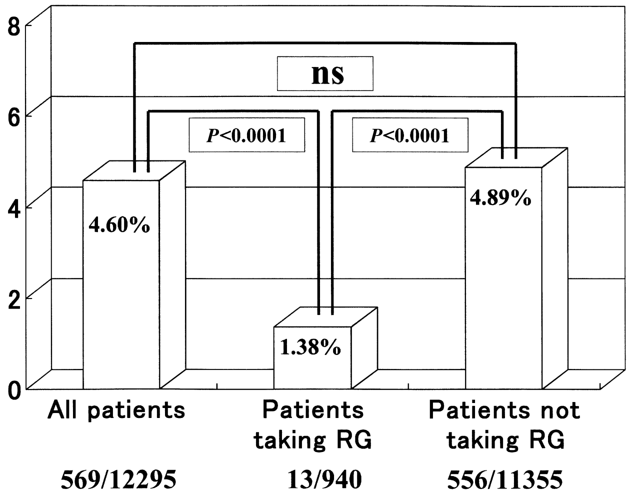


**Fig. 6.** Incidence of CCSC by accumulation investigation for two years.

infectious diseases. In relation to these mechanisms, some researchers have reported their findings. In 1985, Kubo reported that RG extracts activated early immune potential against infection in animal experiments. Sing et al. reported that RG enhanced natural killer activity and cell-mediated immunity against viral antigens (6). RG saponin (ginsenoside) suppresses the degradation of immune potential caused by many stresses (7). More recent research showed that oral administration of RG enhances the immune ability of mucous membranes and protects subjects from viral infection (8).

These reports showing several effects of RG prevention of CCSC are proof of effects of RG on immune activity. RG has one more important activity as a modulator to maintain homeostasis of autonomic-endocrine systems. RG maintains a normal physical condition, thus preventing the onset of CCSC. Therefore, we believe that RG may weaken symptoms of CCSC even if a cold develops.

## General conclusions

As the response to environment and adaptation to the type of stresses, RG changes its action. This strongly suggests RG is not only a remedy but also a modulator that maintains homeostasis of living organisms. This action appears to depend mainly on the effects of RG on the autonomic-endocrine systems.

## References

1 Kaneko H, Nakanishi K, Murakami A, Kaidoh H, Kuwashima

K. The acute effects of massive dose of RG on healthy adults under the condition of cold stress. Ther Res. 1996;17:405–416.
2 Kaneko H. Studies on clinical effects of ginseng: 2nd report; effects of ginseng at acute massive dosage on circulatory function. Proceedings of the 3rd International Ginseng Symposium, Seoul, Korea. 1980. p. 193–196.
3 Kaneko H, Nakanishi K, Murakami A, et al. Vasodilator action of ginsenosides. Clinic and a Study. 1984;61:2657–2662.
4 Kaneko H, Nakanishi K, Murakami A, Kaidoh H, Kuwashima K. The acute effects of red ginseng on subjective tiredness flicker reaction, blood pressure and heart rate of taxi drivers at work. Ther Res. 1996;18:1745–1759.
5 Iwasaka H. Examination of fatigue of an anesthesiologist. Operation region medicine. 1992;13:119–121.
6 Sing VK, Agarwal SS, Gupta BW. Proceedings of 4th International Ginseng Symposium, Seoul, Korea. 1984. p. 225–228.
7 Saito M, Okamoto S, Ishikawa I. Effects of ginsenosides on the stress-induced immunosuppression. Ginseng Rev. 1998;24:108–111.
8 Koike U, Yoo YC, Matsuzaka K, Anuma I. Protective effects of ginsenoside-$Rb_2$, 20(*R*)- and 20(*S*)-ginsenoside-$Rg_3$ on rotavirus infection. Ginseng Rev. 1998;25:7–9.