

Plenary Lecture 1

The Proper Understanding on Pharmacological
Safety and Biological Activity of Korean Ginseng

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Proper Understanding on Pharmacological Safety and Biological Activity on Korean Ginseng

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My topic today is "Proper Understanding on Pharmacological Safety and Biological Activity on Korean Ginseng".

The important point of the pharmacological research on crude herbal medicine including Panax ginseng is how understand the nature of the target drug properly. Crude drug has the quite different nature from the single pure chemicals. The study on isolated pure compound from ginseng is not the study on ginseng itself.

Multiplicity of compounds including, oral administration and chemical change in the gut, and the individuality of the response are the points of the crude drug pharmacology.

For example, about 30years ago, I had had experienced that the added sanou-shashin-to (SST, 三?瀉心湯), a traditional Sino-Japanese herbal drug, to washed rabbit aorta in Magnus apparatus stimulated its contraction. But this drug usually uses for the patients with hypertension to decrease the blood pressure. Why the drug contracted the aorta? I confused at that time first. However, I soon thought that I should make a suitable model system mimic the patient of hypertension. Washed aorta is not suitable as the model of hypertension. So, I first added adrenaline to the system for contraction of the aorta alike the patient, and then added the drug. As the result, SST relaxed the contraction. Both agonist and

antagonist are included usually in crude drug, because of plant were alive under the physiological regulation. Generally speaking, drug, agonist and antagonist, acts on same receptor as musical chairs. If we add the more agonist to the receptor already bound agonist, the response is not so changed, but antagonist compensate the response. The conception that patient with hypertension should avoid ginseng would be the incorrect idea brought from pure drug and lack the biological common sense.

About 30years ago, I proposed so-called Serum Pharmacology (血清薬理学) as the suitable method for pharmacological research of crude drug. As one of such research, the effect of hochu-ekki-to (HET, 補中益氣湯) containing ginseng on the sperm motility will show you.

The topic of the symposium today is "Ginseng, Root of Life". The individual life is started from the encounter of egg and sperm, For this, sperm should swim and swim to meet with egg for a long way. In ancient days in Asian countries, infertility was thought to be women's responsibility under the old, conservative family system. But now, many assisted reproductive technologies could apply recently, and made clear that malignant infertility would be mainly due to male. To treat male infertility, single pure drug is usually ineffective. Androgen, methyl vitamin B12, and so on have theoretically efficacy, but did not show clear effect clinically. I thought that this was the accumulated results of multiple defective points on the reproductive process. In addition to this, the end point of the treatment of infertility should be pregnancy. But when female recognize pregnancy, the fetus already reach the irreversible state of differentiation, and the period is usually with high risk of malformation. So, the safety is essentially important for the treatment of infertility. Due to the diversity of active components and action targets, and the relative safety of crude herbal drugs, I thought that, for the treatment of infertility, KAMPO drugs, Sino-Japanese traditional herbal drugs should become the main drug of the treatment. Then, we checked the activities on sperm motility of KAMPO drugs which are clinically used in male infertility, such as hachimi-jio-gan (HJG、八

味地?丸), ninjin-to (NT、人?湯) and HET.

The system I used at first was so-called "twin-culture tube method" (?子管法). Twin-culture tube is combined the two tubes for cell culture and placed membrane filter between the windows of the tubes. This equipment had developed to observe the interaction between cancer cells and normal cells. The liquid in the tubes can move each other between two rooms, but cells or particles larger than pore size cannot enter to another room. Using this tube, we added Kampo drug in one tube, and washed sperm into another room, and followed the ratio of the swimming sperm time-dependently. As the result, HET and NT, both containing ginseng elongated the sperm motility, but HJG did not.

HET containing ginseng, elongated the motile time of the sperm in vitro, in twin cell system. However, HET was not administered into vagina directly. So, the active compound should be received attacks in the gut, absorbed from the intestine, transported via portal vein, metabolized in liver, and then reached into the seminal fluid. So, the compounds which appeared in the blood newly after drinking HET should be reached into semen, and we tested the components in the serum and seminal fluid. As the result, We could detect some serum components appeared newly after taking of HET in the seminal fluid. Next, the sperms and the fluids got from before or 3- and 6-hours after intake of HET were recombined. As the result, any sperms could swim well in the fluid 3-hour after intake. The results showed that important points are 1) swim-elongation compound or factor should be exist in the circumstance of swimming and 2) this content would be higher in the fluid 3-hr after the intake.

Next, the seminal fluids 3-hours after taking orally HET and the HET without one component herb were isolated, added to the freshly isolated semen, and motility were checked. As the result, the effect of HET without ginseng was extremely reduced (about 16% than HET) and the importance of ginseng in HET was shown. But, for example, ogon,(?芩), scutellaria root (48%), kanzo,(甘草), licorice root

(56%) and other some herbs also had limited but not ignorable roles.

One day I saw the small print of Edvard Munch, famous Norwegian woodblock artist, titled Madonna, and thought that sperm should swim long time and long distance inside of female body, vagina, uterus and tube. So, HET would be the drug given to the female partner. We tested clinical efficacy of HET on male infertility. The both of the couples of male infertility were given HET orally and recommended sexual intercourse 3-hours after taking the drug. This method improved the pregnancy ratio. After this our proposal, many couples received this treatment but there were no trouble or accident related to the blood pressure, though sexual excitement itself would dramatically increase the blood pressure. If ginseng increases the blood pressure, HHT should also increase the blood pressure. But, there is no clinical evidence of the event.

Recently many Japanese people receives stress and the drug reactivity is largely injured. For one patient with hypertension, it was thought that SST is suitable for treatment. But the response against the blood pressure was very limited. For the patient with hypertension like this patient, usually ginseng-containing formula is not applied. But, HET or other ginseng-containing formula is generally effective against stress, so I administered SST at morning and evening and HET at noon and before sleep. And as a result, the blood pressure dramatically and successfully decreased. After this success, I administered combined use of adequate formula and HET for stressful patients. Among these stressful patients, the blood pressure is higher than normal persons usually, however, the average blood pressure decreased, far from increase.

The pharmacological research using one pure compound would be significant for the definite research oriented to pharmaceutical development. However, the estimation or a fairly tale on herbal drug efficacy lining with these results of single component contravened the fact and is never thought scientific. The modern scientific pharmacological research based on the features of herb or herbal medicine would

change the incorrect understanding, including "hypertension due to ginseng".

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