

## Pulse Spectrum Study on the Effect of Sie-Zie-Tang and *Radix Aconiti*

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**Abstract:** Extracts of the traditional Chinese formula Sie-Zie-Tang as well as one of its main components, *Radix Aconiti* were injected into rats intraperitoneally to observe pressure wave spectrum changes at the caudate artery. We found that *Radix Aconiti* decreased the C0 (DC term of the pulse), C5 and C6 (the harmonic proportions of the 5th and the 6th harmonic), but increased C2 and C3 (the harmonic proportions of the second and the third harmonic) significantly. For Sie-Zie-Tang, the increases of C2, C3, and C4 were accompanied by the decreasing of C0. The decreases of C5, C6 were small and not significant. The additional ingredients in the formula reduce toxic side effects (arrhythmia or heart failure caused by faster and stronger heart beat) due to *Radix Aconiti*. For human subjects, low dose Sie-Zie-Tang tends to normalize the Fourier components of the pressure wave. Orally taking the formula elevates the harmonic proportion of the harmonic that is lower than normal, but suppresses the higher one. Our result provides a possible mechanism for heart meridian related herbs. It strengthens heart beats, and normalizes energy distribution to different meridians. The study on Sie-Zie-Tang reveals another formula construction to reduce toxic side effects.

The classification of meridian related herbs was well described in the traditional Chinese medical classic, *Pen-Ts'ao Be Yao*. Can this classification be explicated by modern physiology? Previously, we studied the effects of several meridian related herbs such as *Panax ginseng*, *American ginseng*, *Ganoderma lucidum* (Wang *et al.*, 1994a, b), *Rhizoma Coptidis*, *Radix Bupleuri*, *Cinnamomum cassia Blume* (Wang Lin *et al.*, 1992) and analyzed variations of the pulse spectrum. From the resonance theory (Wang *et al.*, 1989a, b; Wang Lin *et al.*, 1991, 1997), we suggest that each organ and its related meridian is in resonance with a specific Fourier component of pressure wave. The conditions of an organ as well as its related meridian will influence the resonance status. As a result, it will show up on the variation of the corresponding harmonic. Our experimental results on herbs indicated that

the affected Fourier component of the pulse was well correlated with the organ and its related meridian as described in *Pen-Ts'ao-Be Yao*.

Since pressure energy distributed to each organ or meridian is directly related to its blood supply according to its resonance frequency, the meridian related herb effect can therefore be understood as modulating blood supply to this specific meridian and its related organ through changes of blood pressure in the resonant frequency (Wang *et al.*, 1994 b). For heart meridian related herbs, however, their effects on each meridian as well as the heart are not so clearly described in the Chinese medical literature. *Radix Aconiti*, for example, an often prescribed heart meridian related herb, is described in *Pen-Ts'ao Be-Yao*, as "It goes around the 12 meridians, reaches every place of the body, increases kidney live fire, cures all 'cold' diseases." There are some studies on *Radix Aconiti*; its biological active components has been analyzed (including *aconitine*, *mesaconitine*, and *hypaconitine*) (Bisset, 1981; Su and Liu, 1991); its activation mechanism on sodium channels and the effects on excitable membranes of cardiac, neural and muscle tissues (Liu 1991; Pepper and Trautwein, 1967) as well as its pharmacology (Tai *et al.*, 1992b; Lehmann *et al.*, 1992; Chen *et al.*, 1990), toxicity (Tai *et al.*, 1992a: Pharmacopoeia Committee, 1990; Fatovich, 1992) have been reported. However, its mechanism is still unclear.

In this study, we tried to elucidate the effect of Sie-Zie-Tang and its main component *Radix Aconiti* on the Fourier components of the pulse on both human subjects and rats. Our previous study on that formula *Xiao-Jian-Zhong-Tang* showed that the whole formula effect on Fourier components was similar to the linear combination of the individual herb effect, and suggested that it is one of the fundamental bases for formula construction (Wang *et al.*, 1995b).

## Material and Methods

### *Preparation of Extracts*

Ten grams of dry herb *Radix Aconiti* were soaked in 300 ml water for one-half hour then boiled at 100° C for 3 hours to obtain 100 ml water extract (0.1 g/ml). Four dosages, 0.3, 0.4, 1.0 and 1.2 mg/g body weight were tested in rats.

For formula Sie-Zie-Tang used in animal tests, 10 g *Radix Aconiti* were first soaked in 300 ml water for one-half hour, after being boiled at 100° C for 2 hours, 18 g *Rhizoma Zingiberis* and 30 g *Radix Glycyrrhizae* were soaked in the water extract for one-half hour and boiled for another hour to get 100 ml final extract. Two dosages of the formula containing *Radix Aconiti* 0.8 mg/g body weight and 1.2 mg/g body weight were used.

In human experiments, the dosage was 1 ml/kg body weight. For example, a 50 kg subject will receive orally 50 ml extract containing 3 g *Radix Aconiti*, 6 g *Rhizoma Zingiberis*, 10 g *Radix Glycyrrhizae*. The concentrations of each herb in the formula extract are listed in Table 1.

### *Animal Experiment*

Sprague Dawley rats 250 g-430 g were used. For *Radix Aconiti*, five rats were tested; for the

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formula, six rats were used in each dosage set. The rats were anesthetized with urethane. The tail artery was cannulated with an intravenous catheter (B-D), which was filled with heparinized physiological saline, and connected to a pressure transducer (RP-1500 Narco Biosystem). Blood pressure pulse of the tail artery was obtained through a transducer, which was in series with a preamplifier, an A/D converter and an IBM PC (Wang *et al.*, 1992).

**Table 1. Composition of Sie-Zie-Tang**

Medicinal plants	g /ml extract	
	for animal experiment	For human experiment
<i>Radix Aconiti</i>	0.10	0.06
<i>Rizhoma Zingiberi</i>	0.18	0.12
<i>Radix Glycyrrhiza</i>	0.30	0.20

After artery cannulation, a wait of least 40 minutes took place to allow for equilibrium and stabilization of blood pressure wave, then half hour recordings of pressure pulse were taken as control. The extracts of pure herb or the formula Sie-Zie-Tang was injected intraperitoneally into the rat; then 2 more hours recordings for post treatment were taken. Standard deviation of heart rate averaging from four to six consecutive pulses was not allowed to exceed 5%. Recordings of pressure pulse were taken every 5 minutes for about 2.5 hours. The signals were then analyzed by the Fourier analyzer.

### *Human Experiments*

Eight healthy volunteers (3 females, 5 males, 24-50 year-old with no apparent illness) were tested. All subjects were asked not to take any medicine 3 days before the experiment. During the test day, they were not allowed to have any alcohol or caffeine containing beverages, and were food restricted at least one hour before the experiment. A half-hour rest was routinely required before the test. Room temperature was kept between 23 to 25° C. Each subject was asked to lie down and relax with eyes open for five minutes. Pulse pressure on the right hand radial artery was then recorded with a pressure transducer (PSL-2001 Kyowa Electronic Instrument Co. Ltd. Japan), which was fixed on the skin by scotch tape and had an adjustable belt with a small button to give suitable pressure on the transducer. Our criterion of a good measurement was to seek the largest amplitude of the pulse. Pressure pulses were taken before (control), 15, 30, 60, 90 and 120 minutes after 50 ml warm herbal extract was fed to the subject. Output of the transducer was connected to an IBM PC via an A/D converter with 430 data points/sec sampling rate. Pulse spectrum was analyzed with Fourier transform using  $T(\text{period}) = 1$  pulse as described previously.

Standard deviation of heart rate averaging from four to six consecutive pulses in a measurement was not allowed to exceed 5% (Wang *et al.*, 1995a). Variations of pulse spectra were expressed as percent difference of harmonic proportions between post and pre-treatment. Variation of the first harmonic C1 to the sixth harmonic C6 in rats and C1 to C9

for human subjects, as well as the DC term-C0 were calculated. It was defined as:

$$\% \text{ Difference of harmonic proportion} = 100\% \times (\text{Cn}(\text{Ti}) - \text{Cn}(\text{T0})) / \text{Cn}(\text{T0})$$

where Ti = time after herb injection; T0 = control time just before herb injection; Cn = nth harmonic proportion =  $(\text{An}/\text{A0}) \times 100\%$  for n = 1 to 6, or n = 1 to 9; An = amplitude of the nth harmonic of pulse spectrum, A0 = DC component of pulse spectrum, for n = 0, we define C0 = A0.

## Results

### Animal Experiments

Time response curves of different doses of *Radix Aconiti* from five different rats are shown in Figure 1. In three of these five rats (0.42 g/425 g, 0.3 g/244 g, 0.12 g/310 g), arrhythmia occurred 5 to 10 minutes after injection of *Radix Aconiti*, but returned to normal 30 to 90 minutes afterward. No recording was analyzed and data points were missing in Figure 1 for these periods.

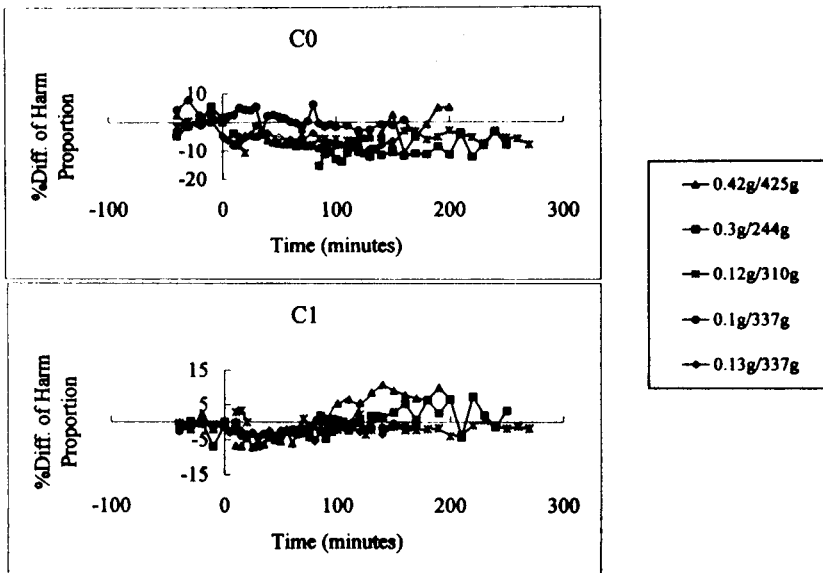
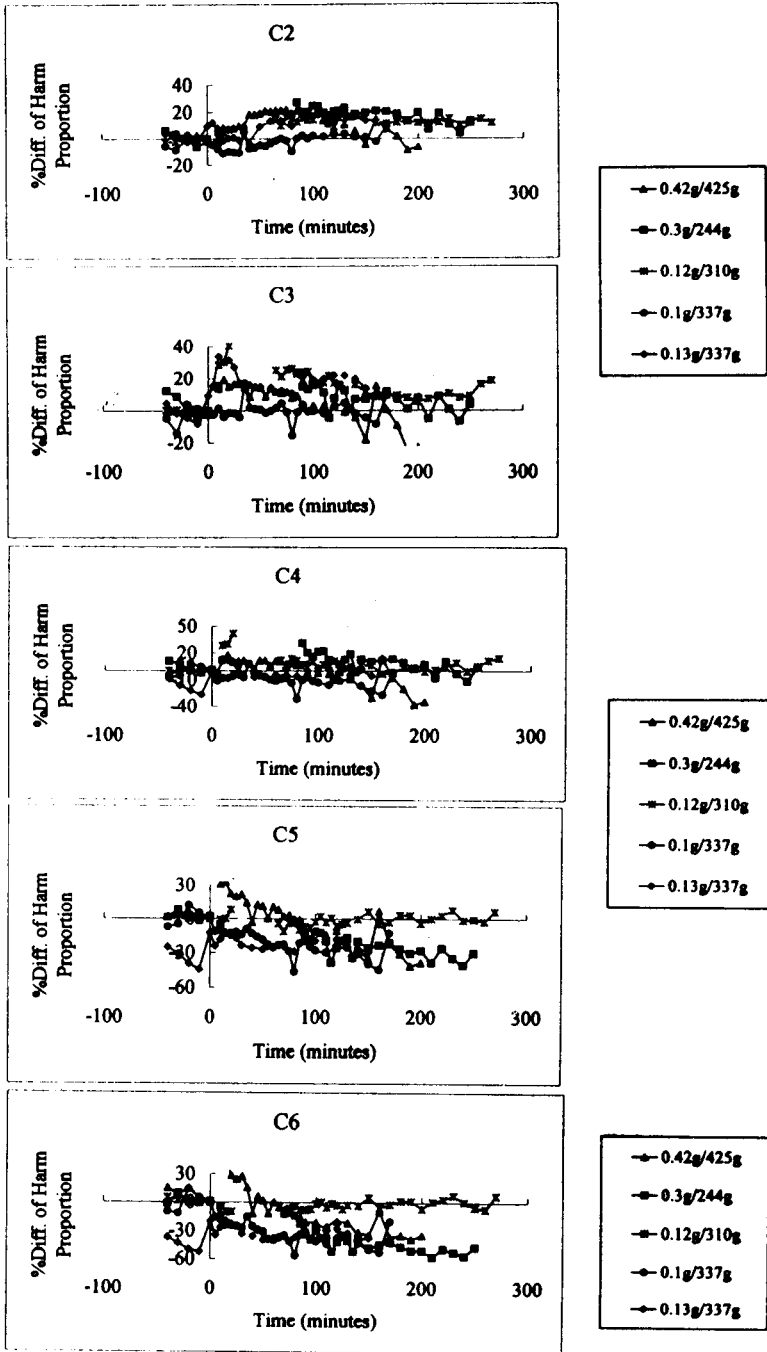


Figure 1. Time course of *Radix Aconiti* effects on rat pulse. The percent differences of harmonic proportions C0 to C6 were presented. Pulse taken at the time just before herb injection (time 0) was used as control. n = 5.

Roughly, most of the data points on the C0, C5, C6 curves are below zero, but most of the data points on C2, C3 curves are above zero. There was little effect on C1 and

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C4 curves. However, following the time axis carefully, we find that all the harmonics, 1 to 6, have a tendency of increasing their harmonic proportions; the higher the harmonic, the faster the increase and decay. For harmonic 4, 5, 6, the increasing periods may be interfered with arrhythmia, hence the outcomes are not clear.

The average effects of Sie-Zie-Tang, which contain *Radix Aconiti* 0.8 mg and 1.2 mg/g body weight are shown in Figure 2. Data on each point were the average of 6 rats. Five different time periods, 10 minutes before herb injection, 30, 60 90 and 120 minutes after injection are presented. The standard error shown in the bar as well as the T-test results for data of the 90 minutes (compared with control) are also shown. 0.8 mg/g body weight shows a slight increasing effect on C2, and the effect on all other harmonics are not significant. 1.2 mg/g body weight significantly increased C2 ( $P < 0.01$ ), C3, and C4 ( $P < 0.05$ ) but decreased C0 ( $P < 0.05$ ). We did not find the prompt increasing responses for C5 and C6, which occasionally appeared in pure *Radix Aconiti* treatment as mentioned above. For Sie-Zie-Tang, the toxic side effects (arrhythmia, or heart failure caused by long period of fast heart rate) happened only for dosages larger than 1.2 mg/g body weight.

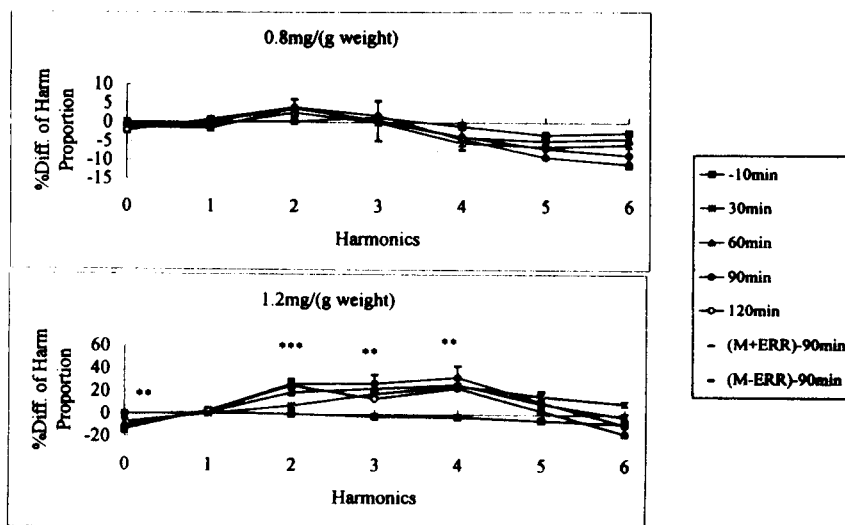


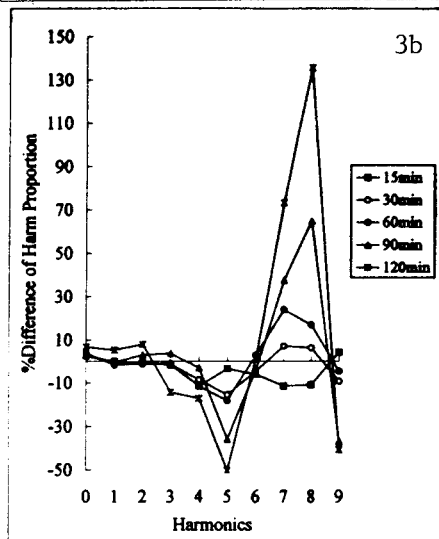
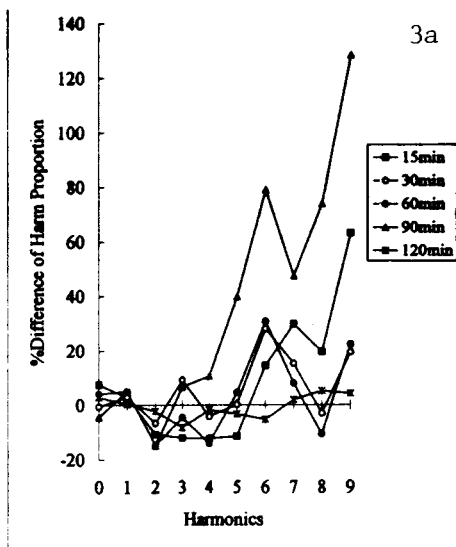
Figure 2. The average Sie-Zie-Tang effect on rat pulse. Average percent differences of harmonic proportion were presented. Pulse spectrums of four post herb injection periods (30, 60, 90 and 120 min) and one prior herb injection (-10 min) were compared with the control (time 0). Mean  $\pm$  SE of the 90 min data were plotted as (M+ERR)-90 min and (M-ERR)-90 min, respectively. T-test results calculated between 90 min and the control data were also shown, \*\*:  $p < 0.05$ , \*\*\*:  $p < 0.01$ ,  $n = 6$ .

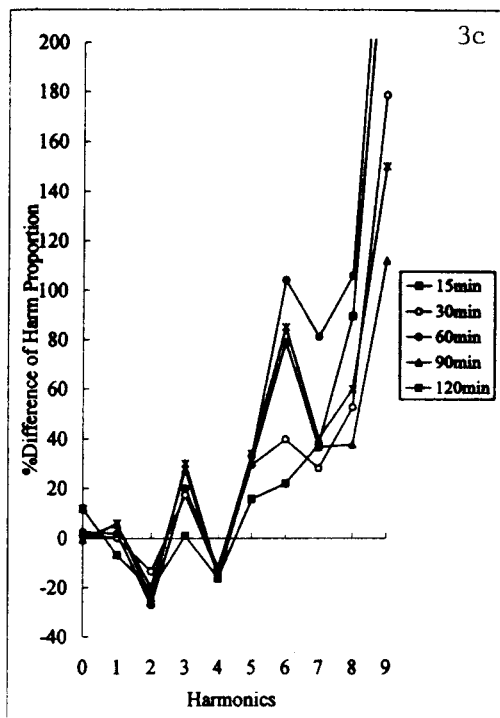
### Human Experiments

In human subjects, harmonics 1 to 9 as well as the DC term (C0) of the pulse spectrum were studied. The effect of Sie-Zie-Tang shows a personalized pattern at the small dose we used, that is, each subject has his/her own pattern. Three typical results are shown in Figures 3.

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In Figure 3a, a peak is shown at C6 after taking the formula. This effect reaches maximum at 90 minutes, then diminishes at 120 minutes. In Figure 3b, the increasing peaks at C7, C8 and the large scale decrease at C5 are noted. In Figure 3c, the increasing peaks at C3, C6 and the large scale decrease at C2 are observed. When comparing each subject's control values with the normal values, we found that for the subject of Figure 3a, the amplitude of C6 of the control is 40% less; for the subject of Figure 3b, the amplitude of C7 is 30% less, C8 is 40% less, but the C5 is 30% more. For the subject of Figure 3c, the amplitude of C3 is 30% less, C6 is 40% less, but the C2 is 10% more. For other subjects, each one has its own pattern, and the effect tends to normalize each subject's pulse spectrum; that means Sie-Zie-Tang extract tends to bring the subject toward a more healthy condition.





Figures 3a, b, c. Samples of the Sie-Zie-Tang effects on three different human subject pulses. Percent differences of harmonic proportion were presented. The pulse spectrums of five post herb feeding periods (15 min, 30 min, 60 min, 90 min, 120 min) were compared with the control at the time just before herb feeding (time 0).

## Discussion

From the animal experiments, our results indicate that extract of pure *Radix Aconiti* improves circulation to the kidney meridian (i.e., lower limbs, C2 effect) and the spleen meridian (C3) but decreases circulation to the stomach meridian (C5) and gall bladder meridian (C6) (Yu *et al.*, 1994; Wang *et al.* 1989a, b). As mentioned in the results, harmonic proportions of the higher harmonics increased for a short period followed by a fast decay. This phenomena may explain the description in traditional Chinese medicine as “it goes around the 12 meridians, reaching every place of the body.”

The effect of Sie-Zie-Tang is slightly modified from that of *Radix Aconiti*. The circulation to the lung meridian (C4) increases along with C2 and C3; the decreasing effect of C5 and C6 shown in pure *Radix Aconiti* treatment is compromised. As described in the traditional Chinese medical classic *Pen-Ts'ao Be Yao*, *Rhizoma Zingiberis* in the formula may play this modifying role; it warms the lung (increase C4), spleen (C3), stomach (C5) and kidney (C2). The pulse spectrum effect of Sie-Zie-Tang seems to be the combination effect of *Radix Aconiti* and *Rhizoma Zingiberis*.



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*Radix Glycyrrhizae*, has a strong de-toxic ability that may be the main consideration in constructing the formula, as we know the toxic side effect of *Radix Aconiti* is greatly reduced by it (*Pen-Ts'ao Be Yao*).

The Sie-Zie-Tang effects on human subjects are not as clear as on rats. The dosage used for humans was quite small, about  $1/6 \times 1/3 \times 1.2$  mg/g body weight.  $1/6$  is the equivalent factor between humans and small animals like the rat (according to our experiment, it does give the same dosage effect). To avoid the possible toxicity of *Radix Aconiti*, we keep our dosage around  $1/3$  of the effective dosage in the rat. When the dose is under 0.8 mg/g body weight, there is no significant effect on the rat (data not shown). In human experiments under the dosage we used, the effects on the lower harmonic are small, however, the effects present a specific pattern at higher harmonics (C5 to C9). The pulse spectrum becomes more balanced, which means the Sie-Zie-Tang extract normalized the pulse spectrum toward a healthy condition.

From this study we may understand the principles of how the heart meridian related herb works. The main purpose of the herb is to improve circulation to the middle (C3, C4) and lower (C2) part of the body, that is to warm up the internal organs and the four limbs. At the same time, circulation to the head (C6) is not expected to reduce and this may be due to a stronger heartbeat. Actually, kidney (C2), spleen (C3) and lung (C4) are weaker when we are not in good health (Yin-Shu-Hoa-Wan). That is, the lower frequencies of the harmonics, which belong to "Yin" is weak ('Shu'), while the higher frequencies of the harmonics was strong (Hoa-Wan). The increase of energy distribution to these three meridians actually improves the health of the subjects. These results are consistent with the human results, which show that Sie-Zie-Tang normalizes the pulse spectrum, a healthy condition. "When the heart is strong, it will distribute blood in a healthy way." (*Pen-Ts'ao Be Yao*). In the formula Sie-Zie-Tang, *Radix Aconiti* does the main job, *Rhizoma Zingiberis* assists it, and *Radix Glycyrrhizae* reduces the toxic effects. All three components form an optimal formula. Pulse spectrum analysis again proves itself to be useful in the understanding of Chinese medicine.

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