

A DOUBLE-BLIND CLINICAL TRIAL OF *PANAX GINSENG* IN AGED SUBJECTS

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ABSTRACT

Panax ginseng has often been suggested as a geriatric restorative. This study is a double blind crossover trial to test whether ginseng can improve function in subjects with the depression and reduced abilities associated with senescence. 49 screened subjects were given 1500 mg Korean Red ginseng and identical placebo each for ten days, with a washout period in between the dosages. Standard tests of mental function, neuromuscular reflexes, responsiveness, mood and well being were used. The subjects were somewhat better at the co-ordination and speed test ("number copying") but tests of concentration and memory ("Concentration", "Paired Association", "Digit Span" and "Object Learning") gave equivocal results. There were small improvements in mood and well being ("Life Satisfaction" and "General Health Questionnaire") while the subjects indicated increased energy, alertness and less sleep, but also less happiness on the daily analogue scales. The major result was a highly significant improvement in reactivity, speed and co-ordination at the tapping test, and the visual, auditory and disjunctive reaction timer. These are the most objective and accurate tests used in this trial. It is therefore concluded that ginseng can increase function in senile individuals. This effect is most easily

visualisable in objective psychophysical tests, rather than the more subjective memory and concentration tests.

INTRODUCTION

Ageing is very often accompanied by fatigue, debility, confusion, incoordination and general impairment of mental and physical function.¹ Yet there are currently few relevant pharmacological materials and these of limited use.² Vasodilators are the most commonly administered drugs, but these only help some patients and there are side effects. Stimulants have gone out of fashion because of toxicity. Tonics, particularly choline analogues and vitamins, can be of use but their effects are uncertain and unclear.³ This has led Fulder to examine the possibilities of *Panax ginseng* as a geriatric tonic, as described in previous reports.^{4,5} *Panax ginseng* is widely used as a restorative remedy for the elderly, and a prophylactic tonic for younger people.^{4,6} Some case reports have appeared,^{7,8} however there are no properly controlled and analysed human trials with old people in the international scientific literature. Preliminary or anecdotal reports give promising indications that ginseng is effective in improvement of mood, psychological performance, and fatigability.^{9,10}

Therefore it was decided to carry out a

precisely controlled clinical study to test whether ginseng can improve mental performance and mood in a geriatric population. The old people were chosen from those presenting themselves to hospital outpatients and general practitioner clinics showing signs of functional deterioration such as fatigue or depression. This study follows a previous preliminary double blind trial which demonstrated that ginseng produced small but consistent increases in several measures of function, competence and mood in nurses under stress at a London hospital.¹¹

METHODS

Elderly patients were selected from clinic records at the geriatric department of St. Francis hospital, London, and from doctors in the local community. The fatigued and debilitated were selected on the basis of a full screening test, medical history and AMT test, to eliminate severely demented, depressed or diseased patients, and those on various classes of drugs. 50 patients remained and 49 completed the study. 6-year Korean red ginseng, heaven grade, was kindly given by Lotte Trading Co. (U.K.) Ltd, ground and tableted. The placebo consisted of inert herbal materials and flavourings. Subjects received 1.5 gm ginseng daily or placebo for 10 days.

The trial design was a crossover. That is each subject acted as his own control. This considerably increases the power and accuracy of the trial. Subjects were first tested on psychological and psychophysical parameters to establish a base line. Then they took ginseng or placebo for ten days (period A), after which they were tested again. This was followed by a three week washout period without any treatment. Subjects were then tested again to give a second baseline, and took the opposite medication for ten days, (Period B) after which they were given the final tests. Subjects were randomly assigned to Group I - ginseng (Period A) then placebo (Period B), or Group II - placebo (Period A) then ginseng (Period B). (Fig. 1)

Subjects were given the following tests; which are published standard psychological and

general well-being tests, adapted to the non-demented aged.

A. Tests of Cognitive Function to Measure Mental Performance

1. *Digit Span Test* requires the subject to repeat back series of numbers spoken to him.

2. *Concentration Test* consists of a series of timed tasks such as counting up from 1 adding 3 each time.

3. *Paired Associate Learning Test* is a standard test of verbal learning ability.

4. *Object Learning Test* is a standard test of visually recorded memory.

5. *Digit Copying Test* requires the subject to copy numbers on a special form, the time taken to complete 100 numbers and the number completed in 3 minutes are recorded.

Tests of Cognitive Function were varied in each session. They measure memory, concentration, attention, recall and mental stamina.

B. Psychophysical Performance Tests

6. *Tapping Meter*. The subject must tap a counter as quickly as possible, and the number of taps within a given period is recorded.

7. *Reaction Timer* measures speed of response to light (visual reaction time), to sound (auditory reaction time) and to either the light or the sound when both are presented in coordination (disjunctive reaction time).

These tests are more objective than the tests of cognitive function, and less subject to variability and uncertainty. They measure co-ordination, reaction, reflexes, decision making and speed.

C. Subjective Tests of Mood, Well-Being and Health

8. *General Health Questionnaire* tests general well-being.

9. *Life Satisfaction Index Z* is a standard measure of mood.

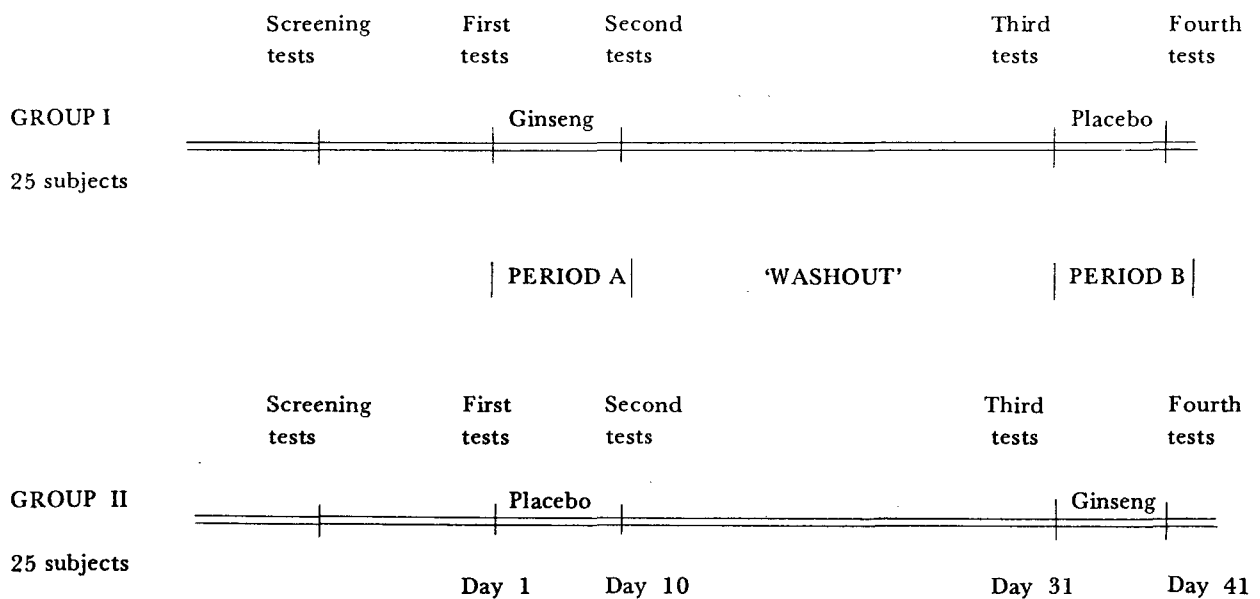


Fig. 1. Trial design

10. *Visual Analogue Scales* are self-recordings of energy, mood, alertness, happiness and sleep quality, which are filled out by the subject every day during the ten day test periods.

Statistical analysis was carried out according to standard methods for quantitative data in the two period crossover clinical trial.¹² A digest of the data is presented here. Full statistical analysis will be published later.

RESULTS

Tests of cognitive function and psychophysical performance were carried out at the beginning and end of each treatment period. Thus there are four measurements: y_0 (base line, period A); y_1 (post treatment, period A); y_0' (base line, period B); y_2 (post treatment, period B), where y is the mean of the measurements for all individual subjects given each treatment. Thus the effects of ginseng against placebo are given both by $(y_1 - y_0) - (y_2 - y_0') = d_A$ in the group of subjects given ginseng in period A and by $(y_2 - y_0') - (y_1 - y_0) = d_B$ in the group of subjects given ginseng in period B. The average of these two values $(d_A + d_B)/2$ gives the overall effect of ginseng versus placebo. The difference between

these two values $(d_A - d_B)/2$ gives an indication of the effects of time alone.

A. Cognitive Function Tests

The values of d_A and d_B , the ginseng effects compared to placebo, are given in Table 1. The Digit Span, Concentration and Object Learning tests show placebo to be slightly better than ginseng. The subjects completed more numbers in 3 minutes, and completed 100 numbers faster when they were given ginseng compared to placebo. However there was so much variability between subjects that the differences in all the tests were not significant.

There was a considerable difference between the mean values of ginseng versus placebo in periods A and B. This could be because of time effects, that is because of changes in the performance of the subjects over the trial period unrelated to the particular treatment given. For example the subjects might improve scores because they improve in motivation or in expectations purely as a result of the interest taken in them during the trial. Time effects can be assessed by the difference $(d_A - d_B)/2$. The results are shown in Table 1. The last column describes the

Table 1. Tests of cognitive function: effects of ginseng versus placebo, and period effects.

Parameter	Ginseng effect Group I d_A	Ginseng effect Group II d_B	Combined ginseng effect $\frac{1}{2}(d_A + d_B)$	Difference between ginseng effects $\frac{1}{2}(d_A - d_B)$	P
Digit span	-8.63	5.04	-1.79	-6.86	0.05
Concentration	-0.25	0.12	-0.13	-0.19	ns
Paired association	1.88	0.67	0.61	1.27	0.05
No. copying (3 mins)	20.91	-12.42	4.25	16.66	0.001
* No. copying (100 nos) (seconds)	12.14	4.28	-3.93	-8.21	0.02
Objects learned	-3.16	-5.13	-4.15	0.98	ns

* Note: A negative result in this test indicates that the test was completed in less time, i.e. performance has improved.

Table 2. Psychophysical reactivity tests: effects of ginseng versus placebo and effects of period.

Parameter	Ginseng effect Group I d_A	Ginseng effect Group II d_B	Combined ginseng effect $\frac{1}{2}(d_A + d_B)$	Difference between ginseng effects $\frac{1}{2}(d_A - d_B)$	P
Tapping rate (taps)	14.85	9.71	12.28	2.57	
* Visual reaction time (secs)	-19.95	3.65	-8.15	-11.8	
* Auditory reaction time (secs)	-10.22	1.56	-4.33	-5.89	
* Disjunctive reaction time (secs)	0.65	-3.0	-1.18	1.82	

* Note: A negative result in these tests indicates that the test was completed in less time i.e. is an improvement in performance.

differences between the ginseng versus placebo effects in the 2 groups of subjects. In the majority of tests there is a significant difference between the two groups indicating a period effect. The presence of period effect would mask any effects of ginseng that exist. It is not easily possible to remove the period effects from the total results because of its variability.

B. The Psychophysical Reactivity Tests

Tests of psychophysical performance are

more tightly controlled than the cognitive function tests. Table 2 shows the values for d_A and d_B , the ginseng versus placebo scores, for both periods. There is a clear improvement in performance in all the tests, highly significant in the case of the tapping test. However the results are variable both within groups and between periods. For this reason period effects were calculated as described above, and the results are shown in Table 2. There is a small difference between the effects of ginseng for the two groups, however

the differences between the base lines is highly significant. This demonstrates that there is an interaction between the treatment received and the period it was given in. For example the washout period may not have been long enough to remove the effects of the first ginseng treatment leaving a carry-over effect on to the subsequent placebo treatment. The effect of ginseng is therefore examined in the first period only during which period effects are unlikely to manifest. It is equivalent to a matched group one period trial in which the ginseng group is compared to a placebo group of the same size. The results in all cases show highly significant improvements in performance (Table 3).

C. Tests of Mood, Well Being and General Health

The scores on the questionnaires examining mood, general health and well being show small and insignificant improvements in mood and satisfaction with life in both the tests. These questionnaires were only given to the subjects at the end of the treatment periods. An examination of the difference between the groups shows that period effects exist but are not significant in the case of the General Health Questionnaire, and are significant in the case of the Life Satisfaction Index.

Table 3. Psychophysical reactivity: effects of ginseng in first period only.

Parameter	Ginseng mean	Placebo mean	Difference
Tapping rate (taps)	7.76	-2.18	9.94
* Visual reaction time (secs)	-26.53	-4.64	-21.89
* Audiotry reaction time (secs)	-10.41	-1.15	-9.26
* Disjunctive reaction time (secs)	-10.99	-4.99	-6.00

* Note: A negative result in these tests indicates that the test was completed in less time i.e. is an improvement in performance.

The analogue scales were filled out by the subjects every day. There was a mixed result (Table 1). The subjects regarded themselves as more alert, and they had more energy, however they were less happy. They slept a bit less, and there was virtually no difference in their waking ability. Period effects occurred in all the subjects, and in some cases were greater than the effects of ginseng.

Several subjects described significant improvements in their feelings of well being, general symptomatology and particularly in removal of depression. There were clearly more reports of this kind in the ginseng treatment periods than the placebo treatment periods. For example on subject described how he felt much better than he could remember for a long time, while in another case the housekeeper of one male subject complained to the nurse that the subject had begun to make sexual advances to her, which had not happened during her 15 years of service.

CONCLUSION

Asiatic Ginseng, long regarded as a potent restorative especially for old people with declining anabolic and metabolic function, is here tested with 49 elderly people. The doses used were small, smaller than that recommended in traditional practice, but equivalent to that recommended by Western suppliers of ginseng preparations. The parameters were chosen so as to assess mental function, psychological co-ordination and well-being, especially in the elderly. The results can be summarised as follows:

- a) Ginseng slightly reduced performance at tests of memory and improved it at tests of the speed of general responses (letter copying).
- b) There were significant changes in performance solely because of participation in the trial, irrespective of the treatment taken. These tended to overshadow specific treatment effects, particularly in the tests of cognitive function, mood and general well being.
- c) Ginseng dramatically improved speed of

performance of tests of reaction time and decision making.

- d) Ginseng produced a small improvement in mood and general well-being. Analogue scales showed that the subjects felt slightly more alert and energetic during the trial, but also less happy and they slept slightly worse.

It may be that ginseng is effective at improving psychophysical reactions in the senile, but not at affecting cognitive or mental function. However this is unlikely as reaction times are known to be limited in old people by central cognitive abilities as much as by neuromuscular mechanisms. Furthermore previous evidence indicates that ginseng acts on central mechanisms of learning and memory more than on movement and reflexes.¹³

It is more likely that ginseng is generally effective at improving mental function but it is much harder to prove this from cognitive human tests than the tests using reflexes and reaction. For the latter are more exact and objective and in practice show less variation, while the cognitive tests are highly subjective and variable.

It is much more difficult to obtain clear statistically significant results in clinical trials

measuring performance than those measuring cure of defined symptoms, and even more difficult, due to variability, in geriatric individuals. For example Ostfield reviewed 285 publications, including 120 human studies covering some 100,000 patients in the case of the systematic use of procaine in the elderly, and found the evidence for its effectiveness still inconclusive.¹⁴ Lehmann and Ban, in a review of stimulants and anabolic substances in psychogeriatrics, write that "Pentylentetrazol, the most thoroughly investigated drug in this category, has only produced positive results in less than a third of the controlled trials. Most of the other well established stimulant and anabolic drugs have given even more ambiguous results."¹⁵

Tests of cognitive function, most of which were designed to detect either psychiatric illness, or advanced senile dementia, are subject to, and confused by subjective levels of motivation and interest, temporary disturbances, physical health, the competence and consistency of the test administrator and other factors. This makes it very difficult to obtain clear results, especially when looking for differences between drug treatment effects as opposed to their more usual role in differentiating demented from the normal. It is therefore not unreasonable to place more reliance on the more objective psychophysical tests. It is interesting in this respect that the most physical and active among the cognitive tests, number copying, also gave consistently positive results with ginseng, while the tests of memory were uncertain or negative.

The assessment of mood is most subjective and in this study, as in similar studies, the results are highly variable. However both questionnaires indicated small improvements. The analogue scales indicated more energy but less sleep. It is interesting that ginseng is regarded as stimulatory and is sometimes used as a stimulant.⁴ Indeed one of the side effects arising from excessive use of ginseng is insomnia.¹⁶ Therefore the reduction in sleep in this study may be a result of ginseng's stimulatory effects.

Noticeable benefits from geriatric psychopharmacological agents usually only arise after

Table 4. Mood and well being scales effects of ginseng versus placebo and period effects.

Parameter	Ginseng effect Group I	Ginseng effect Group II	Combined ginseng effect (d _A +d _B)/2	Difference between Groups
General health questionnaire	2.2	-1.16	0.52	1.68
Life satisfaction index	1.8	2.11	0.16	-1.95
Analogue scales:				
Alertness	-0.5	2.38	0.94	-1.44
Happiness	-0.87	-0.67	-0.77	-0.1
Energy	1.66	2.9	2.28	-0.62
Sleep quality	-1.61	-0.33	-0.97	-0.64
Waking fresh	-1.34	1.0	-0.17	-1.17

several weeks of administration at an appropriate dose. In this trial ginseng was given for only ten days in order to reduce time-based variation. However in retrospect it would have been advisable to administer ginseng, at a higher dosage, for much longer in order to show up cognitive effects.

A survey of the individual subjects' test performances shows that there are a subgroup of individuals in the trial for whom ginseng has made a considerable difference. These individuals also remarked how much better they felt. However their individual scores are swallowed in the extensive variation. One might suggest that as tradition asserts, the effectiveness of ginseng and other adjustive or restorative substances, is critically related to the constitution and health status of the individual.⁴ For example *Panax ginseng* might have no effect on nervous, extravert and active individuals who would be advised to take a less stimulating restorative, such as *Panax quinquefolium*. This individuality in effectiveness is supported by laboratory evidence that links ginseng's triterpenoid active principles with regulatory adjustments in physiological parameters such as blood sugar or corticosteroid levels.^{17,18} These physiological processes are altered by ginseng only when abnormally high or low, such as in stress, but ginseng has no absolute effect on the parameter when it is within 'normal' limits.¹⁹ There is evidence from this trial too that there is a subpopulation of individuals who are affected by ginseng and others who are not. Further study is needed to establish the optimum requirements for ginseng effectiveness.

This study is the first controlled clinical trial on the effect of ginseng on geriatric function. It clearly demonstrates for that even after only ten days administration ginseng is able to improve certain aspects of geriatric function - in particular psychophysical speed, reaction and coordination. This could be of considerable interest because defects in speed, reaction and registration are key aspects of the decline in function in the aged. Indeed they may be responsible for some of the observed cognitive deterioration. This trial has confirmed earlier suggestions of a geriatric effect

of ginseng. Further work on a larger scale is justified to extend this study, particularly because ginseng would be a safer alternative to some currently used geropsychopharmacological agents, most of which have not given unequivocal results in clinical trials.²⁰

I.P. Lee: I'd like to ask you about the statistical approach to your data analysis. You treated the subject with placebo then ginseng, and placebo followed by ginseng. Was this analysis done on the individual basis or as a group.

Fulder: It was not done on the basis of individual because when you are doing a cross-over trial, you are comparing an individual to himself. An individual takes drug and then he takes placebo. When you compare drug versus placebo, you are comparing a person to himself. So we calculated ginseng effect against baseline and placebo against baseline, then drug versus placebo. On that basis we did statistics, so it's a group mean we used.

Chong: Could I ask you a few questions about the population that you studied? You had 50 elderly patients. What was the mean age or the range of the age of the patients that you looked at?

Fulder: They were about sixty. We didn't make any upper limit.

Chong: If there was no upper limit, it was a wide range, Is that right?

Fulder: Yes, they were about sixty.

Chong: Were they all half males and half females?

Fulder: More or less half males and half females.

Chong: The dose that was given seems to me rather high. Do I take it then for geriatric population older than sixty years of age - giving 2gm of ginseng? Do you consider 2gm of ginseng a high dose?

Fulder: No, we got a one and half grams of ginseng. I consider it a very low dose. We should have used more.

Chong: If you consider it a low dose, would you like to recommend about six tablets a day?

Fulder: In a trial of this kind, I would use 2 or 3 grams of ginseng a day. Because I think that you trying to pick up an effect which is subtle and you need a little bit more doses that we used, not much more but a little more.

Chong: Were these patients on any other drugs?

Fulder: They were on some drugs. But we eliminated categories of drugs which we felt were incompatible with the trials, such as hormones or chemotherapy.

Chong: Were they on any sedative drugs or tranquilizers?

Fulder: No.

Chong: Did you ever notice or did the nurses record any side effect — like an increase in blood pressure on the patients during that trial period?

Fulder: We tested blood pressure and we did medical testing as well which I didn't show, but there was no change in blood pressure either down or up during the course of the trial. No side effect was observed except one patient had diarrhea, but she continued with the trial. There was only one side effect of very minor.

Chong: What was the psychophysical testing method you used?

Fulder: We used a tapping meter, which is a box, looks a bit like this one and it has a button.

It requires you to press the button as fast as you can in a given time. And the reaction timer is a standard geriatric instrument to measure the loss of reaction. It's mostly related to the peripheral nervous system but also to central nervous system influence. It also requires the patients to press the button when a light appears or when a sound appears. In disjunctive test, there will be a light and no sound. Therefore, the patients have to know when not to press the button and when to press the button.

이중 맹검법을 이용한 홍삼의 노인병 치료에 대한 임상연구

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인삼이 노령자의 피로 및 쇠약 치료효과에 미치는 영향을 연구하기 위해 런던의 성프란시스병원과 지방의 일반 개업 병원으로부터 50명의 노인들을 모집하였다. 매일 2g의 홍삼 분말을 이중맹검법에 의하여 10일간 투약하였으며, 위약과 홍삼 분말의 투여는 3주간의 간격을 두고 각기 투여하였다. 간호원이 10가지 정신측정 종합테스트와 심리측정 테스트를 하였고, 기분상태 및 일반적인 건강평가를 설문지로 측정하였다. 이 측정을 홍삼 및 위약의 투여기간을 전후하여 실시하였다. 즉, 각각의 테스트를 모두 4번 실시하였다.

심리측정 테스트와 정신측정 종합테스트 결과 홍삼의 투여는 위약과는 달리, 미약하나마 일관성있는 증가를 가져왔다. 그러나 기분상태 및 일반적인 건강 평가는 별 변화가 없었다.

결론적으로 인삼은 강장효과를 갖는다 할 수 있다. 노인병 치료를 평가함에 있어 시도방법 및 기간 등에 의하여 약효의 평가가 모호해지는 경우가 종종 있다. 보다 적절한 임상시험법에 대하여 토론하고자 한다.

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