Experimental Section

Gerontology *25:* 125–131 (1979)

The Effect of Ginseng on Lifespan and Stress Responses in Mice

A.H. Bittles, S.J. Fulder, E.C. Grant and M.R. Nicholls

Department of Human Biology, Chelsea College, University of London, London

Key Words. Ginseng · Lifespan · Mouse · Open field · Stress responses

Abstract. It has been suggested that ginseng can increase long-term resistance to stress and disease and therefore affect the lifespan. We set out to investigate this idea by testing whether the continuous administration of ginseng could affect the lifespan of mice and/or their behavioural response to stress.

270 mice of strain LACa were divided into three groups: one group which was given ginseng from 8 weeks of age, a second group which was given ginseng from 52 weeks of age and an untreated control group. The mice were generally healthy. Their weights remained stable throughout their lifespan and were not altered by ginseng. Ginseng administration did not significantly alter the lifespan. However, ginseng did cause an exaggeration of the behavioural responses to mild stress. This effect was noticeable soon after ginseng administration and subsequently was maintained.

Panax ginseng is currently one of the most widely used plant products in Oriental medicine (1). A wide range of pharmacological properties has been ascribed to the crude ginseng extract (2–4). The most distinctive are antifatigue properties (5–7), a transient and mild regulatory action on carbohydrate metabolism and blood pressure (4, 8), a pronounced increase in the survival rate of animals subjected to a variety of physical and biological stresses (9) and an increase in adrenal cortical capacity and output in response to stress (5, 10). Hence ginseng has been proposed as an agent for geriatric usage (11) and has been incorporated into certain 'geriatric preparations' widely distributed in many Western European countries (12).

With this in mind and in the light of the recent isolation of the active principles of the root, a unique group of dammarene-type triterpenoidal glycosides which *Sanada et al.* (13), *Iida et al.* (14) and *Nagai et al.* (15) termed ginsenosides, it was considered important to assess the effect of the long-term administration of ginseng on the lifespan of a strain of laboratory animals. At the same time, the influence of ginseng on the behaviour of the animals, the

mouse strain LACa, was examined at intermittent intervals throughout their lifespan, with special emphasis on the behavioural responses to mild stress.

Methods

270 LACa mice born on 10th July, 1974, were kept 5 to a cage, the males and females being separated. Where possible the mice were caged together with their litter-mates to reduce the chances of fighting. The mice were divided into 3 groups of 90 animals, each group containing equal numbers of males and females. One group was given ginseng extract from 8 weeks of age until the end of their lifespan, the second was given ginseng from 52 weeks of age onwards while the third group was not treated. The mice were fed and watered *ad libitum*. Mice with ectoparasite infestation were dipped using 'Tetnasol' (ICI Ltd.) which proved very effective. Any animals with large tumours and males with severe damage resulting from fighting, were killed. These totalled 7 animals. The mice were weighed each week and their age at death recorded.

Ginseng was given in the form of a freeze-dried aqueous extract of cultivated white Korean roots of *Panax ginseng*, C.A. Meyer. The extract (G1) was donated by Pharmaton SA of Lugano. The extract was dissolved in drinking water such that each mouse would be expected to have a dose of 8 mg extract/kg body weight/day which corresponds to 40 mg of whole root/kg body weight/day. This dose has been demonstrated to have a noticeable antifatigue action in mouse stamina tests (16), and is roughly comparable to the recommended dose for man.

10 male and 10 female mice from each of the experimental groups, ginseng early, ginseng late and control, were tested for their behavioural response to a situation of mild stress at various stages of their lives. The mice were stressed by placing them individually on a circular, open field under bright illumination for 5 min, a procedure which is recognised to induce a fear reaction and to give quantifiable behaviour data (17). For 10 sec at the end of each minute of the 5 min an electric bell was rung. This bell was placed directly beneath the open field which consisted of a circular piece of glass, 61 cm in diameter, backed with a piece of paper marked into segments of equal area. During the 5-min period, a record was made of ambulation in terms of the number of crossings from one section to another, the amount of time spent crouching, the frequency of defaecation, the frequency of urination and the time spent in grooming.

A cross-over was recorded when both front paws of the animal moved from one section into another. This gives a measure of the amount of movement the animal performs, and is a recognised count of ambulation. The ambulatory behaviour normally occurs as fairly rapid movement across the surface of the open field. This movement is similar to that shown by a mouse in a new environment and is presumably part of the initial exploration of that environment. Crouching was recorded when the animal was still, with the body flattened towards the ground. In the situation studied it is clear that this is a flight response, the eyes remain wide open, the body is not relaxed and occasional muscle tremors and twitches can be seen. Resting behaviour was not seen during these 5-min periods. Grooming, defaecation and urination were occasionally observed.

Results

The mean weights of the mice in each of the three groups is shown in figure 1. After a rapid increase in growth, the weights remained virtually constant until the end of the lifespan. The weights of the treated and control groups were not significantly different.

The survival curves of all the groups are shown in figure 2. The rectangular shape of the curves are typical for animal populations that survive until old age. There were few early deaths and the plateau phase lasted for much of the lifespan. The survival curves show that the pattern of deaths was substantially similar in the three groups.

The mean, median and maximum lifespans are shown in table I. A two-way analysis of variance was carried out with treatment as one factor and sex as the other. This showed that as expected, the females lived significantly longer than the males ($p < 0.01$). There was no signifi-

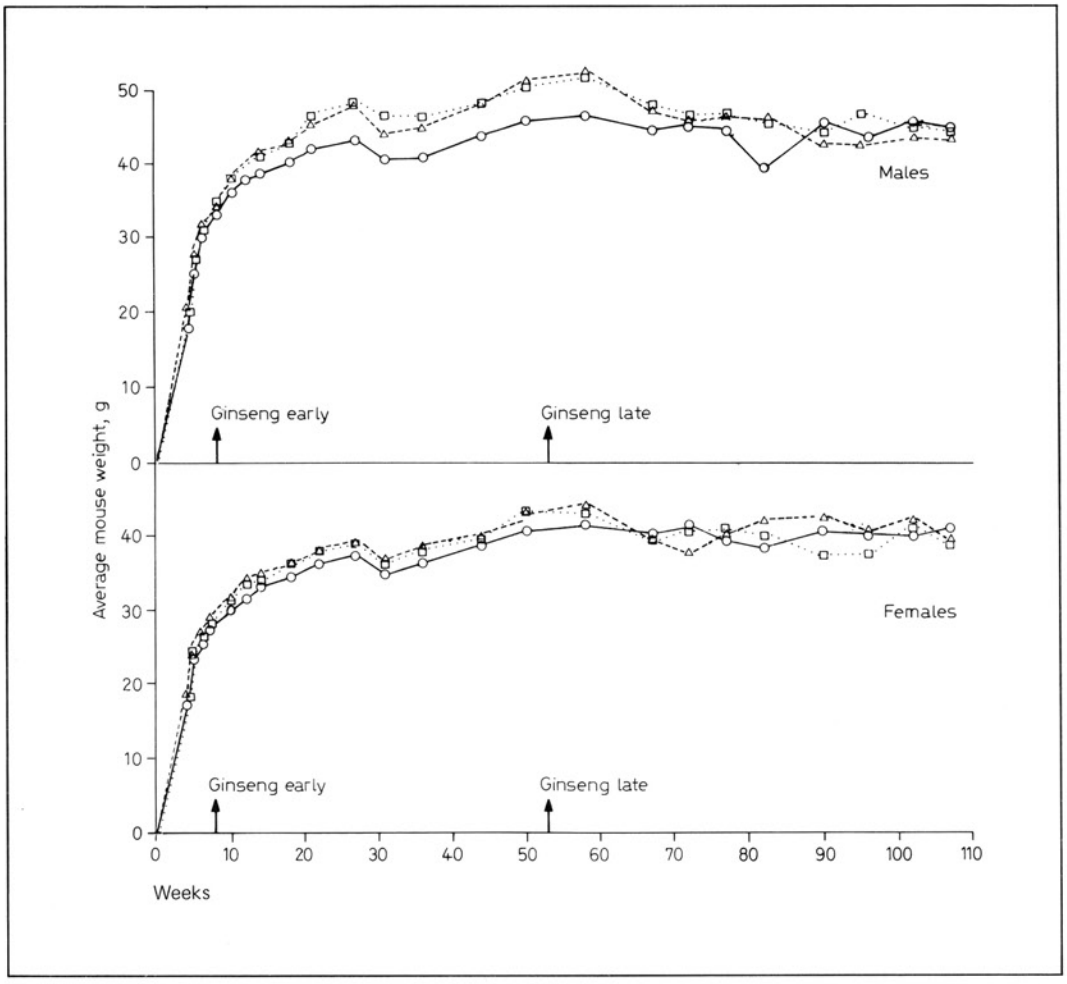


Fig. 1. Weight of LACa mice during their lifespan. Each point represents the average weight of each group of mice, measured individually. ○—○ = Control group, no ginseng; △---△ = ginseng at 40 mg/kg/day given at 8 weeks of age and thereafter; □·····□ = ginseng at 40 mg/kg/day given at 52 weeks of age and thereafter.

cant difference between the lifespans of the treated groups of either sex and the control groups and clearly the long-term administration of ginseng did not significantly affect the overall lifespans.

The behavioural responses to stress are presented in figure 3a, b. The animals receiving ginseng from an early age were different in their behavioural responses from those of the control groups and the differences persisted throughout their lifespans. They crouched for a much longer period of time and showed less ambulatory movement. These differences affected both males and females. Prior to its administration, the group given ginseng from 52 weeks onward showed behaviour patterns similar to those of the control animals; however, from the first testing period after ginseng was given, their

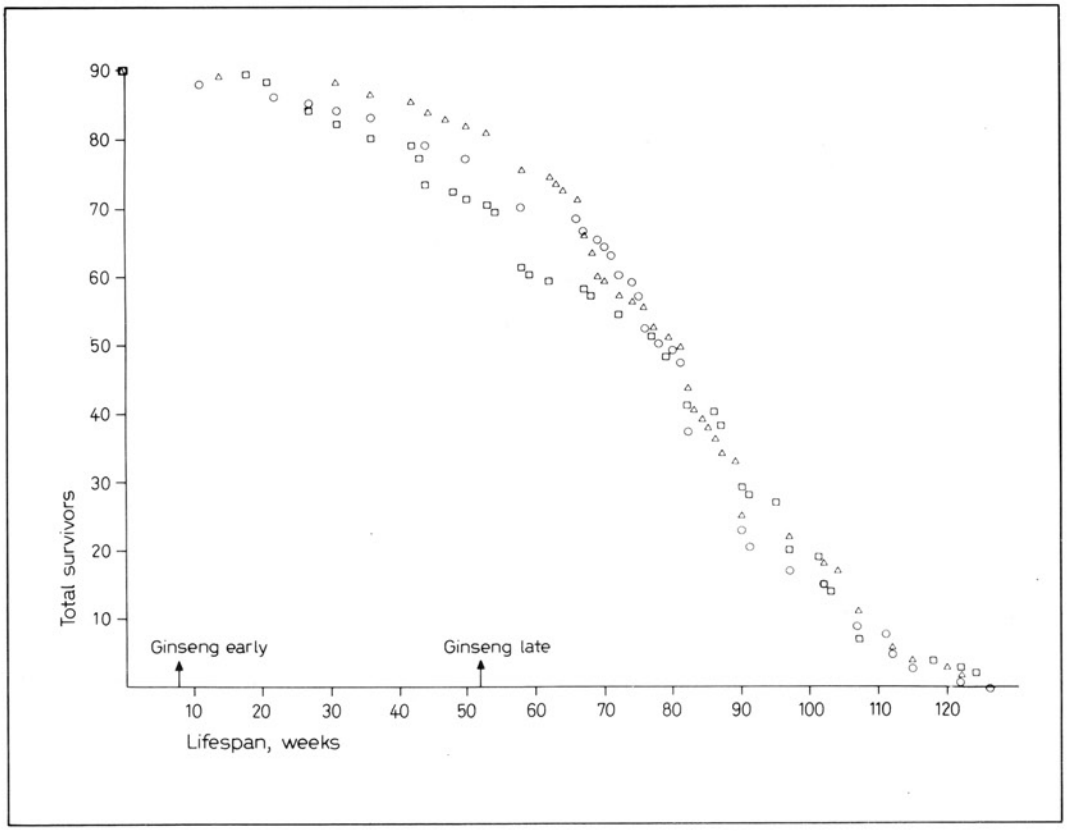
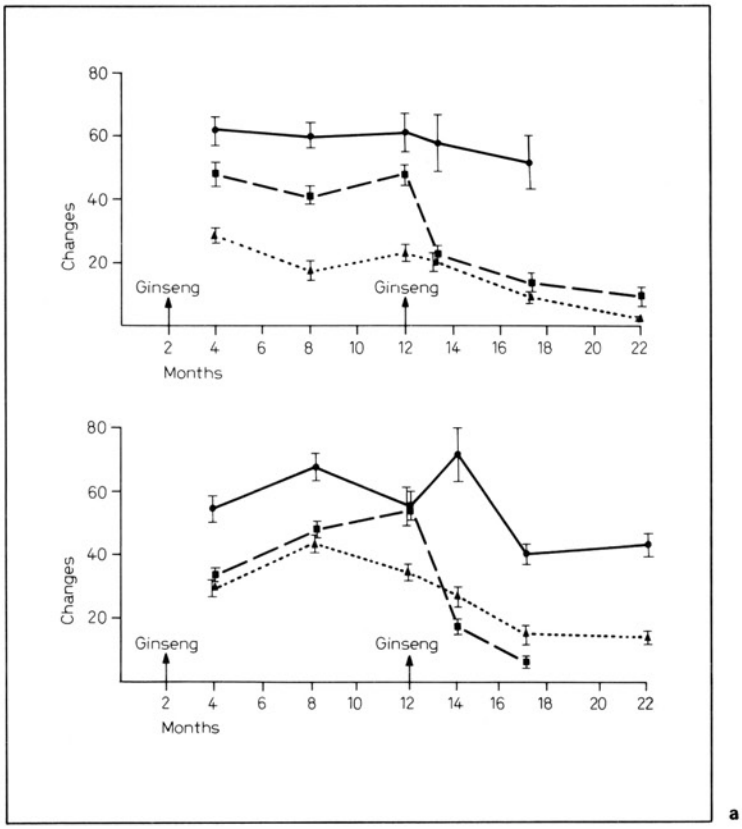


Fig. 2. Survival curve of 270 LACa mice from birth. ○ = Control group, no ginseng; △ = ginseng at 40 mg/kg/day given at 8 weeks of age and thereafter; □ = ginseng at 40 mg/kg/day given at 52 weeks of age and thereafter.

Table I. Lifespan: mean median and maximum values (weeks) in mice

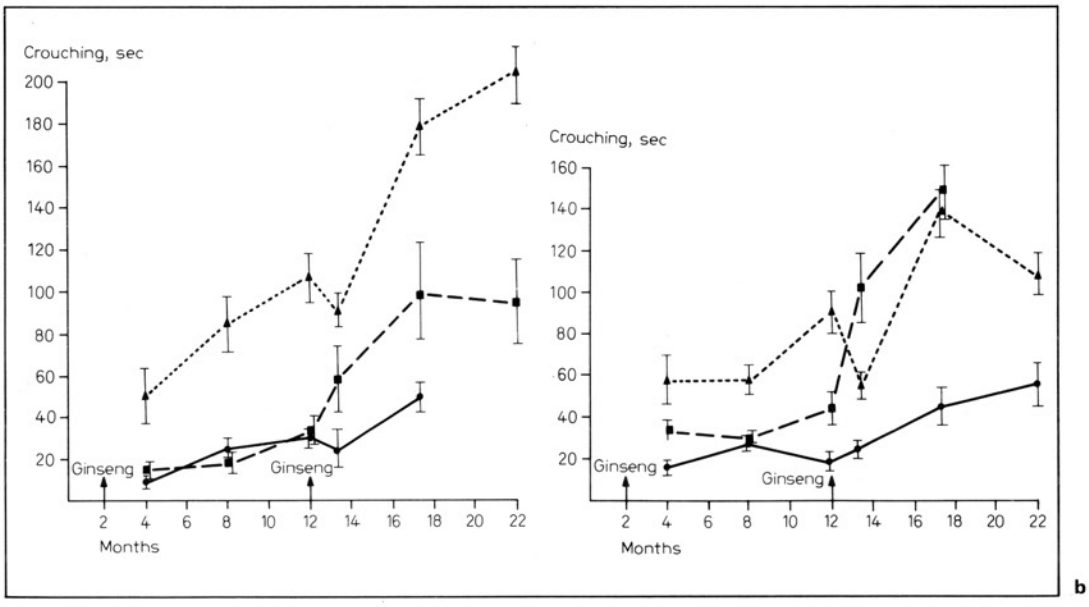
	Treatment	Mean	± SD	Median	Maximum
Males	Control	75.2	23.4	80.25	112
	Ginseng early	74.0	18.9	70.5	112
	Ginseng late	73.4	26.2	74.5	124
Females	Control	82.3	25.9	80.5	124
	Ginseng early	89.6	24.6	89.0	127
	Ginseng late	80.0	28.6	84.0	141

Lifespan parameters represented by the mean and standard deviation of the mean, median and maximum values



a

Fig. 3. **a** Ambulation in the open field. Each point represents the average number of changes for each group of mice tested individually. Top = males; bottom = females. **b** Time spent crouching in the open field. Each point represents the average time in seconds for each group of mice tested individually. Top = males; bottom = females. ●—● = Control group, no ginseng; ▲·····▲ = ginseng at 40 mg/kg/day given at 8 weeks of age and thereafter; ■– – –■ = ginseng at 40 mg/kg/day given at 52 weeks of age and thereafter. Bars through each point represent standard error of mean. This is shown in preference to standard deviation because of small numbers (maximum 10).



b

behaviour pattern shifted to match that of the earlier-treated group. The grooming, defaecation and urination counts were highly variable and showed no consistent differences between the various groups.

Discussion

The mice were healthy and the rectangular survival curve indicated that the population was suitable for a study of lifespan manipulation. Ginseng was given to the two groups from 8 and 52 weeks of age, respectively, and thereafter throughout their lifespan. Administered in this way, ginseng did not cause any adverse reaction as judged by loss of coat condition, increased mortality or weight change. Other observations have indicated that ginseng may act anabolically (18), however, in the present study a lower level of dosage was employed.

Ginseng did not significantly alter the mean, median or maximum lifespans of the treated groups. By comparison a Russian study did demonstrate an increase in the lifespan of white rats given *Panax ginseng* extract (19), however, higher doses had been used and in addition there were so few animals that a statistical analysis was impossible.

There was a minor depression in mortality for a period of approximately 20 weeks after ginseng was administered to each of the test groups. This did not make a statistically significant impact on the lifespans but it cannot be ruled out that ginseng given for a brief period, or intermittently throughout the lifespan could have an augmenting effect on vitality and longevity by comparison with continual administration.

A clear alteration in the behaviour of mice faced with conditions of mild stress was noticed in those groups of animals consuming ginseng. The change began when ginseng was first administered and persisted throughout its continued administration. The animals crouched for a longer time and showed much less exploratory movement. These two major responses are incompatible and in a finite time period must co-vary inversely. In biological terms exploration and crouching or flight are both appropriate responses in a novel situation (20). The balance between these two depends both on the external situation and on species-specific and individual differences in responsiveness (20). Increasing environmental complexity and 'strangeness' and/or increased levels of arousal or responsiveness tend to increase the levels of flight response. Although not specifically tested for, there was no evidence of a general increase in flight behaviour in the treated animals and it could be postulated that the observed behavioural effect of ginseng was due to an increased responsiveness of the animals to external stress.

Stress is controlled by the adrenal glands through the secretion of adrenaline and glucocorticoid hormones. Evidence has been produced suggesting an effect of ginseng on the adrenal cortex and the stress response. *Brekhman* (5) has demonstrated an increase in adrenal weight and reserve capacity in ginseng-treated mice, as measured by both vitamin C and cholesterol content and *Petkov and Staneva-Stoicheva* (10) have shown that ginseng can prevent the depletion of adrenal capacity by repeated stress. Further, ginseng has been shown to increase the level of corticosteroids in the serum and of pituitary adrenocorticotropic hormone (21). The reported prophylactic effect of ginseng against stress and disease may therefore be due to the amplification of endocrine responses. It has been suggested that the active principle functions as a steroid analogue in stimulating hormone production along the hypothalamic-pituitary-adrenal axis (22, 23).

Our results are compatible with this model, and would seem to indicate that further work on the role of ginseng glycosides in the endocrine response to stress would be fruitful.

References

1 Hsu, S.Y.: The genus *Panax* (ginseng) in Chinese medicine. Econ. Bot. *30:* 11–28 (1976).

2 Li, C.P. and Li, R.C.: Introductory note to ginseng. Am. J. Chin. Med. *1:* 249–261 (1973).

3 Court, W.E.: Ginseng. A Chinese folk medicine of direct interest. Pharm. J. *214:* 180–181 (1975).

4 Karzel, K.: Pharmacological aspects of ginseng. Proc. Int. Conf. Gerontol., Lugano 1974, pp. 49–57.

5 Brekhman, I.I.: *Panax ginseng.* Med. Sci. Serv. *4:* 17–26 (1967).

6 Popov, I.M. and Goldwag, W.J.: A review of the properties and clinical effects of ginseng. Am. J. Chin. Med. *1:* 263–270 (1973).

7 Takagi, K.; Saito, H., and Tsuchiya, M.: Effect of *Panax ginseng* root on spontaneous movement and exercise in mice. Jap. J. Pharmac. *24:* 41–48 (1974).

8 Wood, W.B.; Roh, B.L., and White, R.P.: Cardio vascular actions of *Panax ginseng* in dogs. Jap. J. Pharmac. *14:* 284–294 (1964).

9 Brekhman, I.I. and Dardymov, I.V.: New substances of plant origin which increase non-specific resistance. A. Rev. Pharmac. *9:* 419–430 (1969).

10 Petkov, V. and Staneva-Stoicheva, D.: The effect of an extract of ginseng *(Panax ginseng)* on the function of the adrenal cortex; in Chen and Mukerji, Pharmacology of oriental plants, pp. 39–50 (Pergamon Press, Oxford 1965).

11 Luth, P.: A new preparation from the therapy of prophylaxis of senile and degenerative changes. Ars Med., Wien *55:* 756–758 (1964).

12 Sterner, W. and Kirchdorfer, A.M.: Comparative work load tests on mice with a standardised ginseng extract and a ginseng containing geriatric pharmaceutical preparation. Z. Gerontol. *3:* 307–312 (1970).

13 Sanada, S.; Kondo, N.; Shoji, J.; Tanaka, O., and Shibata, S.: Studies on the saponins of ginseng. I. Structure of ginsenocides R0, RB1, RB2, RC, RD. Chem. pharm. Bull., Tokyo *22:* 421–428 (1974).

14 Iida, Y.; Tanaka, O., and Shibata, S.: Studies on saponins of ginseng. The structure of ginsenocides RGl. Tetrahedron Lett. *52:* 5449–5453 (1968).

15 Nagai, M.; Tanaka, O., and Shibata, S.: Chemical studies of the oriental plant drugs XXIV. Structure of ginsenocide RGl. A neutral saponin of ginseng root. Tetrahedron Lett. *27:* 881–889 (1971).

16 Rueckert, K.H.: A new study that proves the great effectiveness of a special extract made from 1st class Korean ginseng roots. Proc. Int. Ginseng Symp., Seoul 1974, pp. 59–64.

17 Broadhurst, P.L.: in Eysenck, Experiments in personality, vol. 1, pp. 1–702 (Routledge & Kegan Paul, London 1960).

18 Kim, J.Y.: Influence of Panax ginseng on the body weights of rats. Korean J. Physiol. *4:* 1–4 (1970).

19 Golotin, V.G.; Berdyshev, G.D., and Brekhman, I.I.: in Conf. USSR Acad. Med. Sci., Scient. Med. Soc. Gerontologists and Geriatricians of the USSR and Ukraine, pp. 94–96 (1968).

20 Berlyne, D.E.: Conflict, arousal and curiosity (McGraw-Hill, New York 1960).

21 Kim, C.; Kim, C.C.; Kim, M.S.; Hu, C.Y., and Lee, J.S.: Influence of ginseng on the stress mechanism. Lloydia *33:* 43–48 (1970).

22 Fulder, S.J.: Ginseng, useless root or subtle medicine? New Scient. *74:* 138–139 (1977).

23 Fulder, S.J.: The growth of cultured human fibroblasts treated with hydrocortisone and extracts of thy medicinal plant *Panax ginseng.* Expl Gerontol. *12:* 125–131 (1977).

Received: February 26, 1978
Accepted: May 5, 1978

Dr. S.J. Fulder, Department of Human Biology,
Chelsea College, University of London,
London SW3 6LX (England)