

An Experimental Evaluation of Anti-stress Effects of Geriforte (An Ayurvedic Drug)

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INTRODUCTION

Recently some plant substances (crude extracts) have been described to induce a state of non-specifically increased resistance (SNIR) in experimental animals and man (Brekhman, 1967; Brekhman and Dordymov, 1969). These workers explored and tested several mixtures of plant medicines used throughout Siberia as folklore medicine. These medicinal mixtures are used for a variety of chronic ailments and as tonics to promote the health of the local people. The plant *Panax ginseng* has gained great prominence in this field. The crude extract as well as its pure glycoside (Panaxoside) are now widely employed clinically for premature ageing and as a revitalizer (Popov *et al.*, 1975). It has been used in cardiovascular and central nervous system (CNS) diseases (Gianoli, 1975). It has an anabolic effect, increases immune response and improves physical efficiency in athletes (Brekhman, 1975).

The theoretical basis for the existence of a new group of medicinal substances was laid down by Lazarev (1958) who phrased the concept of "A state of non-specifically increased resistance (SNIR)". The medicinal substances causing SNIR were variously named as "Adaptogens" or "Athenktotropics" (Eger, 1961). In general "Adaptogens" means those drugs adapting or causing adaptive reaction and they appear to increase the general defence power of the organism. Corroborative and tonic plants are among the most ancient medicinal remedies of the folk medicine in different parts of the world. Ancient medical literature on Ayurveda gives a vivid and comprehensive description of this group of plant medicines which are tonic, prevent disease and postpone ageing. "Geriforte", a combination of several plant ingredients is claimed to be a restorative tonic of old age and is being used in India for this purpose. The reports on the biochemical changes, and various clinical benefits of this drug have become available recently (Lobo *et al.*, 1975; and Vagh *et al.*, 1975), however, this drug has never been evaluated for its "Adaptogenic" properties. The present study was, therefore, undertaken to explore and evaluate the "Adaptogenic" activity in Geriforte.

MATERIALS AND METHODS

Geriforte powder was used throughout this study. The constituents and their amounts in 500 mg of the powder are as follows:

Chyavanprash concentrate	100 mg	Shilajeet	20.0 mg
Exts. <i>Capparis spinosa</i>	13.8 mg	<i>Terminalia chebula</i>	15.0 mg
<i>Cichorium intybus</i>	13.8 mg	<i>Mucuna pruriens</i>	10.0 mg
<i>Solanum nigrum</i>	6.4 mg	<i>Myristica fragrans</i>	10.0 mg
<i>Cassia occidentalis</i>	3.2 mg	<i>Piper longum</i>	10.0 mg
<i>Terminalia arjuna</i>	6.4 mg	Mace	10.0 mg
<i>Achillea millefolium</i>	3.2 mg	<i>Eugenia caryophyllata</i>	5.0 mg
<i>Tamarix gallica</i>	3.2 mg	<i>Elettaria cardamomum</i>	5.0 mg
Mandur bhasma	5.0 mg	<i>Carum copticum</i>	5.0 mg
Saffron	5.0 mg	<i>Curcuma longa</i>	5.0 mg
Amber	2.0 mg	Exts. <i>Berberis aristata</i>	10.0 mg
Makardhwaj	10.0 mg	<i>Adhatoda vasica</i>	10.0 mg
<i>Asparagus adscendens</i>	10.0 mg	<i>Eclipta alba</i>	10.0 mg
<i>Caesalpinia digyna</i>	10.0 mg	<i>Celastrus paniculatus</i>	5.0 mg
<i>Asparagus racemosus</i>	20.0 mg	<i>Argyreia speciosa</i>	10.0 mg
<i>Withania somnifera</i>	30.0 mg	Abhrak bhasma	10.0 mg
<i>Glycyrrhiza glabra</i>	20.0 mg	Loh Bhasma	5.0 mg
<i>Centella asiatica</i>	20.0 mg	Jasad bhasma	10.0 mg

Processed in *Phyllanthus emblica*, *Terminalia chebula*, *Eclipta alba*, *Asparagus racemosus*, *Allium cepa*, *Allium sativum*, *Phyllanthus niruri*, *Boerhaavia diffusa*, *Tinospora cordifolia*, *Berberis aristata*, *Raphanus sativus*, *Tribulus terrestris* and Dashamoola.

All the experiments were carried out in about 300 albino mice and rats.

Method		Animals
1.	Swimming endurance	Mice
2.	Effect on adrenals after 5 hr swimming	Mice
3.	Effect on hexobarbital narcosis	Mice
4.	Antiulcerogenic activity	Chemically induced
		Restraint ulcer
5.	Protective effect against CCl ₄ -induced hepatotoxicity	Rats
6.	Milk-induced leucocytosis	Mice
7.	Anabolic effect (body weight, temp., spontaneous motor activity)	Rats
8.	Acute LD ₅₀	Mice

The results were statistically analysed.

1. *Physical endurance test: Effect on swimming performance*

Mice were used in different groups. Geriforte in doses of 50, 100 and 150 mg/kg body weight was administered orally for 3 days to the swimming test and 1 hr before on the test day. The mice were allowed to swim till exhaustion (swimming time/survival time) in porcelain tanks filled with water kept at a temperature of 28-29°C. The end point taken was death due to drowning. Swimming time for each animal was noted.

2. *Effect on weight, cortisol and ascorbic acid content of adrenal glands (5 hours swimming)*
Groups of 10 mice were used. The first group received physiological saline only (normal, non-swimmer group). The second group was exposed to stress (swimming) and received physiological saline (control group). Other groups were treated with different doses of Geriforte administered orally 1 hour before the swimming and were sacrificed after the test. The adrenals were decapsulated, weighed and ascorbic acid as well as the cortisol contents of the adrenal glands were determined.
3. *Effect on hexobarbital sleeping time:*
This was tested in mice, each group consisted of 20 animals. Hexobarbital 40 mg/kg i.p. was used to produce the hypnotic response. Duration of sleeping time was judged by the presence and loss of righting reflex. Geriforte in graded doses was given to different groups of animals orally 1 hour before administration of hexobarbital.
4. *Antiulcer effect in rats:*
 - i. Restraint ulcers were induced in albino rats by tying the limbs for 2 hours at 4°C (Senay and Lavine, 1967).
 - ii. Chemical stress was induced by i.p. injection of 200 mg/kg i.p. aspirin (Djahanguiri, 1969).The ulcer index was calculated by the method of Alphin and Ward (1969).
5. *Protective effect against carbon tetrachloride (CCl₄) induced hepatotoxicity in rats:*
The method of Srinivasan *et al* (1968) was followed.
6. *Milk-induced leucocytosis in mice:*
Albino mice were divided into groups of 10 animals each. Leucocyte count was made in the blood samples collected from the tail vein of the mice. Effect of grade doses of Geriforte was observed on leucocytosis and the dose decreasing by 50% the leucocytes (PD₅₀) was calculated.
7. *Anabolic activity:*
Four groups of rats between the age group of 3-4 months were taken. All were kept on the same diet. The controls did not receive any drug; others were treated with different doses of Geriforte. Daily body weight by Triple Beam Balance, spontaneous motor activity by photoactometer and rectal temperature were recorded.
8. *Acute toxicity study*
Acute toxicity study was done by the method of Smith (1960) in albino mice.

RESULTS

Swimming endurance

The survival time of swimming mice increased with different doses of Geriforte as compared to control (non-drug treated). The results are summarised in Table 1. These findings were statistically significant.

Group	No. of animals	Drug	Dose (mg/kg p.o.)	Duration of swimming in min \pm SE	'p' value
I	20	Saline	0.25 ml	365 \pm 14	–
II	20	Geriforte	50	425 \pm 15	<0.01
III	20	Geriforte	100	500 \pm 21	<0.01
IV	20	Geriforte	150	590 \pm 18	<0.01

Effect on adrenal weight, ascorbic acid and cortisol contents

The results are summarised in Table 2. The adrenal weight after 5 hr swimming was significantly increased as compared to the non-swimmer group. Pre-treatment with Geriforte prevented the increase in adrenal weight significantly. Ascorbic acid and cortisol contents of adrenals after 5 hr swimming were markedly reduced. Geriforte prevented these changes significantly.

Group	No. of animals	Drug	Dose (mg/kg p.o.)	Physical stress	Adrenal wt. (mg/100 g) body wt \pm SE	Adrenal ascorbic acid content (mg/100 g) \pm SE	Adrenal cortisol (mg/100 g) \pm SE
I	10	Saline	0.25 ml	None	12.5 \pm 1.1	271 \pm 15	2.4 \pm 0.06
II	10	Saline	0.25 ml	Swimming	16.8 \pm 1.3	137 \pm 9	1.2 \pm 0.05*
III	10	Geriforte	50	Swimming	12.8 \pm 0.9	223 \pm 18	2.05 \pm 0.07 [#]
IV	10	Geriforte	100	Swimming	11.8 \pm 0.06 [#]	225 \pm 13	2.30 \pm 0.06 [#]
V	10	Geriforte	150	Swimming	11.6 \pm 0.7 [#]	260 \pm 17	2.32 \pm 0.03 [#]

* $p < 0.001$ and [#] $p < 0.01$

Effect on hexobarbital sleeping time - Geriforte reduced the sleeping time significantly although in a large dose (Table 3).

Group	No. of animals	Drug	Dose (mg/kg p.o.)	Sleeping time in min \pm SE
I	20	Saline	0.25 ml	23.3 \pm 3.2
II	20	Geriforte	100	15.2 \pm 2.4*

* $p < 0.01$

Anti-ulcer effect – Geriforte in doses of 100 mg/kg orally, prevented both restraint and chemically induced ulcers, significantly ($p < 0.001$). Results are summarised in Tables 4 and 5.

Protective effect on CCl₄-induced hepatotoxicity in rats: Pretreatment with Geriforte prevented the increase of liver weight and volume induced by CCl₄ (Table 6).

Group	No. of animals	Drug	Dose (mg/kg p.o.)	% ulcer	Mean ulcer index
I	20	Saline (Control)	0.5 ml	100	36
II	20	Geriforte	100	20*	5

* $p < 0.001$

Group	No. of animals	Drug	Dose (mg/kg p.o.)	% ulcer	Mean ulcer index
I	10	Saline (Control)	0.5 ml	90	36
II	10	Geriforte	100	30*	11

* $p < 0.001$

Group	No. of animals	Drug	Dose (g/kg p.o.)	Weight (g/100 g body wt) \pm SE	'p' value	Volume (ml/100 g body wt) \pm SE	'p' value	% mortality
I	10	Saline	0.5 ml	2.14 \pm 0.14	-	2.25 \pm 0.12	-	0
II	10	CCl ₄	2 ml	3.58 \pm 0.22	<0.001	4.2 \pm 0.01	<0.001	60
III	10	CCl ₄ + Geriforte	2 ml + 100 mg	2.21 \pm 0.24	<0.001	2.31 \pm 0.30	<0.001	20

Effect on milk-induced leucocytosis:

The dose of Geriforte producing 50% reduction in leucocyte count (PD₅₀) was 71.3 \pm 5.2 mg/kg orally.

Anabolic effect – The drug produces a gradual and constant increase in body weight of the treated groups as compared to non-drug treated group kept on the same diet. Spontaneous motor activity and body temperature were affected insignificantly.

LD₅₀ in mice – The approx. LD₅₀ of the drug was between 5 to 6 g per kg orally.

DISCUSSION

It is a well-known fact that stress of any nature produces a non-specific state in the organism i.e. the state of stress or “stress syndrome” which is characterised by adrenal hypertrophy, depletion of adrenal ascorbic acid and cortisol and a decrease in the size of lymphoid tissue (Selye, 1955). Any damaging or potentially damaging stimulus (stressor) besides, having its own specific effects, induces the secretion of adrenal corticosteroids and catecholamines, cardiovascular alterations and gastrointestinal lesions. The change observed in the stress syndrome have been explained on the basis of activation of hypothalamo-hypophyseal-adrenal axis (Selye, 1938). The corticoids, thus released, help animals in combating stressful situations. Stress has been suspected to be one of the mechanisms leading to disease under

certain circumstances (Selye, 1971). During the last decade, the Brekhman group of workers (1967, 1969) and recently several others (Sandberg, 1975; Rukert, 1975; Singh *et al.*, 1976, 1977) demonstrated that certain plant extracts and some of the glycosides obtained from these produce a state of non-specifically increased resistance (SNIR) in animals and human beings. These workers have also described the usefulness of such agents in a variety of diseases of cardiovascular and CNS origin and as preventives of ageing process (Gianoli, 1975 and Papov *et al.*, 1975). *Panax ginseng* has been of special importance in this respect.

The concept of “Adaptogens” as a separate group of medicinal substances was first developed by Lazarev (1958). However, later on in 1961 Eger named such substances as “Athenktotropic” in the Anglo-American medical literature.

Reactivity is the basic feature of the living system and ageing is closely related to changes in reactivity and to decrease of adaptation capacity resulting from a progressive decrease in self-regulatory mechanisms. It is possible to help the optimal running of the self-regulatory mechanisms. It is possible to help the optimal running of the self-regulatory and adaptive processes by pharmacological influences and thus stem the advance of ageing (Petkov, 1975). The recent cybernetic theory on ageing, indicates that the cause of ageing lies in changes of the fundamental biochemical process. Therefore, it is possible to minimise these changes with drugs.

Though the concept of adaptogenic property in drugs appears to be incredible from the pharmacological point, there is now ample proof that such substances do occur and they have opened a new vista in the field of therapeutic agents of modern medicine. Such a concept never existed in any system of medicine all over the world with the exception of “Ayurveda” which itself means a system of medicine which will enhance life with good health.

The usefulness of Geriforte and its various properties have been recently described by various workers. It is known to induce cellular regeneration, prevent arteriosclerosis, increase hormone utilisation, enhance protein and carbohydrate metabolism and produce reduction in serum lipid (Lobo *et al.*, 1975; Sheth, 1975; Sahgal and Sood, 1975). Besides, it has been proved useful clinically by producing a feeling of well-being, increasing mental activity, lessening fatigue, increasing appetite and sexual functions in the ageing (Vagh *et al.*, 1975). These multiple properties of the drug clearly indicated the possible presence of “Adaptogenic” properties in it. Therefore, a rational approach was made to evaluate its antistress properties. For this, various stressful situations were induced in animals. The prolongation of survival time and prevention of stress-induced changes in adrenals, prevention of stress-induced ulcers and milk-induced leucocytosis, indicate the anti-stress properties of Geriforte.

The present study clearly indicates that Geriforte increases the resistance of the organisms by inducing a state of non-specifically increased resistance (SNIR), irrespective of the nature of stress. As the drug prevents aspirin ulcers, it is less likely that it acts through hypothalamohypophyseal-adrenal axis. It may be having corticosteroid sparing property or may act on CNS cells, and block the alarm reaction of stress.

SUMMARY

Geriforte, a combination of several plant ingredients is being used in India as a restorative tonic in old age. In the present study, this Ayurvedic drug has been evaluated for anti-stress (“Adaptogenic”) activity by inducing various stressful situations in animals.

The survival time of swimming mice increased with different doses of Geriforte. The drug also prevented changes in adrenals (increase in weight and reduction of ascorbic acid and cortisol contents) induced by stress (5 hr swimming). Both restraint and chemically-induced ulcers were prevented by 100 mg/kg of Geriforte. Furthermore, pretreatment with Geriforte prevented the increase of liver weight and volume induced by carbon tetrachloride and also the milk-induced leucocytosis. Gradual and constant increase in body weight was observed in the rats taking the drug. However, no effect was observed on spontaneous motor activity and body temperature. It has some central nervous system stimulant activity as judged by the reduction of hexobarbital sleeping time. The LD₅₀ as determined in acute toxicity studies on mice was between 5-6 g/kg orally.

Prolongation of survival time, prevention of stress-induced changes in adrenals, restraint ulcers, liver toxicity, milk induced leucocytosis and the innocuous nature of the drug indicate the presence of anti-stress (“adaptogenic”) properties in Geriforte.

REFERENCES

1. Alphine, R.S. and Ward, J.W., An investigation of antihistaminic activity and gastric ulceration. *Europ. J. Pharmacol.* (1969): 6, 61.
2. Brekhman, I.I., Panax ginseng. *Med. Sci. Serv.* (1967): 4, 17.
3. Brekhman, I.I. and Dordymov, I. V., New substances of plant origin which increase non-specific resistance. *Ann. Rev. Pharmac.* (1969): 9, 419.
4. Brekhman, I.I., Ancient ginseng and pharmacology of the future, *Symposium of Gerontology* (1975): Lugano.
5. Djahanguiri, B., Effect of a single dose of phentolamine and MJ 1999 on aspirin-induced gastric ulceration in rats. *J. Pharm. Pharmacol.* (1969): 21, 541.
6. Eger, W., *Med. Exptl.* (1961): 4, 251. Quoted from Lazarev, N.V. and Brekhman, I. I., Influence of preparations of *Eleutherococcus senticosus* Maxim., on neoplastic disease. *Med. Sci. Serv.* (1967): 4, 9-13.
7. Finney, D.T., *Probit analysis* (1952): 2nd Ed. Cambridge University Press.
8. Gianoli, A.C., 10 years of revitalization therapy in clinic and practice. *Zeitschrift fur Parklinische Geriatric* (1975): Nr. 7, 186-192.
9. Lazarev, N. V., *Farmacol Toxicol.* (1958): 21, 81. Quoted from Ref. No.4.
10. Lobo, E., Kulkarni, R.D. and Desai, R.R., Special Pharmacology of Geriforte. *Probe* (1975): 4, 266.
11. Petkov, V., Possibilities for optimizing reactivity by Pharmacology agents. *Symposium of Gerontology* (1975): Lugano.

12. Popov, I.M., Clinical use of ginseng extract as adjuvant in revitalization therapies, *Proceedings of International Ginseng Symposium* (1975): The Central Research Institute, Republic of Korea, p. 115.
13. Roe, J.H. and Kuether, C.A., The determination of ascorbic acid in whole blood and urine through the 2, 4-dinitro phenylhydrazine derivative of dehydro ascorbic acid. *J. Biol. Chem.* (1949): 147, 399.
14. Ruckert, K.H., News from the Ginseng Research of Pharmaton Laboratories. *Symposium of Gerontology* (1975): Lugano.
15. Sahgal, V.K. and Sood, N.K., Geriforte: An indigenous geriatric tonic in hyperlipidaemia. *Probe* (1975): 4, 277.
16. Sandberg, F., The significance of adaptogenic substances for the organism. *Symposium of Gerontology* (1975) Lugano.
17. Selye, H., Experimental evidence supporting the conception of "Adaptation Energy", *Am. J. Physiol.* (1938): 123, 758.
18. Selye, H., *Stress* (1955); Montreal.
19. Selye, H., The Psychosocial environment and psychosomatic diseases. (1971): Ed. L. Levi, Oxford University Press, London, New York, Toronto p. 299.
20. Senay, E.C. and Levine, R.J., Synergism between cold and restraint for rapid production of stress ulcers in rats. *Proc. Soc. Exptl. Biol.* (1967): 124, 1221.
21. Sheth, S.C., Blood lipids and the liver. *Probe* (1975): 4, 269.
22. Singh, N., Kulsreshtha, V.K., Kohli, R.P. and Chatterjee, A., Glycoside from *Nerium indicum* producing a state of increased non-specific resistance in animals. *Proceedings of IV Indo-Soviet Symposium held at C.D.R.I., Lucknow, India* (1976): p.30.
23. Singh, N. Agrawal, A.K., Lata, A. and Kohli, R.P., Experimental Evaluation of adaptogenic properties of *Withania somnifera*. *Proceedings of 12th Scientific Seminar on Indian Medicine*. B.H.U. Varanasi India (1977): p.4
24. Smith, G.W., Pharmacological screening tests, *Progress in Medicinal Chemistry* (1960): 1, 1, Butterworths, London.
25. Srinivasan, S., Prabhu, U.R. and Balwani, J.H., Effect of an indigenous during preparation on carbon tetrachloride hepatotoxicity. *Ind. J. med. Res.* (1968): 56, 879.
26. Vagh, V.T., Kapadia, H.D. and Pavri, D.N., Clinical evaluation of an indigenous geriatric tonic. *Probe* (1975): 4, 292.
27. Zenker, N. and Bernstein, D.E., The estimation of small amounts of corticosterone in rat plasma. *J. Biol. Chem.* (1958): 231, 695.