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Panax ginseng and *Eleutherococcus senticosus* may exaggerate an already existing biphasic response to stress via inhibition of enzymes which limit the binding of stress hormones to their receptors

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Summary A mechanism of action for *Panax ginseng* (PG) and *Eleutherococcus senticosus* (ES) is proposed which explains how they could produce the paradoxical effect of sometimes increasing and sometimes decreasing the stress response. The mechanism suggests that this biphasic effect results from increased occupancy of positive and negative feedback stress hormone receptors by their natural ligands due to inhibition of specific enzymes which function to limit receptor occupancy. Specifically, it is suggested that PG inhibits 11-beta hydroxysteroid dehydrogenase one and ES inhibits catechol-*O*-methyl transferase, both of which reside in close proximity to stress hormone receptors and catalyse the degradation of stress hormones into inactive compounds. In addition, it is suggested that the increased energy said to result from PG and ES may be a consequence of their increasing the occupancy of stress hormone receptors which function to redistribute the body's energy reserves from regeneration to activity. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Panax ginseng (PG) has been used by practitioners of Chinese medicine for the last 4000 years to treat a vast array of diseases where a lack of vitality in one or more organ systems is considered to be a predisposing factor (1,2). The variety of ailments that PG is used to treat has made it difficult to understand and categorise its pharmacological nature and mechanism of action (3). In traditional Chinese medicine PG is said to increase 'Chi' energy, the deficiency of which is understood to allow disease processes to predominate (2). Animal studies conducted in the latter half of the 20th century demonstrated that PG and a plant more recently discovered by Russian scientists, *Eleutherococcus senticosus* (ES), attenuated organ and tissue damage induced by various stressors and, in addition, increased the length of time until exhaustion in forced exercise trials (4–7). This suggested that PG and ES altered an organism's response to stress in a manner which improved adaptation to stress (8,9). Hence the term 'adaptogen' was coined to classify PG and ES and their respective active constituents,

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eleutherosides and ginsenosides. The choice of the term 'adaptogen', and the specific organs and tissues chosen to analyse the effects of adaptogens, suggest that the motivation to evaluate PG and ES in relation to stress was generated by the work of Selye (10,11). He coined the term 'general adaptation syndrome' to describe the process by which various stressors produce perturbation to organs and tissues, e.g., adrenal hypertrophy, thymus involution and gastrointestinal ulceration. These observations implied that a component of the stress response acted independently of the type of stressor and established the idea of stress *per se* as a cause of disease in its own right.

While Selye's stress and adaptation model has been helpful in explaining how PG and ES exert their beneficial effects, the model, on its own, does not provide scope for a detailed understanding of how this occurs. In seeking such an understanding, researchers have turned to more recent paradigms, e.g., increased nucleic acid synthesis (12–16), alterations in brain monoamine concentration (17–19), increased binding of glucocorticoids to their receptors in the brain and limbic system (3), agonism of type II glucocorticoid receptors (20,21), cyclic phosphodiesterase inhibition (22–24), and increased nitric oxide (NO) production (25,26). Each of these studies used a recently emerged paradigm to attempt to explain in greater detail the results of PG and ES experiments undertaken in the context of Selye's original stress and adaptation model. For example, the discovery by Rivier and Shen (27) that NO acts as a local hormone with a large array of effects on the body including effects on the hypothalamic-pituitary-adrenal axis (HPA-axis) (27) represented a new paradigm, which has been harnessed by Kim et al. (26) to explain the previously documented effects of PG on the HPA-axis. Of course, the relative merit of a mechanism of action for any drug will be judged by how well it explains the drug's reported actions. In turn, researchers will conceptualize and prioritize the importance of reported actions in the light of their own experimental results and various nuances of their scientific background. With this in mind, a plausible mechanism of action was required by the current author to explain the unexpected finding that ES increased, rather than decreased, the stress response in a group of endurance athletes, as indicated by a 29% decrease in the testosterone to cortisol ratio (TCR) (28). It should be noted that there are other reports of adaptogens increasing the stress response. Hiai et al. (29,30) observed a significant and large increase in adrenocorticotrophic hormone (ACTH) and corticosterone 15 minutes after intraperitoneal injection of PG (7 mg/kg). How could these data be consistent with the results of studies documenting a decrease in stress-induced damage with adaptogen supplementation (4,5,7)? An answer to this question was provided by the results of Nörr (31) who observed that an oral dose of ES (3 mg/kg/day for seven weeks) produced a 102% increase in corticosterone levels in unstressed rats in comparison with unsupplemented controls, while in rats exposed to the stress of saline injection (a stressor severe enough to cause a six-fold increase in corticosterone in unsupplemented rats) ES decreased corticosterone by 45%. ES, therefore, appeared to have a biphasic effect on the stress response, increasing it at low stress levels and decreasing it at high stress levels. There is evidence suggesting that PG also has a biphasic effect on the stress response. Kim et al. (32) measured the effect of PG on the stress response (as indicated by adrenal ascorbate loss) over a nine hour period in mice subjected to continuous heat stress. When the stress response was rising from baseline during the initial stages of the experiment (one hour after stressor onset) the stress response in PG treated mice was 104% higher than in unsupplemented controls ($P < 0.05$). Soon thereafter, however, the stress response began to drop in the supplemented group and was equal to the control group by the time adrenal ascorbate loss reached 84% of its peak in the control group (one hour and 40 minutes after stressor onset). From this point until the end of the experiment the stress response in the supplemented group was significantly lower than in the control group and was up to 43% and 49% lower ($P < 0.05$) at three and five hours post stressor onset, respectively. Clearly, any mechanism capable of explaining how PG and ES increase the stress response would have to explain how they could decrease it also, and it was with this aim in mind that the following hypothetical mechanisms were developed.

HYPOTHESIS

PG and ES exaggerate an already existing biphasic response to stress via inhibition of enzymes which limit the binding of stress hormones to their receptors. This general mechanism of action can be divided into two parts. First, it is suggested that PG and ES increase the occupancy of stress hormone receptors by stress hormones, which, when occurring at positive and negative feedback regulatory sites, exaggerates an already existing biphasic stress response. Second, it is suggested that the most likely way PG and ES increase the occupancy of stress hormone receptors is via inhibition of specific enzymes which serve to decrease the binding of stress hormones to their receptors. Specifically, it is suggested that PG inhibits 11-beta hydroxysteroid dehydrogenase isozyme one (11-HSD1), an enzyme that resides in close proximity to type II glucocorticoid receptors (type II GRs) and catalyses the oxidation of glucocorticoids into their inactive 11-dehydro form (33). In the case of ES, it is suggested that it inhibits catechol-*O*-methyl tranferase (COMT), an enzyme which resides in close proximity to

noradrenaline receptors and catalyses the methylation of noradrenaline into its inactive metabolite, normetanephrine.

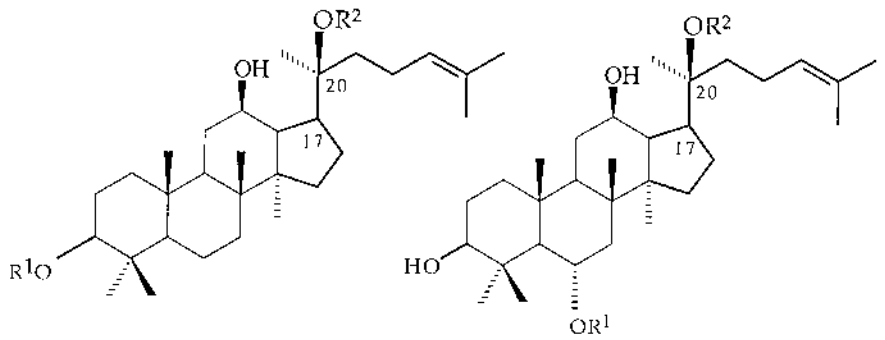
Development of a mechanism of action for PG

The mechanism suggested above for PG is, in part, a revision of a mechanism first proposed by Fulder (3) who administered PG to adrenalectomised and ovarectomised rats and observed increased binding of injected radiolabelled corticosterone in the hippocampus, hypothalamus, pituitary, amygdala, septum and cortex. Fulder suggested that this increased binding was evidence that PG saponins increase the sensitivity of hypothalamic cells responsible for glucocorticoid feedback. He reasoned that the increased sensitivity would produce '... an ACTH/corticosteroid surge, followed by a more effective feedback control of corticosteroid levels ...', which is what was observed by Kim et al. (32). The suggestion that sensitisation of hypothalamic cells to corticosteroids would lead to an ACTH/corticosteroid surge assumes that corticosteroids accelerate their own release (positive feedback) and that this process occurs in the hypothalamus. Fulder's assumption regarding the existence of positive feedback is supported by more recent data (34, 35). The glucocorticoid receptors which mediate this response, however, appear to reside principally in the hippocampus, rather than the hypothalamus (35). In contrast, type II GRs residing in the hypothalamus, in combination with those in the pituitary, appear to be primarily responsible for negative feedback (35,36). This is a case of the same type of receptors having different functions, either negative or positive feedback in this case, in accordance with the roles of the tissue in which they reside. An additional point to observe is that the data of Ratka et al. (34) suggests that the positive and negative feedback effects of type II GRs on corticosterone levels are temporally separated over the course of a stress response, i.e., positive feedback occurs before negative feedback. This suggests a naturally occurring biphasic response to stress.

With regard to the way in which PG may increase the sensitivity of cells responsible for glucocorticoid feedback, Fulder (3) speculated that PG saponins may increase the '... passive diffusion of corticosteroids across the (cell) membrane'. Insight gained from recent developments in the field of glucocorticoid physiology has led to the current author's hypothesis that PG saponins increase the glucocorticoid occupancy (and, therefore, the sensitivity) of glucocorticoid receptors by inhibiting 11-HSD1. The first important piece of information leading to this hypothesis was the description of an enzyme (11-HSDI), associated with type II GRs, whose function, it had been proposed, was to moderate glucocorticoid occupancy of these receptors (37). The second vital piece of information was the finding that the active ingredient in liquorice, glycyrrhizic acid, which shares a triterpene structure with the ginsenosides (see Figure 1), mediated its pharmacological action of sodium and water retention by inhibiting 11-HSD2 (an isozyme related to 11-HSD1 associated with type 1 GRs in the kidney and hypothalamus) (33). A synthesis of these two pieces of information led to the hypothesis that, analogous to liquorice saponin's inhibition of 11-HSD2, saponins in PG may inhibit 11-HSD1, thereby allowing more corticosteroid to bind to type II GRs, which, when occurring at positive and negative feedback sites, exaggerates an already existing biphasic response to stress.

Development of a mechanism of action for ES

In the case of a mechanism of action for ES, the structures of its two most potent adaptogenic compounds, eleutherosides B and E, are quite different from any of the ginsenosides or corticosteroids, suggesting a different mechanism to PG. Consistent with a general mechanism for adaptogens, eleutherosides could increase the occupancy of receptors to any of the main stress hormones, e.g., corticosteroids, noradrenaline, ACTH, or corticotrophic releasing hormone (CRH). The only one of these that appears to share any structural similarity with eleutherosides is noradrenaline. In keeping with the traditional pharmacological principle that enzyme inhibition is often the mechanism for a drug's action, the question arose, is there an enzyme which when inhibited increases the binding of noradrenaline to its receptor? There are two enzymes which fall into this category, catechol-*O*-methyl transferase (COMT) and monoamine oxidase (MAO), which catalyse the conversion of noradrenaline into the inactive compounds normetanephrine and 3,4-dihydroxyphenyl glycolaldehyde, respectively. Given that structural homology with any of these three ligands (i.e., noradrenaline or its two products) could provide a basis for enzyme inhibition, the next question was, do eleutherosides share any structural homology with any of these compounds? One obvious structural moiety possessed by normetanephrine and eleutherosides B and E (but not by noradrenaline or 3,4-dihydroxyphenyl glycolaldehyde) is a methyl substituted catechol ring, i.e., a methoxyl group instead of a hydroxyl group at the 3 position on the phenol ring (see Figure 2). Hence, it is proposed that eleutherosides B and E inhibit COMT and in so doing allow more noradrenaline to bind to noradrenaline receptors including those responsible for positive and negative feedback of the stress response, i.e., alpha-one and alpha-two receptors, respectively (38, 39).



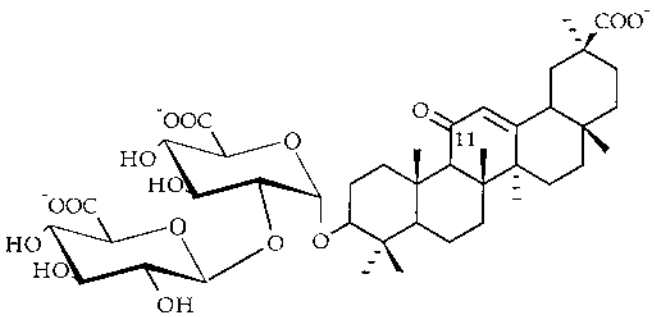
20 (S)-Protopanaxadiol

20 (S)-Protopanaxatriol

Ginsenoside	R^1	R^2
Rb_1	Glc^2-Glc	Glc^6-Glc
Rb_2	Glc^2-Glc	Glc^6-Ara(p)
Rc	Glc^2-Glc	Glc^6-Ara(f)
Rd	Glc^2-Glc	Glc

Ginsenoside	R^1	R^2
Re	Glc^2-Rha	Glc
Rf	Glc^2-Glc	H
Rg_1	Glc	Glc
Rg_2	Glc^2-Rha	H

Glc = glucose
Ara (p) = arabinose (pyranose)
Ara (f) = arabinose (furanose)
Rha = rhamnose



Glycyrrhizic acid

Fig. 1 The triterpene structure of the ginsenosides and glycyrrhizic acid.

IMPLICATIONS THESE MECHANISMS HAVE WITH REGARD TO THE CONCEPT OF 'CHI' ENERGY

So far, the discussion of the proposed mechanisms has been concerned only with explaining the biphasic effects of PG and ES and for this reason has been primarily focussed on positive and negative feedback receptors for stress hormones. The majority of stress hormone receptors, however, are not concerned with feedback, but instead with the mediation of many other effects including the daily process of redistributing the body's energy reserves from regeneration and anabolism to arousal and activity (40). It is possible, therefore, that the wide ranging effects of PG and ES, including the increased 'Chi' energy described in Chinese medicine, may be a consequence of their increasing the occupancy of stress hormone receptors throughout the body. This mechanism contrasts with one presented for PG by Pearce et al. (20) and Lee et al. (21). Both papers presented data suggesting that PG saponins have a mild affinity for type II GRs (Km approximately 100- to 1000-fold higher than dexamethasone) and suggested that the glucocorticoid-like effects ascribed to PG may be a direct consequence of type II GR agonism. The mechanism proposed by the current author, however, suggests that rather than exerting its

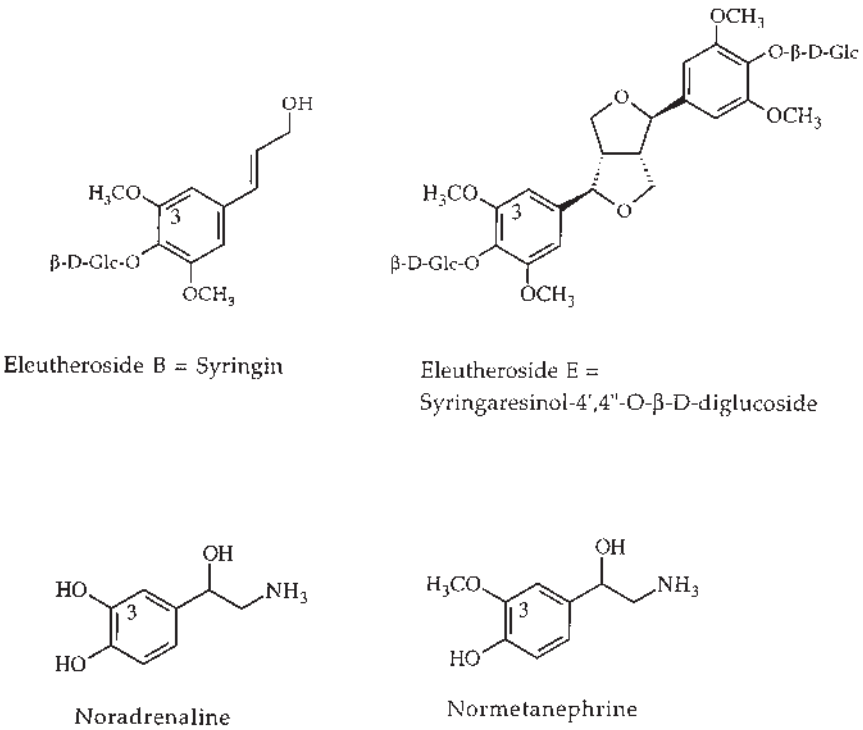


Fig. 2 The structures of eleutherosides B and E in comparison with noradrenaline and normetanephrine, the respective substrate and product of catechol-O-methyl transferase.

effects by binding directly to type II GRs, PG increases the occupancy of these receptors by their endogenous ligand (glucocorticoids) via inhibition of 11-HSD1.

CONCLUSION

The relative lack of coherent models explaining the mechanism of action of PG and ES at the molecular level may be part of the reason why these drugs have not yet been examined in large scale placebo controlled clinical trials in humans exposed to severe stressors, e.g., surgery, radiotherapy and chemotherapy. The mechanisms of action presented for PG and ES in this paper represent an explanation of both the biphasic effects of these drugs and the increased energy resulting from their use. The mechanisms could be tested in two ways. First, using *in vitro* enzyme inhibition assays, the affinity of these drugs for 11-HSD1 and COMT could be evaluated. Second, the model as it applies to PG and ES relies on the function of type II GRs and noradrenaline receptors, respectively. Therefore, if the effects of PG and ES were blocked by specific inhibitors of these receptors, it would suggest that the receptors were part of their mechanism of action. It is important to remember, however, that the results such experiments can, at best, only ever be consistent with a proposed mechanism of action and that experimental proof of an action mechanism has always been problematic in pharmacology. Coherent action mechanisms, however, remain an important element in drug research and the potential value PG and ES hold in decreasing the ill-effects resulting from severe stressors warrants their ongoing investigation. The mechanisms of action presented herein may provide a conceptual framework from which to build when designing future research on this class of drugs.

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REFERENCES

1. Baranov A. I. Medicinal uses of Ginseng and related plants in the Soviet Union: Recent trends in the Soviet Literature. *J Ethnopharmacol* 1982; **66**: 339–353.
2. Fulder S. J. *The Root of Being: Ginseng and the Pharmacology of Harmony*. London: Hutchinson, 1980.
3. Fulder S. J. Ginseng and hypothalamic-pituitary control of stress. *Am J Chin Med* 1981; **9**(2): 112–118.
4. Brekhman I. I., Dardymov I. V. Pharmacological investigation of glycosides from Ginseng and Eleutherococcus. *Lloydia* 1969; **32**(1): 46–51.

5. Brekhman I. I., Kirillov O. I. Effect of Eleutherococcus on Alarm Phase of Stress. *Life Sci* 1969; **8**(1): 113–121.
6. Nishibe S., Kinoshita H., Takeda H., Okano G. Phenolic compounds from stem bark of *Acanthopanax senticosus* and their pharmacological effect in chronic swimming stressed rats. *Chem Pharm Bull* (Tokyo) 1990; **38**(6): 1763–1765.
7. Singh N., Verma P., Mishra N., Nath R. A comparative evaluation of some anti-stress agents of plant origin. *Indian J Pharmacol* 1991; **23**: 99–103.
8. Brekhman I. I., Dardymov I. V. New substances of plant origin which increase nonspecific resistance. *Annu Rev Pharmacol* 1969; **9**: 419–430.
9. Wagner H., Nörr H., Winterhoff H. Plant adaptogens. *Phytomedicine* 1994; **1**: 63–76.
10. Selye H. Studies on adaptation. *Endocrinology* 1937; **21**(2): 169–188.
11. Selye H. The general adaptation syndrome and the diseases of adaptation. *J Clin Endocrinol* 1946; **6**(2): 117–230.
12. Oura H., Hiai S., Nakashima S., Tsukada K. Stimulating effect of the roots of Panax ginseng C. A. Meyer on the incorporation of labeled precursors into rat liver RNA. *Chem Pharm Bull* (Tokyo) 1971; **19**(3): 453–459.
13. Oura H., Hiai S., Seno H. Synthesis and characterization of nuclear RNA induced by Radix ginseng extract in rat liver. *Chem Pharm Bull* (Tokyo) 1971; **19**(8): 1508–1605.
14. Hiai S., Oura H., Tsukada K., Hirai Y. Stimulating effect of Panax ginseng on RNA polymerase activity in rat liver nuclei. *Chem Pharm Bull* (Tokyo) 1971; **19**(8): 1656–1663.
15. Bezdetko G. N., Brekhman I. I., Dardymov I. V., Zil'ber M. L., Rogozkin V. A. Effect of Eleutherococcus glucosides on RNA polymerase activity in nuclei from skeletal muscles and liver after physical strain. *Vop Med Khim* 1973; **19**(3): 245–248. (Russ) [CA 79: 62204j]
16. Dardymov I. V., Bezdetko G. N., Brekhman I. I. Incorporation of phosphorous-32 into rat liver RNA during physical exercise and under the effect of glycosides from Eleutherococcus senticosus. *Vop Med Khim* 1972; **18**(3): 267–269. (Russ) [CA 77: 97282u]
17. Petkov V. Effect of ginseng on the brain biogenic monoamines and 3′5′-AMP system: Experiments on rats. *Arzneimittelforschung* 1978; **28**(1): 388–393.
18. Itoh T., Zang Y. F., Murai S., Saito H. Effects of Panax ginseng root on the vertical and horizontal motor activities and on brain monoamine-related substances in mice. *Planta Med* 1989; **55**: 429–433.
19. Watanabe H., Ohta H., Imamura L., Asakura W., Matoba Y., Matsumoto K. Effect of Panax ginseng on age-related changes in the spontaneous motor activity and dopaminergic nervous system in the rat. *Jpn J Pharmacol* 1991; **55**(1): 51–56.
20. Pearce P. T., Zois E., Wynne K. N., Funder J. W. Panax ginseng and Eleutherococcus senticosus extracts – in vitro studies on binding to steroid receptors. *Endocrinol Jpn* 1982; **29**(5): 567–573.
21. Lee Y. J., Chung E., Kwang Y. L., Lee Y. H., Huh B., Lee S. K. Ginsenoside-Rg1, one of the major active molecules from Panax ginseng, is a functional ligand of glucocorticoid receptor. *Mol Cell Endocrinol* 1997; **133**: 135–140.
22. Nikaido T., Ohmoto T., Kinoshita T., Sankawa U., Nishibe S., Hisada S. Inhibition of cyclic AMP phosphodiesterase by lignans. *Chem Pharm Bull* (Tokyo) 1981; **29**(12): 3586–3592.
23. Stancheva S. L., Alova L. G. Ginsenoside Rg1 inhibits the brain cAMP phosphodiesterase activity in young and aged rats. *Gen Pharmacol* 1993; **24**(6): 1459–1462.
24. Sharma R. K., Kalra J. Ginsenosides are potent and selective inhibitors of some calmodulin-dependant phosphodiesterase isozymes. *Biochemistry* 1993; **32**(19): 4975–4978.
25. Gillis N. C. Panax ginseng pharmacology: A nitric oxide link? *Biochem Pharmacol* 1997; **54**: 1–8.
26. Kim D. H., Jung J. S., Suh H. W. et al. Inhibition of stress-induced plasma corticosterone levels by ginsenosides in mice: Involvement of nitric oxide. *Neuroreport* 1998; **9**: 2261–2264.
27. Rivier C., Shen G. H. In the rat, endogenous nitric oxide modulates the response of the hypothalamic-pituitary-adrenal axis to interleukin-1 beta, vasopressin and oxytocin. *J Neurosci* 1994; **14**(4): 1985–1993.
28. Gaffney B. T. The effects of extracts of Eleutherococcus senticosus or Panax ginseng on endurance athletes and a quantitative analysis of the extracts contents. Unpublished doctoral thesis, Department of Human Biology and Movement Science, Royal Melbourne Institute of Technology, 1999.
29. Hiai S., Yokoyama H., Oura H., Yano S. Stimulation of pituitary-adrenocortical system by ginseng saponin. *Endocrinol Jpn* 1979; **26**(6): 661–665.
30. Hiai S., Yokoyama H., Oura H. Features of ginseng saponin-induced corticosterone secretion. *Endocrinol Jpn* 1979; **26**(6): 737–740.
31. Nörr H. Phytochemische und pharmakologische untersuchungen der adaptogendrogen *Eleutherococcus senticosus, Ocimum sanctum, Codnopsis pilosula, Rhodiola rosea* und *Rhodiola crenulata*. Unpublished doctoral thesis, der Fakultät für Chemie und Pharmazie der Ludwig-Maximilians-Universität München, 1994. (German)
32. Kim C, Kim C. C., Myung S. K., Chang Y. H., Jong S. R. Influence of Ginseng on the stress mechanism. *Lloydia* 1970; **33**(1): 43–48.
33. Stewart P. M., Wallace A. M., Vallentino R., Burt R. D., Shackelton C. H. L., Edwards C. R. W. Mineralocorticoid activity of liquorice: 11-beta-hydroxysteroid dehydrogenase deficiency comes of age. *Lancet* 1987; **2**: 821–823.
34. Ratka A., Sutanto W., Bloemers M., De Kloet E. R. On the role of brain mineralocorticoid (type I) and glucocorticoid (type II) receptors in neuroendocrine regulation. *Neuroendocrinology* 1989; **50**: 117–123.
35. van Haarst A. D., Oitzl M. S., De Kloet E. R. Facilitation of feedback inhibition through blockade of glucocorticoid receptors in the hippocampus. *Neurochem Res* 1997; **22**(11): 1323–1328.
36. De Kloet E. R. Brain corticosteroid receptor balance and homeostatic control. *Front Neuroendocrinol* 1991; **12**(2): 95–164.
37. Roland B. L., Krozowski Z. S., Funder J. W. Glucocorticoid receptor, mineralocorticoid receptors, 11-hydroxysteroid dehydrogenase -1 and -24 expression in rat brain and kidney: in situ studies. *Mol Cell Endocrinol* 1995; **111** (Rapid paper): R1–R7.
38. Al Damluji S., Bouloux P., White A., Besser M. The role of alpha-2-adrenoceptors in the control of ACTH secretion; interaction with the opioid system. *Neuroendocrinology* 1990; **51**: 76–81.
39. Al Damluji S. Adrenergic control of the secretion of anterior pituitary hormones. *Baillieres Clin Endocrinol Metab* 1993; **7**(2): 335–392.
40. Chrousos G. P., Gold P. W. The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. *JAMA* 1992; **267**(9): 1244–1252.