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# Adaptogenic effect of *Bacopa monniera* (Brahmi)

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**Abstract**

As stress is linked to many diseases, research on an effective antistress agent (adaptogen) from plants has gained importance. We report the investigations on the adaptogenic property of a standardized extract of *Bacopa monniera* against acute (AS) and chronic stress (CS) models in rats. *Panax* root powder (*Panax quinquefolium*) was taken as a standard. Male SD rats, weighing 180–200 g, exposed to immobilization stress for 150 min once only for AS and for seven consecutive days in CS, were fed with *B. monniera* or *Panax* root powder daily for 3 days in AS and for 7 days in CS, 45 min prior to each exposure of stress. Rats were sacrificed immediately after stress, the blood was collected, and the plasma was separated out for biochemical estimation. Adrenals, spleen, and thymus were dissected for organ weight and stomach for ulcer score. AS exposure significantly increased the ulcer index, adrenal gland weight, plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK) but significantly decreased the spleen weight. Pretreatment with *B. monniera* at 40 mg/kg po significantly reduced the AS-induced increase in the ulcer index, adrenal gland weight, plasma glucose, AST, and CK. A dose of 80 mg/kg po significantly reversed the AS-induced changes in adrenal gland weight, spleen weight, plasma glucose, ALT, and AST. *Panax* root powder, 100 mg/kg po, significantly reversed the AS-induced changes in spleen weight, plasma ALT, AST, and CK. CS exposure resulted in a significant increase in the ulcer index, adrenal gland weight, plasma AST, and CK with a significant decrease in the thymus and spleen weight, plasma triglyceride, and cholesterol. Pretreatment with low dose of *B. monniera* extract at 40 mg/kg significantly reversed changes in ulcer index and plasma AST only, whereas the pretreatment with higher dose significantly reversed CS-induced changes in ulcer index, adrenal gland weight, CK, and AST. *Panax* root powder significantly reversed CS-induced increase in ulcer index, adrenal gland weight, CK, and AST. On the basis of our result, it is concluded that the standardized extract of *B. monniera* possesses a potent adaptogenic activity.


*Keywords:* *Bacopa monniera*; *Panax quinquefolium*; Immobilization stress; Adrenal gland; Spleen; Thymus; Glucose; Lipids; Aminotransferases; Creatine kinase

## 1. Introduction

Stress can be described as the sum total of all the reactions of the body, which disturb the normal physiological equilibrium and result in a state of threatened homeostasis. Stress is an internationally recognized phenomenon fortified by advancement of industrialization and a demanding civilization. Thus, every person today faces stressful situations in day to day life. Stress represents reaction of body to stimuli that tend to disturb its normal physiological equilibrium or homeostasis and has been defined as nonspecific response of the body to any demand imposed on it (Selye, 1936). Since the introduction of adaptogens (Lazarev, 1947), several plants have been investigated, which were once used as tonics due to their adaptogenic and rejuvenating properties in traditional medicine (Rege et al., 1999). The drugs of plant origin are gaining increasing popularity and are being investigated for remedies of a number of disorders including antistress adaptogenic activity (Edzard, 1998). Starting from *Eleuthrococcus senticosus* and *Panax ginseng* (Wagner et al., 1994), these initial studies opened a vast area for research and substantial work has also been carried out on plants such as *Withania somnifera* (Singh et al., 1982) *Ocimum sanctum* (Bhargava and Singh, 1981), and *Emblica officinalis* (Katiyar et al., 1997).

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*Bacopa monniera* (Linn) Pennel [syn: *B. monniera* Wettst; *Gratiola monniera* (Linn); *Herpestis monniera* (Linn) HB&K; *Moniera cuncifolia* Michx] (family: *Scrophulariaceae*) is a perennial creeper found throughout India in wet, damp, and marshy areas (Chopra et al., 1956). An infusion of the plant has been used in Indian folklore as a nerve tonic since times immemorial (Chunekar, 1960).

In the ancient Indian system of medicine, viz., *Ayurved*, *B. monniera* has been classified under *Medhya rasayana*, i.e., medicinal plants rejuvenating intellect and memory. The ancient classical *Ayurvedic* treatises, viz., *Charak samhita*, *Susrutu samhita*, and *Astanga hrdaya*, have prescribed *B. monniera* for the promotion of memory, intelligence, and general performance. Therefore, this plant has been investigated in several laboratories in India for its neuropharmacological effect (Aithal and Sirsi, 1961; Malhotra and Das, 1959; Prakash and Sirsi, 1962). However, its traditional memory-enhancing claim could be established experimentally by our previous reports for the cognitive-enhancing property of *B. monniera* in several animal experimental models of learning (Singh et al., 1988; Singh and Dhawan, 1982, 1992, 1997).

The extract of *P. ginseng* has been used widely as an adaptogen, immunomodulator, memory enhancer, and hepatoprotective (Brekhman and Dardymov, 1969; Wagner et al., 1994), as well as for its anabolic properties (Emilia et al., 2000) in various stress models. A systemic evaluation of the antistress properties of these plants has not been done so far. In the present study, we are reporting the antistress properties of *B. monniera* and used *Panax quinquefolium* (American ginseng), another variety of ginseng used widely for comparison.

## 2. Methods

### 2.1. Animals

All animal experiments were performed in accordance with our institutional guidelines after obtaining the permission from Laboratory Animal Ethics Committee. Naïve adult male Sprague–Dawley rats weighing 180–200 g were used. They were housed three to four per cage at temperature 22 ± 2 °C and 12/12-h light/dark (8:00 a.m. to 8:00 p.m.) under controlled environment. Rats were fed standard laboratory food, and water was given ad libitum. The rats were kept for 7 days in laboratory for habituation.

### 2.2. Drugs

The standardized extracts of *B. monniera* prepared within 3 months were used in the study. The shelf life of these extracts is 2 years. The whole plant of *B. monniera* was dried in shade and then powdered plant material was extracted with distilled water. The aqueous extract was discarded and the residual plant material was extracted thrice with 90% ethanol. The residue obtained after removing the solvent was dried in vacuo and macerated with acetone to give a free-flowing powder. The extract of *B. monniera* contained 55–60% bacosides estimated as bacoside A. The estimation method involves acid hydrolysis of bacosides, which yields quantitatively a transformed aglycone–ebelin lactone; this contained a conjugated triene system and is estimated by UV spectrophotometer at 278 nm (Pal and Sarin, 1992). The crude powder of ginseng root *P. quinquefolium* was purchased from Sigma, USA (Cat. No. G 7253).

### 2.3. Drug administration

Both drugs were suspended in 0.5% gum acacia, and a fine emulsion was made having uniform particle distribution. The extracts administered orally daily for 3 days in case of acute stress (AS) and for 7 days in case of chronic stress (CS). Both drugs were prepared fresh daily before administration.

### 2.4. Procedure

The rats were divided into control nonstress group, AS, and CS groups, and drug-treated groups for both AS and CS. Each group consists of 7 rats. The AS drug groups were fed with extracts of *B. monniera* (40 and 80 mg/kg po) or *P. quinquefolium* (100 mg/kg po) daily for 3 days. A parallel group of rats were fed with vehicle for the same number of treatment days but were not immobilized and they were used as nonstress control group to obtain baseline data for various parameters. On the second day after feeding drug or vehicle, animals were fasted overnight with free access to water. On the third day, 45 min after feeding the drug or vehicle, rats were stressed except the nonstress group. In CS, the drugs were feed daily 45 min prior to stress regimen up to seven consecutive days except that the rats were fasted over night on the sixth day after completion of the experimental regimens of drug feeding and stress exposure. A parallel group of nonstress control group was also taken as described above and scarified on seventh day along with the CS group of rats.

Among the various methods employed, immobilization has been used extensively and accepted widely for studying the stress-induced physical as well as psychological alterations and the consequences of the stress (Al-Mohaisen et al., 2000; Marty et al., 1997). In our experiments, the stress was produced by restraining individual animal inside an acrylic hemicylindrical plastic tube (4.5-cm diameter, 12 cm long) for a period of 150 min once only in AS and once daily for seven consecutive days in CS. The rats were sacrificed immediately after stress under ether anesthesia, the abdomen and thorax were cut open, and blood was collected through cardiac puncture. The blood was centrifuged at 2000 rpm × 20 min at 4 °C and the plasma was separated. The

plasma was used to estimate glucose, triglycerides, cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK) using autoanalyzer (Synchron Cx-5, Beckman) with their respective kits (Beckman Coulter International, Switzerland). Our previous findings have shown that AS does not produce any changes in plasma triglyceride and cholesterol, and hence these were not determined in AS (Rai et al., 2001). The adrenals, spleen, and thymus were dissected and they were weighed after removal of adhering tissues. Stomach was dissected out and cut open along the greater curvature for scoring the incidence of ulcer. Ulcer index was calculated according to the method of Gupta et al. (1981).

### 2.5. Statistical analysis

The results are expressed as means ± S.E.M. The statistical significance was determined by two-way ANOVA followed by a post hoc Tukey–Kramer test. A probability $P$ value of less than .05 was taken to indicate statistical significance.

## 3. Results

### 3.1. Effect of drug treatment on AS- and CS-induced alterations in ulcer index and organ weight

AS ($P<.001$) and CS ($P<.001$) exposure resulted a significant increase in the scores of ulcer index. Pretreatment with *B. monniera* extract (40 mg/kg po) significantly decrease ulcer index in comparison to AS ($P<.05$) as well as in CS ($P<.05$); whereas at 80 mg/kg po, it significantly decreased ulcer index in CS ($P<.05$) only. *P. quinquefolium* (100 mg/kg po) significantly ($P<.05$) decreased the ulcer index in CS only (Fig. 1).

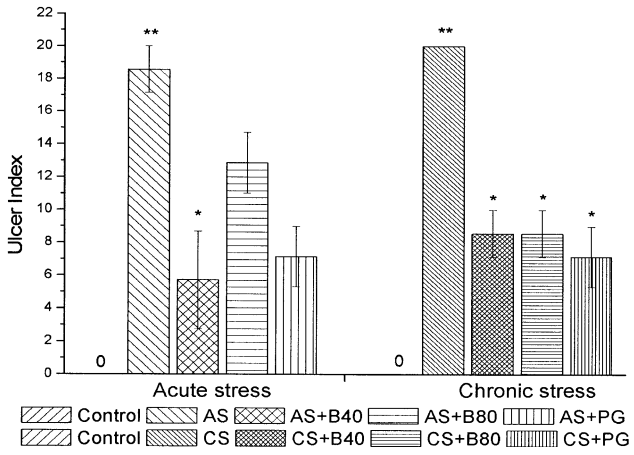


Fig. 1. Bar diagram representing the ulcer index score under AS ($F=13.47$, $df=4$) and CS ($F=54$, $df=4$) of control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. * * $P<.001$ as compared to the respective control group, * $P<.05$ as compared to the respective stress group.

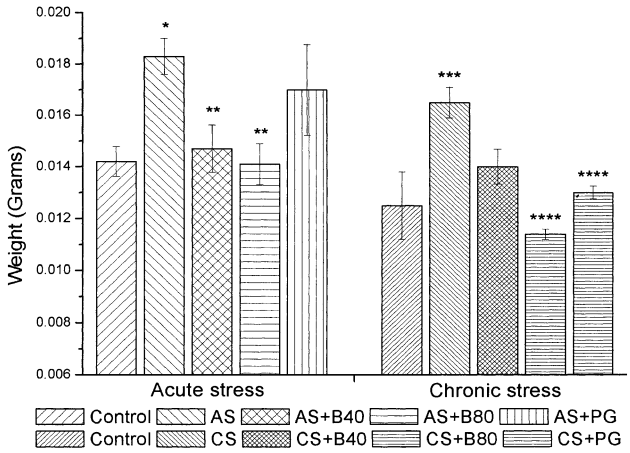


Fig. 2. Bar diagram representing the changes in adrenal gland weight (hypertrophy) under AS ($F=4.412$, $df=4$) and CS ($F=6.217$, $df=4$) for control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. * $P<.05$ as compared to the control group (for AS), * * $P<.05$ as compared to the AS, * * * $P<.01$ as compared to the control group (for CS), * * * * $P<.01$ as compared to the CS group.

Exposure to AS ($P<.05$) and CS ($P<.01$) significantly increased the adrenal gland weight. Pretreatment with *B. monniera* extract at 40 mg/kg po and 80 mg/kg po significantly ($P<.05$) decrease the adrenal gland weight in AS. In CS, *B. monniera* extract (80 mg/kg po) significantly ($P<.01$) decreased the adrenal gland weight only. Similarly, *P. quinquefolium* (100 mg/kg po) significantly ($P<.01$) decreased the adrenal gland weight in CS only (Fig. 2).

A significant decrease was found after AS ($P<.01$) and CS ($P<.05$) exposure in spleen weight. Pretreatment with *B. monniera* extract at 80 mg/kg ($P<.05$) and *P. quinquefolium* (100 mg/kg) ($P<.05$) significantly increased the spleen weight in AS. Neither *B. monniera* extract nor *P. quinquefolium* was effective to restore CS-induced decreased spleen weight to a significant extent (Fig. 3).

CS exposure resulted in a significant decrease in the thymus weight ($P<.01$). No significant change was observed after AS. Neither *B. monniera* extract nor *P. quinquefolium* was effective to restore CS-induced decrease in thymus weight to a significant extent (Fig. 4).

### 3.2. Effect of drug treatment on AS- and CS-induced alterations in biochemical parameters

AS exposure resulted in a significant increase in the plasma level of glucose ($P<.01$). Pretreatment with *B. monniera* extract at 40 mg/kg po ($P<.01$) and 80 mg/kg po ($P<.05$) significantly decreased the circulating glucose level. No significant effect was found in plasma glucose level

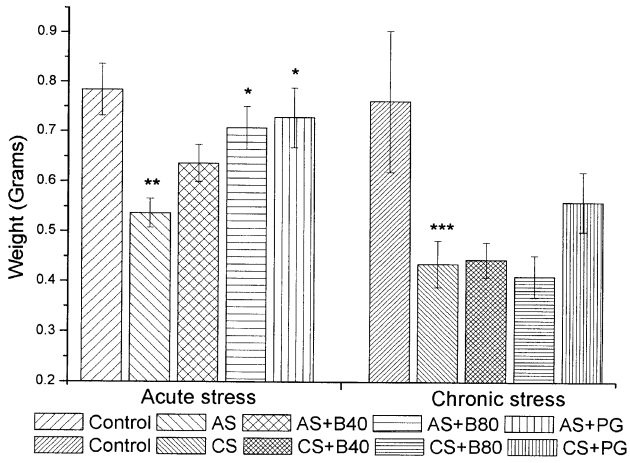


Fig. 3. Bar diagram representing the changes in spleen weight (atrophy) under AS ($F=3.642$, $df=4$) and CS ($F=3.528$, $df=4$) for control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. $**P<.01$ as compared to the control group (for AS), $*P<.05$ as compared to the AS, $***P<.05$ as compared to the control group (for CS).

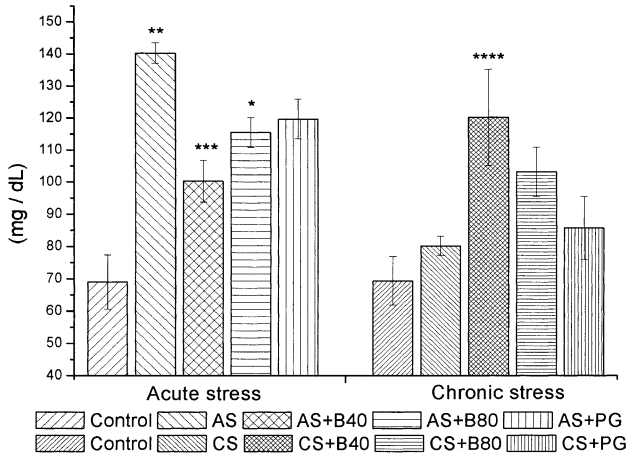


Fig. 5. Bar diagram representing the changes in plasma glucose level under AS ($F=17.24$, $df=4$) and CS ($F=3.257$, $df=4$) for control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. $**P<.01$ as compared to the control group (for AS), $***P<.01$ $*P<.05$ as compared to the AS, $****P<.01$ as compared to the control group (for CS).

after CS exposure, but pretreatment of *B. monniera* extract at 40 mg/kg po significantly ($P<.01$) increased the plasma glucose level following CS (Fig. 5).

Exposure to CS resulted in a significant decrease in the plasma level of triglyceride ($P<.01$) and cholesterol ($P<.05$) as compared to respective control. No significant change was observed after *B. monniera* extract or *P. quinquefolium* pretreatment (Fig. 6).

Exposure to AS significantly increased the plasma ALT level ($P<.05$) in comparison to control. No significant effect was observed after CS exposure. Pretreatment with *B. monniera* extract at 80 mg/kg po ($P<.01$) and *P. quinquefolium* at 100 mg/kg po ($P<.01$) significantly decreased the ALT level as compared to AS (Fig. 7).

Exposure to AS ($P<.01$) and CS ($P<.01$) resulted in a significant increase in plasma AST level as compared to respective control. Pretreatment with *B. monniera* extract at 40 mg/kg po ($P<.05$) and 80 mg/kg po ($P<.01$) and *P. quinquefolium* at 100 mg/kg po ($P<.01$) significantly decreased the AST level as compared to AS. Moreover, pretreatment with *B. monniera* extract at 40 mg/kg po

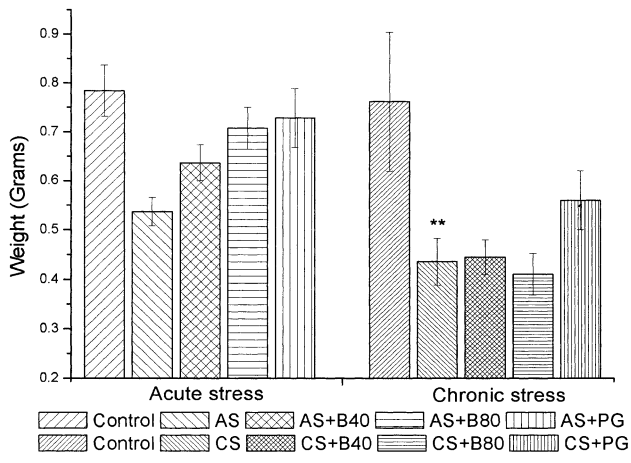


Fig. 4. Bar diagram representing the changes in thymus weight (atrophy) under AS ($F=2.732$, $df=4$) and CS ($F=9.476$, $df=4$) for control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. $**P<.01$ as compared to the respective control group (for CS).

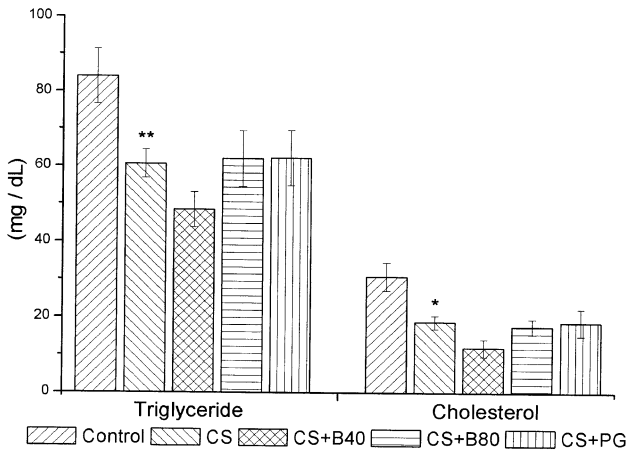


Fig. 6. Bar diagram representing the changes in plasma triglyceride ($F=4.076$, $df=4$) and cholesterol ($F=5.139$, $df=4$) under CS for control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. $**P<.01$, $*P<.05$ as compared to the control group (for CS).

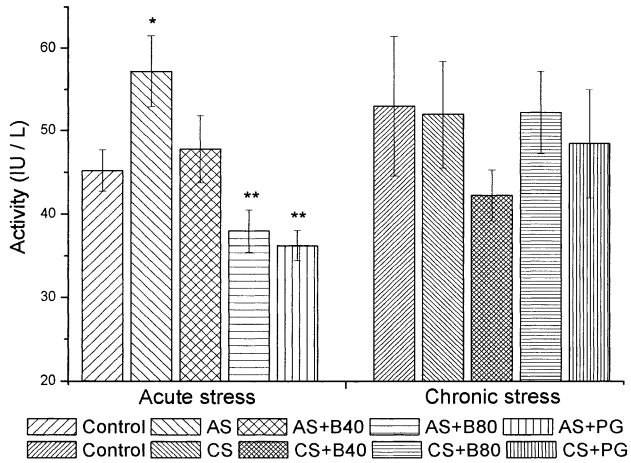


Fig. 7. Bar diagram representing the changes in plasma ALT activity under AS ($F=6.232$, $df=4$) and CS ($F=0.515$, $df=4$) for control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. * $P<.05$ as compared to the control group (for AS), * * $P<.01$ as compared to the AS.

($P<.01$) and 80 mg/kg po ($P<.05$) and *P. quinquefolium* at 100 mg/kg po ($P<.05$) also significantly decreased the ALT level as compared to CS (Fig. 8).

Exposure to AS and CS resulted a significant increase in the plasma level of CK activity ($P<.01$) as compared to respective control. Pretreatment with *B. monniera* extract at 40 mg/kg po ($P<.05$) and *P. quinquefolium* at 100 mg/kg po ($P<.01$) significantly decreased the CK level as compared to AS. The pretreatment with *B. monniera* extract at 80 mg/kg po ($P<.05$) and *P. quinquefolium* at 100 mg/kg

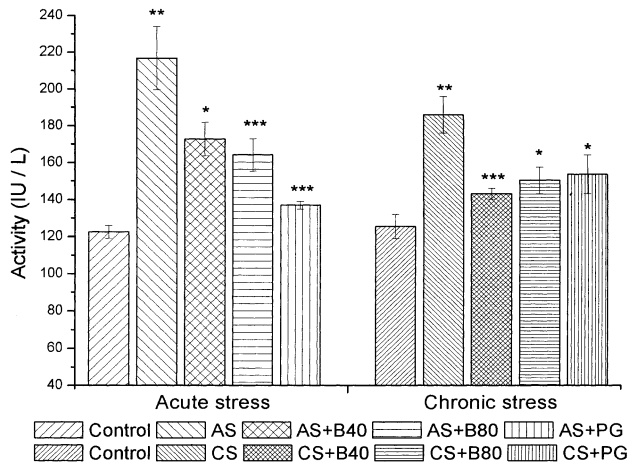


Fig. 8. Bar diagram representing the changes in plasma AST activity under AS ($F=15.32$, $df=4$) and CS ($F=12.18$, $df=4$) for control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. * * $P<.01$ as compared to the respective control group, * $P<.05$, * * * $P<.01$ as compared to the respective stress group.

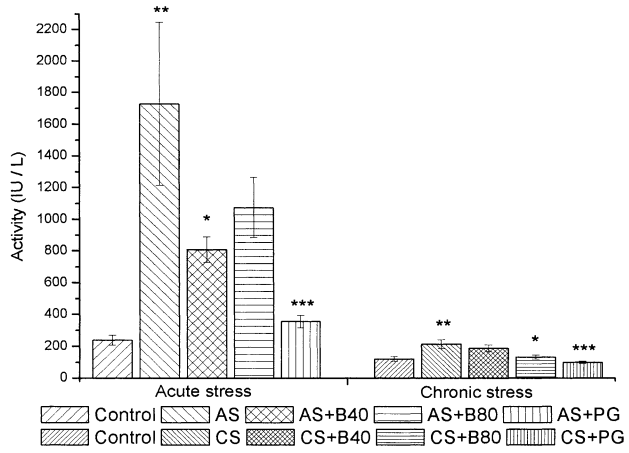


Fig. 9. Bar diagram representing the changes in plasma CK activity under AS ($F=6.004$, $df=4$) and CS ($F=7.818$, $df=4$) for control-, stress-, and drug-treated groups. The stress group was compared with their respective control group, and the drug-treated groups were compared with their respective stress group. Results are represented as mean ± S.E.M. with $n=7$ in each group. * * $P<.01$ as compared to the respective control group, * $P<.05$, * * * $P<.01$ as compared to the respective stress group.

po ($P<.01$) significantly decreased the CK activity as compared to CS (Fig. 9).

## 4. Discussion

Stress is elicited by environmental, social, or pathological conditions occurring during the life of living beings and determines changes in the nervous, endocrine, and immune systems. Considerable evidence published in the last decade has focused on alterations of neurochemical, biochemical, and molecular effect caused by stress in these systems (Ben-Eliyahu et al., 1991; Chrousos and Gold, 1992; Jiang et al., 1990; Smith, 1996; Ueyama et al., 1997).

Normally such stress-induced changes are self-limiting and adaptive in nature until and unless events that override threshold limits become irreversible and pathological (McCarty, 1987). Advancement in the understanding of processes leading to explore the reason for stress-induced disorders cannot obscure the simple fact that the exhaustion of energy supply still forms the basis that triggers the disorders and collapse of energy metabolism following glucose deprivation in circulation (Aloe et al., 2002). The desire to control the coping mechanism has led to emergence of science of adaptation, focusing to elucidate the mechanism that may help in the modification so that insufficient, excessive, and unnecessarily responses can be prevented.

The stress response is sub-served by a complex system with the subsequent involvement of hypothalamus–pituitary–adrenal (HPA) axis (Akil and Morano, 1995; Levine, 2000; Rivier and Plotsky, 1986). Stress resulted in ulcer incidences due to involvement and hyper activation of paraventricular nucleus (PVN) in the hypothalamus. This causes a decrease in mucosal blood flow and hypercontractility

through its descending projections, which influence the activity of vagal efferent, and the resulting imbalance between defensive and aggressive factors induces pathogenesis of ulcers (Zhang and Zheng, 1997). The prolonged activation of PVN of hypothalamus from CS results in an increased index of ulcers in comparison to AS.

Stress-induced adrenal hypertrophy found both in AS and CS was the result of activation of the HPA axis, which is highly responsive to stress and is one of the principal mechanism by which an organism mobilizes its defense against stress events (Makara and Haller, 2001; McEwen, 2000).The prolonged activation of HPA axis resulted in an increase in the adrenal hypertrophy in CS as compared to AS. The sympathetic nervous system in response to stress results in the secretion of corticosterone from adrenal cortex and epinephrine from adrenal medulla (Selye, 1950; Walker et al., 1986). These hormones are deemed as necessary manipulators in the body against stress response and help in combating stress.

During stress, nerve terminals accelerate recruitment of lymphocytes to blood from spleen, which is a major storage pool of lymphocytes (Kappel et al., 1998). This results in the squeezing of the spleen causing reduction in weight observed in AS as well as in CS exposures. However, the atrophy of thymus was found only during CS exposure and not during AS. The transient activation of HPA axis and release of neurochemicals do not have profound impact on thymocytes as in AS, but persistent high level of corticosterone during CS causes apoptosis and necrosis in immature T and B cells resulting in the decline of thymus weight (Pedersen and Hoffman-Goetz, 2000; Rabin et al., 1996).

The AS-induced significant increase in blood glucose, ALT, AST, and CK might be the outcome of AS-induced secretion of corticosterone from cortex, epinephrine from medulla, and epinephrine from sympathetic nerve terminals to provide substrate for energy metabolism and the assurance of availability of ATP demand in the muscles, CNS, and organ of demand. The hyperglycemic effect of epinephrine and corticosterone has also been reported by other authors (Armario et al., 1996; K-Fougia et al., 2002; Vallee et al., 1996). The exogenous administration of corticosterone (dexamethasone) has been reported to induce hyperglycemia (Wass et al., 1996) and induces insulin resistance independent of glucose transport (Nicolson, 1997; Tappy et al., 1994). Increased levels of stress hormones and sympathetic innervations have profound effect on metabolism. The acute demand of glucose was fulfilled by the increase in glucogenolysis from liver during AS. However, during CS, this available source depletes. Thus, it utilizes fat as a secondary substrate and gluconeogenesis starts in response to corticosterone. ALT and AST enzymes catalyze the transfer of the γ-amino groups of alanine and aspartate, respectively, to the γ-keto group of ketogluterate, leading to the formation of oxaloacetic acid and pyruvic acid. In contrast to ALT, which is found primarily in liver, AST is present in many tissues, including the heart, kidney, brain, and skeletal muscles. As a result of transamination, amino acid can enter the citric acid cycle and then function in the intermediary metabolism of carbohydrate and lipids (Daniel and Kurt, 1998). As the literature survey has indicated, administration of ginseng root extract does not induce any physiological change in unstressed rats (Bhattcharyya and Sur, 1999; Mitra et al., 1996), and the statutory subacute toxicological studies conducted in our institute have shown that *B. monniera* does not produce any per se change in the parameters studies. Thus, these studies were not done in the present investigation.

The pretreatment of *B. monniera* at lower dose reversed the AS-induced ulcer index, adrenal hypertrophy, hyperglycemia, AST, and CK activities. This clearly demonstrates its potential antistress activity. The same extract at higher dose was able to revert AS-induced adrenal hypertrophy, atrophy of spleen, hyperglycemia, ALT, and AST activities. The decrease in the adrenal gland weight shows its potential role in attenuating the activation of HPA axis. The involvement of HPA axis during stress causes adrenal enlargement, spleen atrophy ulcers, and metabolic changes. Pretreatment with *P. quinquefolium* only reverted AS-induced spleen atrophy, ALT, AST, and CK activities but was unable to produce any significant effect on ulcer index, adrenal hypertrophy, and hyperglycemia. Thus, it seems to have a direct action on the peripheral metabolism and enzymes in AS. The main axis of stress was not attenuated by this pretreatment during AS.

CS leads to a prolonged activation of HPA axis; thus, more pronounced effect on ulcer index and adrenal gland weight was found. The prolonged activation of stress hormones results in gluconeogenesis after utilization of the primary carbohydrate source during the AS demand on the first exposure. Thus, it mobilizes the lipids' sources for energy substrate. Pretreatment with *B. monniera* extract at low dose was able to restore CS-induced ulcer index and AST activity only, while the same at higher dose reverted ulcer index, adrenal hypertrophy AST, and CK activities. Pretreatment with *B. monniera* in CS resulted in the elevation of the glucose level in the circulation, which can be easily available energy substrate and help the organism to combat the stress demand at its internal and external environment. This elevation of the glucose in the CS by bacopa treatment represents its restorative properties, which can be achieved by enhancing the enzymes involved in glucogenolysis and gluconeogenesis, which are the main rate-limiting step in conversion of the noncarbohydrate source to carbohydrate. Pretreatment with *P. quinquefolium* also reversed ulcer index, adrenal hypertrophy, AST, and CK. Similarly, other adaptogens such as *W. somnifera* (Singh et al., 1982) and *O. sanctum* (Bhargava and Singh, 1981) has been reported to be effective against stress-induced gastric ulcers and adrenal gland hypertrophy; therefore, the profile of the *B. monniera* is similar to *W. somnifera* and *O. sanctum*.

Here, *B. monniera* at higher dose and *P. quinquefolium* are showing antistress effect by attenuating the systemic HPA axis response. This shows that *B. monniera* is effective

both in AS as well as in CS via attenuating the HPA axis. *P. quinquefolium* treatment attenuates the HPA axis response only in case of CS but fails during AS. The other reversal during the AS may be the peripheral effects of the *P. quinquefolium*, which may be the same in case of low dose of *B. monniera* treatment during the CS.

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