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A prospective, randomized, placebo-controlled, double-blind comparative pilot study to evaluate the efficacy of *Chlorophytum borivilianum* on physical performance

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» Abstract

OBJECTIVES: The objective was to study the adaptogenic effect of *Chlorophytum borivilianum*(CB) on physical performance when exposed to accustomed activity (AA) and unaccustomed activity (UA) and the effect of CB on heart rate (HR) and blood pressure (BP) in the presence of UA and the effect on muscle strength in comparison with placebo.
MATERIALS AND METHODS: A placebo-controlled, double-blind clinical study was initiated after ethics committee approval in healthy volunteers with fixed-dose regimen. Consented volunteers (n = 60) were assigned randomly into two groups of study drug (3 g/day) or placebo (3 g/day) for 2 months. They were evaluated at days 0, 30, and 60 with physical stressors (6-min walk test [6MWT] – distance, HR, and BP; 6-min exercise test [6ETC] – distance, maximum and average speed; and fixed workload test [FWT] – systolic BP, diastolic BP [DBP], and HR on cycle ergometer) and Jammar's dynamometer test for handgrip strength test on each visit.
RESULTS: In 6MWT in CB group, distance on day 30 (456 ± 42.1) and day 60 (468.3 ± 0.4) was significantly increased when compared with day 30 (422.6 ± 45.7) and day 60 (419.6 ± 45.1) of the placebo group. On day 60, distance in 6ETC in CB group was 2.92 ± 0.6 which was significantly more than that of placebo group 2.4 ± 0.6. On day 60, in FWT, DBP in the CB group was 75.8 ± 4.4 which was significantly low compared to the placebo group 82.4 ± 7.4 ($P < 0.05$).
CONCLUSION: CB increased physical performance when exposed to AA even after one month and in case of UA increase in performance was seen when CB was administered for two months thus validating its adaptogenic (anti-stress) potential.

Keywords: Adaptogenic activity, cycle ergometer, safed musli

» Introduction

Stress is the biological response which is controlled by the brain as a result to a challenging stimulation of a physical or mental nature. Stress as defined by Hans Selye is "the nonspecific response of the body to a stimulus or event, whether it is caused by the pleasant or unpleasant condition."[1] Stressor is any agent which produces stress. All stressors, whether physical or emotional, would provoke the same physiological reaction. The brain perceives the everyday activity as a stress, which ranges from walking down the road to handing a challenging report on time.[2],[3]

According to a survey done by the National Institute of Mental Health and Neurosciences, 20 million people in India need help for severe mental disorders, while a further 50 million suffer from mental illnesses which are not very serious. These diseases have physical symptoms originating from psychological or emotional causes, most common of which are stress (20%), anxiety (24.4%), and depression (18.5%).[4]

In response to stress, there is an activation of the hypothalamic–pituitary–adrenocortical (HPA) axis; this axis regulates the release of stress hormones such as epinephrine, norepinephrine, and cortisol, which are associated with mental and physical health functioning.[5] Prolonged and repeated activation of the HPA axis can be hazardous to health in acute and chronic conditions.

Stress is an important cause of cardiovascular, metabolic, and lifestyle disorders in developing as well as in developed countries. Prolonged exposure to stress can lead to the development of hypertension, stroke due to cardiac hyperreactivity, and increase in cholesterol and metabolic changes like hyperglycemia can lead to the development of diabetes, obesity, etc.

The body prevents the hazardous effects of the compensatory mechanism produced by stressors. In this context, adaptogens are endogenous substances which help the body to adapt to stress, also support normal metabolic functions of the body, and help to restore balance. There are various endogenous cytokines, interferons, and peptides, which act as an adaptogen.

Adaptogens are substances, which improve an individual's ability to cope with stress and normalize the physiological response of the body and help the body to adapt and enhance physical performance.[6] Since the endogenous adaptogens cannot be given prophylactically and exogenously and are not available, hence search for an exogenous substance which will work as an adaptogen is essential.

The current treatment modalities for the management of mental stress are behavioral therapy, relaxation exercises, de-addiction therapy in case of addiction and meditation, and drugs such as tricyclic antidepressants and benzodiazepines.[7]

However, there is no drug available in modern medicine, which can be given prophylactically and which can empower the body to tackle the physical stress and decrease the body's response to various stressors and improves physical as well as mental performances without any adverse event and preventing the long-term health-related problem due to stress.

Chlorophytum borivilianum (CB), commonly known as safed musli, has an adaptogenic property.[8] Conventionally, CB is used as a general health promotive substance; it is one of the main constituents of chyawanprash.[9] It is extensively used in ayurvedic prescription as a single or compound formulation for an aphrodisiac, physical weakness, and frailty for thousands of years ago. Despite these, there are very few clinical studies done, and hence, to generate and strengthen the data, this drug was selected.

The objective of our study was to evaluate the effect of CB on physical performance when subjected to accustomed activity (AA) and unaccustomed activity (UA) and its effect on heart rate (HR) and blood

pressure (BP) in the presence of UA and its effect of muscle strength. AA was included in our exercise protocol to evaluate the effect of CB on activities of daily living, i.e., walking, and UA, i.e., strenuous physical activities were included to evaluate the effect of CB on cardiovascular parameters in the presence of physical stress.

» Materials and Methods

This was an investigator-initiated, pilot study, designed as a prospective, randomized, placebo-controlled, double-blind, two-arm comparative study in healthy adult volunteers with fixed-dosage regimen. Institutional Ethics Committee approval (EC/89/2016) was taken before conducting the study, and it has been registered on the Clinical Trial Registry of India (CTRI/2017/08/009586).

Volunteers were informed about the study by word of mouth, and those who were coming to institute on a daily basis were recruited in the study. Volunteers who fulfilled the eligibility criteria (male/female between the age groups of 18 and 45 years, normal hematological and biochemical investigations, and not performing any strenuous activity) were included in the study. Those with a history of allergy or intolerance to study drug, addiction, lower- or upper-limb injury, and already taking other rasayana herbs, pregnant/lactating women, and those with other serious disorder or if volunteers did walk continuously >1 h as a part of exercise regimen were excluded from the study.

The standardized powder form of the root of CB was used. Maize starch powder was used as a placebo. The dose of the study drug and placebo was 3 g/day. The dose of the drug was selected from standard ayurvedic textbooks.[10],[11],[12] Both study drug and placebo were given in a capsule form orally. Each capsule containing 500 mg of the drug was given as two capsules three times a day (TDS) after a meal for 60 days.

Since the study was double blind (outcome assessor and volunteers were blinded), capsules of both study drug and placebo were of a same size and color (dark orange), and these drugs were dispensed by the investigator who generated the randomization codes.

Sixty volunteers were recruited after taking an audiovisual written informed consent. Volunteers were checked for the healthy status by clinical history, examination, complete blood count, fasting blood sugar levels, liver function test, and renal function test.

After screening, they were randomized using online software into two groups, i.e., 30 in CB and 30 in the placebo group. Randomization was done after successful screening procedure on baseline visit (day 0). Randomization codes were generated by the investigator who was not assessing the outcomes.

The evaluation was done on three visits: baseline visit (day 0), day 30, and day 60.

Effect of physical stress on physical performance in AA was assessed by 6-min walk test (6MWT), in which volunteers were asked to walk at their normal speed (no running) for 6 min in the 20 m long corridor. The variables assessed in this test were distance covered in 6 min and HR and BP before and after the test. AA (nonspecific not as per protocol), i.e., walking, was done by the volunteers on a routine basis in addition (protocol specific) AA, i.e., 6MWT, was performed and recorded on test days.

The second test was 6-min exercise test (6ETC) on a cycle ergometer which was done to evaluate the effect of CB in the presence of UA. In this volunteer were asked to pedal the cycle ergometer for 6 min at the fixed resistance of 75 watts and without any speed limit. Variables in this test were maximum distance and maximum and average speed.

Muscle strength was evaluated using hand dynamometer, and an average of three readings was taken for analysis.

Effect of UA on HR and BP was assessed by measuring cardiovascular parameters: BP and HR, and stressors used for the same were fixed workload test (FWT) on a cycle ergometer. This test is similar to 6ETC except that in this test, volunteers had to pedal the cycle at the fixed speed of 50 rpm.

After baseline visit, volunteers were asked to come to the study site after 30 and 60 days for the next visits, and this same exercise protocol was followed on these days.

Study drugs for the first 30 days were given to the volunteers on baseline visit, i.e., day 0, and for the next 30 days, it was given on the next visit on day 30. Compliance was assessed by counting the number of capsules in the container on day 30 and day 60. Compliance of >80% was necessary to continue the study.

All the tests were performed in an air-conditioned room (24°C–26°C), and during each test, a rest period of 15–20 min was given to the volunteers for the hemodynamic stabilization.

Statistical analysis

This was a pilot study, and hence, formal sample size calculation was not done. Repeated measures ANOVA was used for the within-group analysis for parametric data. For nonparametric data, Friedman test was used. *Post hoc* Tukey's test was applied when repeated measures ANOVA showed a significant difference of $P < 0.05$. For comparison of all the variables, between the placebo group and study group at each visit, unpaired *t*-test (parametric data) and Mann–Whitney test (nonparametric data) were used. IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY) was used for the analysis of the data.

» Results

The data were collected, compiled, and analyzed from May 2016 to October 2017, after executing the approved protocol in each volunteer. Sixty-seven volunteers were screened, out of which 60 healthy adult volunteers were included in the study [Figure 1]. Seven volunteers were not eligible to participate in the study. Out of 60 volunteers, 19 were female and 41 were male. These 60 volunteers were randomly divided into two groups, 30 volunteers per group. All the 60 volunteers completed the study. Data were expressed as mean ± standard deviation, and $P < 0.05$ is considered as statistically significant.

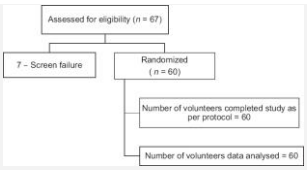

Figure 1: Flow diagram of study volunteers

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Mean of the age of the 60 volunteers was 28.53 ± 5.12 years (median: 27.5 years). The mean body mass index was 22.67 ± 1.80 kg/m^2. Clinical examination and all the investigations were normal. Resting HR, i.e., before starting the tests, was 79.404 ± 6.62 beats/min, and systolic BP (SBP) was 118.10 ± 6.72 mmHg and diastolic BP (DBP) was 73.09 ± 7.69 mmHg.

CB, when administered daily to healthy individuals for 2-month duration, has shown the significant change in all the variables of physical performance when exposed to AA, i.e., distance in 6MWT has increased from 431.66 ± 38 (day 0) to 468.33 ± 0.43 m on day 60 in comparison to placebo and day 0. In the same test, HR after the test decreased from 85.30 ± 9.31 to 78.30 ± 8.26 on day 60 when compared with day 0 and placebo. SBP was also decreased on day 60 in the CB group when it was compared with the placebo ($P < 0.05$) [Table 1].

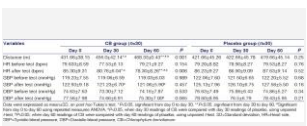

Table 1: Effect of *Chlorophytum borivilianum* and placebo on physical performance of healthy volunteers when exposed to accustomed activity (6-min walk test)

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In the presence of UA in 6ETC, distance traveled in 6 min increased significantly from 2.57 ± 0.55 to 2.92 ± 0.63 km on day 60 when compared to day 0 and placebo. Maximum speed also increased significantly from 32.96 ± 7.51 (day 0) to 37.50 ± 6.46 km/h on day 60 when compared with day 0 and placebo. A significant increase in average speed was also seen on day 60 (28.49 ± 5.62) when compared with day 0 (24.36 ± 5.54) and placebo ($P < 0.05$) [Table 2].

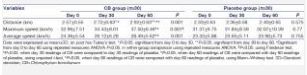

Table 2: Effect of *Chlorophytum borivilianum* and placebo on physical performance of healthy volunteers whenexposed to unaccustomed activity (6-minute exercise test)

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In FWT also, we found a significant decrease in the SBP in the CB group when compared with placebo group, but in within-group comparison, decrease in SBP was not significant. DBP also showed a significant decrease on day 60 (75.83 ± 4.47) when it was compared to day 0 (78.96 ± 8.22) and placebo. HR also decreased significantly from 107.00 ± 17.18 on day 0 to 96.56 ± 17.96 on day 60 ($P < 0.05$) [Table 3].

Table 3: Effect of *Chlorophytum borivilianum* and placebo on heart rate and blood pressure of healthy volunteers when exposed to unaccustomed activity (fixed workload test)

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Handgrip strength also showed a significant increase from 26.56 ± 7 on day 0 to 29.06 ± 7.49 on day 60 when compared to day 0 of CB group, but when it was compared with placebo, it was not significant ($P < 0.05$) [Table 4].

Table 4: Effect of *Chlorophytum borivilianum* and placebo on muscle strength of healthy volunteers when exposed to unaccustomed activity (handgrip strength test)

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» Discussion

The brain perceives the everyday activity as stress. UA is anyway considered as a physical stressor, but AA like day-to-day activities such as walking are also considered as stressful events because it can also activate HPA axis.[13]

In Indian system of medicine, i.e., in Ayurveda, it has been mentioned that herbs with rasayana property possess adaptogenic activity and were formerly known as tonics or rejuvenating herbs. CB belongs to the category of rasayana herbs.

The present study was planned to validate the effects of herb CB, which is known to have

adaptogenic/antistress properties.

Exogenous substance can be called as adaptogen if it is to fulfill all of the following criteria the definition of adaptogen which are, (a) an adaptogen is nontoxic to the recipient, (b) an adaptogen produces nonspecific effects in the body – an increase in the power of resistance against various stressors including physical, chemical, or biological agents, and (c) an adaptogen has a normalizing influence on physiology irrespective of the direction of change from physiological norms caused by the stressors.[14]

As we can see from the results of our study, CB satisfies this definition of an adaptogen, i.e., it has produced a significant response against physical stressors, as it has significantly changed all the variables in both accustomed and UAs. All these results prove that CB increases the body's resistance when exposed to stressor like physical exercise. The results obtained in the placebo group are nonsignificant when compared to CB which demonstrates that CB has produced a nonspecific response and it did not affect any normal body function and did not show any adverse events. All these factors fulfill the criteria mentioned above in the definition of adaptogen, and hence, it can be considered as an adaptogen.

There are no clinical studies for the evaluation of adaptogenic activity of CB, and our study is a first of its kind for evaluation of its adaptogenic activity. However, there are few animal studies in which these properties were evaluated. There were two experimental studies which were done for evaluation of antistress activity of CB. A study conducted by Deore and Khadabadi in rats evaluating the antistress effects of CB, four animal models, i.e., swim endurance test, anoxic stress tolerance test, chronic stress-induced behavioral despair test, and cold restraint ulcers (stress ulcers) was used. After giving the drug for 21 days (100–300 mg/kg of the alcoholic extract), increase in swim time and decrease in the ulcer index were observed. It was concluded that lower dose of CB exerted antistress effects, and a higher dose of CB was as effective as 1 mg/kg diazepam in decreasing stress as evaluated by a cold-water restraint test and measuring biochemical alterations in serum.[15]

In another study by Kenjale *et al.*, adaptogenic and antioxidant activities of CB were evaluated. The crude root powder of the CB was used. Chronic cold restraint stress model was used for the antistress evaluation. Antioxidant activity was assessed by doing an assay of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity. The authors found a significant reduction in the number of ulcers in a dose-dependent manner in animals in CB group as compared to controls. CB group showed a better protection against ulcers than even diazepam group. CB also showed a dose-dependent decrease in serum corticosterone and inhibition of the DPPH-free radical in a dose-dependent manner. Hence, it was concluded that CB has antistress and antioxidant activity.[8]

Since there was no clinical study of CB for evaluation of antistress effect, we compared the clinical studies in which another rasayana herb was used, and exercise protocol similar to our study was used. In this context, we found a study done by Tripathi *et al*.,[16] in which the authors had used the similar bicycle ergometer protocol and hand dynamometer like our study, but the study drug was *Withania somnifera* (WS). Duration of this study was 28 days, so we compared day 30 readings of our study. Increase in physical performance was more in their study compared to our study, but WS did not show any significant decrease in the HR and BP when compared with CB. This can be explained by the fact that WS belongs to the group of balya herbs which is also known to have more potent balawardhak (muscle strengthening) activity. However, the CB has shown a better effect on cardiovascular parameters compared to that of WS.

Another study was conducted by Salve *et al.*,[17] in which they used similar exercise protocol (on a cycle ergometer and hand dynamometer) using *Tinospora cordifolia* (TC) which is also a well-known adaptogen, used very commonly. This study was also of 28 days, and hence, their results were compared with our day 30 results. When we compared the results of our study with their results, it was seen that improvement in physical performance was better in CB group than the TC group, and the adaptogenic activity was better in TC group compared to the CB group. According to Ayurveda, TC is considered as one of the best rasayana herbs, and it is known to have an excellent adaptogenic activity. Hence, the better effect of TC compared to that of CB can be explained.

Raut *et al*. conducted a study which was designed to assess dose-related tolerability, safety, and activity of WS formulation in healthy volunteers.[18] They also used cycle ergometer for evaluation of exercise tolerance and adaptogenic effect of WS. However, they did not get any significant increase in all the variables, i.e., distance and maximum and average speed, unlike our study which showed a significant increase in all the variables. WS has also demonstrated muscle strengthening effect which resembles the muscle strengthening effect of CB.

From the studies mentioned above, it is clear that like other rasayana herbs, CB also has an adaptogenic effect. In few studies, we have found that CB was not as good as WS in improving physical performance, but in another study, it was found to be better than TC, and the adaptogenic activity of CB was better than that of WS, but it was less than that of TC. This may be because WS is a potent balawardhak drug, and TC is a more potent adaptogen, but our study drug, CB has shown both balawardhak and adaptogenic effect. Hence, we can hypothesize that CB may be noninferior to WS and TC, however, to prove this head on clinical trials should be done.

In our study, we also found that CB is safe when given in the dose of 3 g/day for 60 days, as there were no adverse events during the study period. We also found two clinical studies of CB which one was done to study the effect of CB and velvet bean on sleep quality and the second study was done to evaluate the effect of CB and velvet bean on growth hormone in exercise-trained men.[19],[20] In these two studies also, no adverse events were observed which prove that CB is safe to administer.

We have concluded that CB acts as an adaptogen but how this adaptogen herb works and what is the mechanism of action is still a mystery. However, as mentioned earlier in the discussion, antioxidant property of the herb might be responsible for its adaptogenic activity which might correlate with high polyphenol and flavonoid contents of CB root.[8]

Limitation of this study was that we did not measure the biochemical parameters of stress such as blood cortisol level or probe into the mechanism of action of CB.

We can recommend that adaptogenic activity of CB should be compared with other herbs with adaptogenic property by doing head-on clinical trials. It can be given as a nutraceutical, which will help to improve the physical performance and prevent the hazardous effects of acute and chronic stress in the day-to-day stressful life. This drug can also be given to debilitated adults and those who require high-intensity exercise such as athletes and army soldiers.

» Conclusion

We would like to conclude that CB had shown a significant adaptogenic activity in the presence of AA even when it was administered for a shorter duration, i.e., for 30 days. This implies that CB has a better effect on physical performance in the presence of AA even after a short duration of administration. In the presence of UA, improvement in the physical performance was seen on day 60, which proves that CB had produced a significant effect on UA when it was administered for a longer duration. In FWT also, there was a decrease in the DBP and HR on day 60 which was statistically significant.

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Conflicts of interest

There are no conflicts of interest.

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