Experimental evaluation of *Streblus asper* hydroalcoholic extract for antistress activity

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**ABSTRACT**
Stress is the causative factor for various diseases and disorders faced by the majority of the diseased population. The leaves of *Streblus asper* (*S. asper*) are attributed to neuropharmacological properties as per literature. The *S. asper* hydroalcoholic extract was tested for antistress activity in animals. The study deals with the evaluation of *S. asper* hydroalcoholic extract for adaptogenic activity using cold immobilization stress. The *S. asper* hydroalcoholic extract (200 and 400 mg/kg) was administered to treatment groups 1 hour before stress methods for ten consecutive days. Induction of the stress procedure was repeated for ten days. Rats fasted overnight on 10th days, On 11th days the blood was collected from the retro-orbital vein for biochemical estimation under anaesthesia. Liver function profiles (SGOT, SGPT, and ALP), lipid profiles (TC, TG, HDL, LDL, and VLDL), differential leukocyte count (neutrophils, eosinophils, lymphocyte, and monocyte), and organs weight (adrenal gland, spleen, liver, and kidney) were evaluation parameters of adaptogenic activity in the cold immobilization stress. The dose group 400 mg/kg p.o. of *S. asper* hydroalcoholic extract for adaptogenic activity in cold immobilization showed significant variation (P<0.1) when is compared with the stress control group. Therefore, it was revealed that *S. asper* hydroalcoholic extract showed potential adaptogenic activity.

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**INTRODUCTION**
Stress is the threatend homeostatic condition of the human being, and it is characterized in the form of non-specific response of the body (Khan and Ali, 2010). Stress carries numerous physiological alterations in the living system. Still, several mechanisms of the body counteract to keep up homeostasis (Pasha et al., 2014). It was revealed that various diseases and disorders like hyperglycemia, raised blood pressure, gastric ulcers, and chronic depression caused by stress (Pawar and Shivakumar, 2012). The immune function is suppressed, and the corticosterone level is elevated during stress situations which accelerate the formation of free radicals (Ramanth and Rekha, 2009; Abbas et al., 2019). Therapy of stress includes an alternative system of medicine, allopathic which is being currently available. Still, allopathic medicine drugs, especially benzodiazepines category, are having various adverse effects (side effect, tolerance, and dependence) which limit its uses. Thus herbal formula-
tion needs for management of stress on long term use (Habbu et al., 2010). Rasayanas of Ayurveda are effective adaptogenic agents because they seem to prolong, Selye’s proposed stage of the “General adaptation syndrome”, the stage of resistance to stress, and prevent the final and third stage of exhaustion (Habbu et al., 2012).

In the current scenario, we need safer and economical herbal drugs as adaptogenic agents that can withstand stress without modifying the biological functions of the body. Plant Adaptogens like Withania somnifera (Saleem and Nagasirisha, 2014), Elutherococcus senticosus (Zhang et al., 2010), Panax ginseng (Rai et al., 2003), Bacopa monniera (Bharathi et al., 2009), Sidacordifolia (Sumanth and Mustafa, 2009), Ocimum sanctum (Gupta et al., 2007), Butea frondosa (Soman, 2004), and Hypericum perforatum (Kumar et al., 1999) were reported. Streblus asper is a gnarled tree known by several common names mostly Sihor, Siamese rough rush. It is geographically present in the drier portion of India, Malaysia, Thailand, and Sri Lanka. S. asper contains myricetin, naringenin, kaempferol, quercetin, and ginkgoth flavonoids (Neekhra et al., 2019; Anbari et al., 2019). Some of the discovered flavonoid derivatives with a flavone-like structure such as quercetin and kaempferol have been therapeutically reported for adaptogenic activity. Therefore, we attempt to investigate the adaptogenic activity of S. asper hydroalcoholic extract using cold immobilization stress in rodents.

MATERIALS AND METHODS

Animal

Male Wistar rats were selected randomly from the animal house, having a standard weight of 160±20 g. The room temperature was kept at 22±2°C with free access to water and food. Before the beginning of the experiment, animals were shifted to the laboratory and food, and water was removed. All conditions were maintained according to the CPCSEA guideline. The institutional animal ethical committee permitted the study protocol. (Approve Ref No. SRGI/COP/A/29/2016, CPCSEA Reg No. 1624/P0/a/CPCSEA)

Plant material

The plant material (leaves of S. asper) was collected from the forest region of Lakhimpur Kheri district, Uttar Pradesh, India, and authenticated by taxonomist of CSIR-NBRI, Lucknow, India. The voucher specimen of the plant was deposited in the herbarium for future reference (NBRI/CIF/526/2016).

Preparation of extract

The dried powdered material (leaves of S. asper) was taken and subjected to solvent extraction. The extraction was carried out for 16 h with the hydroalcoholic solvent using the material to solvent ratio of 1:5 (w/v).

The hydroalcoholic extract was concentrated by evaporation of the solvent at low temperature till complete drying. Dried extract material was weighed and calculated the different extractive values.

Quantitative estimation of kaempferol in Streblus asper hydroalcoholic extract

The high-performance liquid chromatography (HPLC) analysis was performed using an LC-20AD, Shimadzu, Japan, with SPD 20A UV detector. The mobile phase consisted of solvent A: B [55:45]. Solvent A is acetonitrile, and solvent B is water containing 0.1 % o-phosphoric acid. The separation was performed using isocratic elution (0-20 min) with a flow rate of 1.0 ml/min and a column temperature of 25°C. The injection volume was 20μl, and the UV detection was performed at 370 nm absorbance for kaempferol. For the preparation of the sample solution, accurately 10 mg sample was dissolved in 10 ml acetonitrile: water 50:50. Transferred this solution in 10 ml volumetric flask, and the volume was made up with the same solvent (Rajesh et al., 2009).

Administration of the extracts

S. asper hydroalcoholic extract was dissolved in distilled water. The diazepam was suspended in 2% gum acacia, administrated intraperitoneally (i.p.) before 30 min of induction of stress. Hydroalcoholic extract of two different dose levels 200 mg/kg and 400 mg/kg were administrated 1 hr before the initiation of stress.

Experimental design

S. asper hydroalcoholic extract was tested using this model at different doses. The rats were divided into five groups of five animals, each of both sex and treated with respective extracts at a dose of 200 and 400 mg/kg b.w. Orally one hour before stress exposure daily of 10 days in cold immobilization stress.

The stress was induced by exposing rats (five groups) to the cold condition of 4-7°C for four h. The rats were then shifted from their home cages and individually placed in plastic containers with a partition to separate individual rats. The refrigerator had placed containers which were maintained at a temperature from 4 to 7°C. Rats were returned to home cages after four h. This procedure was repeated for
Table 1: Effect of S. asper hydroalcoholic extraction serum liver function test in rats

| S. No. | Treatment group                        | SGOT (U/L)       | SGPT (U/L)       | ALP (U/L)   |
|--------|----------------------------------------|------------------|------------------|-------------|
| 1      | Normal Control (10 ml/kg)              | 143.550±9.910    | 98.94±2.57       | 167.22±6.24 |
| 2      | Stress Control (10 ml/kg)              | 270.560±6.736### | 177.78±4.44###  | 314.16±2.12### |
| 3      | S. asper hydroalcoholic extract (200 mg/kg) | 235.23±8.84*    | 153.61±7.32*    | 283.82±5.95* |
| 4      | S. asper hydroalcoholic extract (400 mg/kg) | 217.620±7.450** | 146.78±8.08**   | 270.95±7.60** |
| 5      | Standard drug diazepam (1 mg/kg)       | 158.790±2.640*** | 111.59±7.124*** | 214.30±8.37*** |

Value are expressed as mean± SEM (n = 5), one way ANOVA followed by Dunnett’s test; ### P<0.001 when compared to normal control * P <0.5, **P <0.1, ***P <0.05 when compared with the stress group.

Table 2: Effect of S. asper hydroalcoholic extraction lipid profiles level in rats

| S. No. | Treatment group                        | TC (mg%)         | TG (mg%)         | HDL (mg%)      | LDL (mg%)       | VLDL (mg%) |
|--------|----------------------------------------|------------------|------------------|----------------|----------------|------------|
| 1      | Normal Control (10 ml/kg)              | 75.66±1.861      | 65.54±1.09       | 53.71±3.32     | 20.44±0.59     | 13.10±0.21 |
| 2      | Stress Control (10 ml/kg)              | 96.32±1.44###    | 98.86±2.80###   | 13.96±3.21###  | 40.3±1.13###   | 19.69±0.56### |
| 3      | S. asper hydroalcoholic extract (200 mg/kg) | 86.04±2.06*     | 89.26±2.44*     | 26.35±2.315*   | 33.78±1.11*    | 17.85±0.48* |
| 4      | S. asper hydroalcoholic extract (400 mg/kg) | 82.54±3.68**    | 86.22±2.14**    | 28.69±2.86**   | 32.36±1.48**   | 17.24±0.42** |
| 5      | Standard diazepam (1 mg/kg)            | 76.33±2.07***    | 67.16±1.65***   | 39.77±3.84***  | 22.18±1.13***  | 13.43±0.32*** |

Value are expressed as mean± SEM (n = 5), one way ANOVA followed by Dunnett’s test; ### P<0.001 when compared to normal control * P <0.5, **P <0.1, ***P <0.05, when compared with the stress group.

Table 3: Effect of S. asper hydroalcoholic extraction differential leukocyte count in rats

| S. No. | Treatment group                        | Neutrophils      | Eosinophils      | Lymphocyte     | Monocyte       |
|--------|----------------------------------------|------------------|------------------|----------------|----------------|
| 1      | Normal Control (10 ml/kg)              | 23.6±0.92        | 2.40±0.24        | 74.6±1.56      | 6.6±0.2        |
| 2      | Stress Control (10 ml/kg)              | 35.01±1.14###    | 3.8±0.2#         | 66.8±1.49###   | 6.8±0.37###    |
| 3      | S. asper hydroalcoholic extract (200 mg/kg) | 28.46±0.46*     | 3±0.31           | 70.8±1.2*      | 6.4±0.4*       |
| 4      | S. asper hydroalcoholic extract (400 mg/kg) | 26.58±0.50**    | 2.8±0.37         | 71.6±1.4**     | 6.4±0.24**     |
| 5      | Standard diazepam (1 mg/kg)            | 26±2.07***       | 2.6±0.2*         | 73±1.28***     | 6.2±0.37***    |

Value are expressed as mean± SEM (n = 5), one way ANOVA followed by Dunnett’s test; ### P<0.001 when compared to normal control * P <0.5, **P <0.1, ***P <0.05, when compared with the stress group.
Table 4: Effect of S. asper hydroalcoholic extract on organs weight in rats

| S. No. | Treatment group                                | Adrenal Gland (nM/gm) | Kidney (U/gm)  | Spleen (nmol/gm) | Liver (U/mg) |
|--------|-----------------------------------------------|-----------------------|----------------|-----------------|--------------|
| 1      | Normal Control (10 ml/kg)                     | 38.8±1.8              | 0.859±0.027    | 0.76±0.07       | 6.04±0.10    |
| 2      | Stress Control (10 ml/kg)                     | 50.0±1.6###           | 1.050±0.054### | 0.44±0.03###    | 7.77±0.28### |
| 3      | S. asper hydroalcoholic extract (200 mg/kg)   | 43.0±1.3*             | 0.932±0.024*   | 0.637±0.02*     | 7.01±0.072*  |
| 4      | S. asper hydroalcoholic extract (400 mg/kg)   | 42.2±1.6**            | 0.923±0.014**  | 0.692±0.04**    | 6.7±0.23**   |
| 5      | Standard diazepam (1 mg/kg)                   | 38.86±1.7***          | 0.856±0.014*** | 0.74±0.07***    | 6.33±0.19*** |

Value are expressed as mean± SEM (n = 5), one way ANOVA followed by Dunnett’s test; ###P<0.001 when compared to normal control, *P<0.5, **P<0.1, ***P<0.05, when compared with the stress group.

Figure 1: HPLC chromatogram of standard marker kaempferol

Figure 2: HPLC chromatogram of Streblus asper hydroalcoholic extract showing the presence of kaempferol
ten days at a specific time between 12:00 noon to 4:00 p.m. Rats were free to food and water, on the 11th-day animals were sacrificed by cervical dislocation, blood was collected from the arterial jugular and serum was separated from some part of collected blood. The serum was used for the estimation of various biochemical parameters using different biochemical kits (Erba/Span Kits). The weights of organs such as the liver, adrenal gland, kidney and spleen were recorded after washing with ice-cold saline (Kannur et al., 2017).

**Statistical analysis**

All the values are expressed as mean ± SEM. Statistical differences between means were determined by one way ANOVA followed by Dunnett’s post hoc test. \( P < 0.05 \) was considered significant. The statistical analysis was done using Instat \(^\circ\) software (Graph pad Inc., Santabarba, CA)

**RESULTS**

**HPLC analysis of the extract**

A simple HPLC method was developed for the detection of kaempferol (marker compound) in the standardized hydroalcoholic extract. As shown in Figure 1, a sharp, symmetrical chromatographic peak was obtained for kaempferol standard using the chromatographic conditions described above. Figure 2 shows the presence of a kaempferol peak in the standardized hydroalcoholic extract sample at a retention time of 7.28 min.

**Evaluation of the adaptogenic activity of the extract in rats**

**Effect on liver function test**

Serum liver function test parameters like SGOT, SGPT and ALP were found to be increased in cold immobilization stress in rats which were significantly decreased (\( *P < 0.5, **P < 0.1, ***P < 0.05 \)) in rats on pretreatment with *S. asper* hydroalcoholic extract (200 and 400 mg/kg) and diazepam (1 mg/kg) (Table 1).

**Effect on lipid profiles**

Lipid profiles (TC, TG, HDL, LDL, and VLDL) were found to be altered in cold immobilization stress on rats. Increased level of lipid profiles was significantly reduced (\( *P < 0.5, **P < 0.1, ***P < 0.05 \)) on pretreatment with *S. asper* hydroalcoholic extract (200 and 400 mg/kg) and diazepam (1 mg/kg) (Table 2).

**Effect on differential leukocyte count**

Differential leukocyte counts (Neutrophils, Eosinophils, Lymphocyte, and Monocyte) were increased in cold immobilization stress model on rats. Increased level of differential leukocyte counts was significantly reduced (\( *P < 0.5, **P < 0.1, ***P < 0.05 \)) on pretreatment with *S. asper* hydroalcoholic extract (200 and 400 mg/kg) and diazepam (1 mg/kg) (Table 3).

**Effect on organ weights**

Organs weight (Adrenal gland, Kidney, Spleen, and Liver) was increased in cold immobilization stress on rats. Increased level of organs weight was significantly reduced (\( *P < 0.5, **P < 0.1, ***P < 0.05 \)) on pretreatment with *S. asper* hydroalcoholic extract (200 and 400 mg/kg) and diazepam (1 mg/kg) (Table 4).

**DISCUSSION**

The studies observed so far mark that hydroalcoholic extract had a protective action on the animals against the alterations inflicted due to cold stress, such as changes in the serum liver function test and lipid profile levels, differential leukocyte count as well as the weight of the organs. The phytochemical and HPLC analysis indicates the seed to be a complex multi-component entity. Flavonoids, terpenoids were found to be present in the leaves. The presence of kaempferol was also confirmed. It results in hypothalamic-pituitary axis (HPA) activation, leading to the release of the adrenocortical hormone responsible for stressful response, further releasing of corticosterone hormone (Bhatia et al., 2011). In cold immobilization stress repeated exposure of rats for ten days to the stressful condition was carried, as it causes a wide range of physiological and neuroendocrine changes (Sutanto and de Kloet, 1994). The effect of stress on lipid profiles could be due to the liberation of corticosterone from the adrenal cortex that could mobilize lipids from adipose tissues. Lipid profiles levels (TG, TC, HDL, LDL, and VLDL) altered after exposure of rats to cold stress. The 400 mg/kg dose of *S. asper* leaves hydroalcoholic extract caused a significant restoration in the altered lipid profiles levels.

The cold stress exposed to rats leads to elevated levels of SGPT, SGOT and ALP due to secretion of corticosterone from the cortex, the adrenaline from medulla and nor-adrenaline from sympathetic nerve terminals which supply substrate for energy metabolism and the confirm the ATP demand in the muscles, CNS, and other organs (Lailatussifa et al., 2016).

In stress conditions, the second substrate, such as fat used for glucose formation and gluconeogenesis proceed in response to corticosterone. The trans-
fer of γ-amino groups of alanine and aspartate are being catalyzed by ALT and AST enzymes respectively, to γ- keto group of keto-glutarate, resulting in the formation of oxaloacetic acid and pyruvic acid (Barua et al., 2018). The 400 mg/kg dose of S. asper leaves extract caused significant reduction (P<0.1) in the levels of SGPT, SGOT and ALP in comparison to the stress control group. Corticosterone mediated enhanced metabolism may be attributed to meet the increased demands of the body organs during stress (Wu et al., 2013; Othman et al., 2013). Thus, weights of liver, kidney and adrenal gland were increased in rats subjected to cold stress whereas spleen weight was reduced.

The treatment of cold stress exposed rats with 400 mg/kg dose of S. asper leaves hydroalcoholic extract signiﬁcantly restored the altered weight of liver, adrenal gland, kidney and spleen close to control animals. Also, treatment with 400 mg/kg had a normalizing effect on the differential leukocyte counts, which were altered signiﬁcantly following cold stress. These results suggest that the hydroalcoholic extract of S. asper leaves possess significant antistress activity and could be explored in the management of stress in clinical settings.

CONCLUSION

Thus, the dose 400 mg/kg of S. asper hydroalcoholic extract has markedly affected on the biochemical parameter levels (liver function test and lipid profile) as well as differential leukocyte count and organs weight in which exhibited nearly effect to that of standard diazepam drug. However, the effect of S. asper hydroalcoholic extract signiﬁcantly improved various parameters as compared to stress control. This result can be indicated that the use of S. asper hydroalcoholic extract as a complementary treatment in future for attenuation of stress-induced biochemical alteration. Therefore, S. asper will mark as an adaptogenic agent category and served as a therapeutic agent into a clinical setting in future.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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