

Evaluation of Anti-stress Activity of *Orthosiphon stamineus Benth.* Lamiaceae Methanol Leaves Extract on Wistar Albino Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SP and KB developed the protocol, designed the experimental study and involved in the collection of literature, preparation of extract and screening of phytoconstituents present in the extract. Authors SP, KB and RSV involved in the evaluation of anti-stress activity and biochemical analysis. Authors SP, KB and AK involved in data interpretation and performed the statistical analysis. Authors SP and KB wrote the first draft of manuscript. Authors AK and RSV edited and completed the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The present study was aimed to determine the in-vivo anti-stress activity of *Orthosiphon stamineus* methanolic leaves extract using Wistar albino rats.

Methodology: In forced swimming endurance stress test and chronic cold restraint stress test Wistar albino rats of either sex was randomly divided into five groups of four animals each.

Methanolic leaves extract of *Orthosiphon stamineus* (200 mg/kg and 400 mg/kg p.o) was administered for 7 days for swimming stress method, whereas 10 days for cold stress method and last day, blood was collected by retro-orbital route to estimate blood cell count and biochemical parameters. to assess the anti-stress activity in Wistar albino rats. *Withania somnifera* (WS) (100 mg/kg p.o) was selected as reference standard.

Results: Results are expressed as mean \pm SEM and data was analysed by Student's t-test. From the results, it is found that methanol extract of *Orthosiphon stamineus* have significantly increase RBC, WBC, DLC count and other biochemical parameters in both forced swimming endurance and chronic cold restraint test. Furthermore, forced swimming stress is more significant when compared to cold restraint stress.

Conclusion: The results indicate that methanolic leaves extract of *Orthosiphon stamineus* possesses significant anti-stress activity.

Keywords: *Orthosiphon stamineus*; methanol; forced swimming endurance stress; chronic cold restraint stress; *Withania somnifera*.

ABBREVIATIONS

RBC : Red Blood Cell;
WBC : White Blood Cell;
DLC : Differential Leukocyte Count;
BUN : Blood urea nitrogen;
ACTH : Adrenocorticotrophic hormone.

1. INTRODUCTION

Stress can be considered as the whole reaction of the body, in which the normal physiological condition are being disturbed and result in a state of threatened homeostasis. Stress is an internationally recognized phenomenon fortified by advancement of industrialization in a demanding civilization. Thus, every individual is likely to face stressful situation in day to day life. Stress represents a reaction of the body to a stimulus that tends to alter its normal physiological equilibrium or homeostasis [1]. There is also activation of the HPA (hypothalamic-pituitary-adrenal) axis. Activation of the hypothalamus leads to the release of hormones that travel through the bloodstream to the pituitary gland, which in turn secretes other hormones and activates the adrenal gland which releases the stress hormone, cortisol [2].

Adaptogenic herbs, also known as adaptogens, are substances that enhance the ability to resist stress, anxiety, trauma and fatigue. Along with their role to relief fatigue, an important role of adaptogens is to aid longevity and the effects of aging on the cells. The examples of most popular adaptogenic plants are *Panax ginseng*, *Withania somnifera* (Ashwagandha) and so on [3].

Orthosiphon stamineus or Misai Kucing is a traditional herb that is widely grown in tropical

areas [4]. It was typically consumed as a herbal tea [5] and it is believed that *Orthosiphon stamineus* leaves have diuretic properties and has been used to remove stones from the kidneys. It is also widely applied to cure rheumatism, fever, hepatitis, gallstones, eruptive, hypertension, diabetes, epilepsy and as well as promoting health and well-being [6].

The aim of this study was to determine the in vivo anti-stress activity of *Orthosiphon stamineus* leaves extracts on Wistar albino rats, because there is not much evidence about the scientific data for its anti-stress activity even though this plant has been used in folklore medicine for relieving some stress related disorders. Hence, this study is to discover the plant extract with significant anti-stress activity.

It is hypothesized that any herbal extracts rich in adaptogenic phytoconstituents will possess significant anti-stress activity as it will be a new drug for effectively combating the problem of stress in daily human life. Thus, this plant was evaluated for anti-stress activity in stress induced Wistar albino rats for first time.

2. MATERIALS AND METHODS

2.1 Plant Material

Orthosiphon stamineus leaves, of white flower variety, was selected. The *O. stamineus* leaves were purchased from the local supplier from Seremban, Malaysia in the month of September 2016. The leaves were authenticated by Pharmacognosist, KPJ Healthcare University College, Nilai, Negeri Sembilan, Malaysia (Reference No: KPJUC/CRI/PA/2016 (23)).

2.2 Preparation of Plant Extract

The plant leaves were dried in shade at room temperature. The dried leaves were subjected to size reduction by using blender, to make it into coarse powder. Then, the powdered leaves (500 g) were extracted with methanol solvent by using cold maceration technique for 10 days. At the end of extraction, the extracts were collected by filtration using whatmann filter paper [7]. The filtered extract was evaporated and concentrated using rotary vacuum evaporator under reduced pressure to get semisolid mass and kept in desiccator until further use [8].

2.3 Preliminary Phytochemical Screening

The qualitative chemical tests were performed for identifying the presence and absence of phytoconstituents such as alkaloids, carbohydrates, glycosides, proteins and amino acids, sterols, fixed oils and fats, phenolic compounds and tannins, triterpenoids, saponins, gums and mucilage and flavonoids in crude methanolic extracts of *O. stamineus* leaves using standard methods [9].

2.4 Pharmacological Screening

2.4.1 Animals

Healthy adult Wistar albino rats weighing 200-250 g were obtained from the animal house of the KPJ Healthcare University College, Nilai, Malaysia. The animals of either sex were well ventilated and maintained under standard husbandry conditions at an ambient temperature ($25 \pm 2^\circ\text{C}$) had 12 hour day and night schedules with a spacious, hygienic cage during the course of the experimental period. The animals were fed with standard pellets and water *ad libitum* during the study period [10]. The experimental protocol has been approved by KPJUC Animal & Ethical committee (Reference No. KPJUC/CRI/BPS/EC/2016/15).

2.4.2 Forced swimming endurance test

2.4.2.1 Principle and procedure

When rats forced to swim in a restricted space from which they cannot escape, become immobile after an initial period of vigorous activity. It has been suggested to observe the immobility signifies behavioural "despair" resembling a state of mental depression and have to use to screen anti-depressants. It is now recognized that this behavioural depression is fairly a common consequence of stress. It is also

evidence that the animal's ability to cope with the stress largely influenced by the neurochemical consequence of stress. Thus, exposure of rats to inescapable and severe stress lead to depletion of central nor adrenaline and serotonin, postulated to be the cause of endogenous depression.

Stress has been exerted by keeping rats in cylindrical vessels (length 48 cm and width 30 cm) filled with water to a height of 25 cm. Extract was given to rats for 7 days, the rats was allowed to swim till exhausted in separate tanks filled with water. Then, end point was taken when the animal's starts drowning and swimming time for each animal was noted. The mean for swimming time for each group has been calculated. On the 8th day blood was collected by retro-orbital route to estimate biochemical parameters like blood glucose, triglycerides, cholesterol, BUN, ACTH and blood cell count (RBC, WBC, and DLC) [11].

2.4.2.2 Experimental design

The Wistar albino rats (200-250 g) of either sex were randomly divided into five groups of four each. The different groups have been assigned as below:

- Group I: Normal control (Normal saline-0.1 ml)
- Group II: Stress control
- Group III: Standard group (*Withania somnifera*/Ashwagandha) (100 mg/kg)
- Group IV: *Orthosiphon stamineus* extract (Methanol) (200 mg/kg)
- Group V: *Orthosiphon stamineus* extract (Methanol) (400 mg/kg)

2.4.3 Chronic cold restraint stress

2.4.3.1 Principle and procedure

The animals were subjected to cold stress by exposing them to $4 \pm 1^\circ\text{C}$ for 2 hours. The animals have been taken from their house cages and individually placed in plastic containers lined with bedding material. Then, the containers have been placed inside the refrigerator such that the temperature to which the animals exposed at $4 \pm 1^\circ\text{C}$, they was returned to their home cages after 2 hours. This procedure has been repeated for a period of 10 days. On the 11th day blood was collected by retro-orbital route to estimate biochemical parameters, like blood glucose, cholesterol, triglycerides, BUN, ACTH estimation and also for blood cell count (RBC and WBC) [12].

2.4.3.2 Experimental design

The Wistar albino rats (200-250 g) of either sex were randomly divided into five groups of four each. The different groups have been assigned as below:

- Group I: Normal control (Normal saline-0.1 ml)
- Group II: Stress control
- Group III: Standard group (*Withania somnifera*/Ashwagandha) (100 mg/kg)
- Group IV: *Orthosiphon stamineus* extract (Methanol) (200 mg/kg)
- Group V: *Orthosiphon stamineus* extract (Methanol) (400 mg/kg)

2.4.4 Biochemical analysis

The animals were mild anesthetized using ether and the blood samples of each animals were separately collected by retro-orbital puncture and transferred into Eppendroff's tubes (1 ml) containing 50 µl of anticoagulant (10% trisodium citrate). Then the plasma was separated and estimated for various biochemical parameters like glucose, cholesterol, triglycerides, BUN, ACTH and blood cell count (RBC, WBC, DLC) [13].

2.4.5 Statistical analysis

All the results were expressed as mean ± standard error of mean (SEM). The statistical significance was determined by using Student's t-test. The significant differences between the groups were determined using a comparison tests with the value of P < 0.05, P < 0.01, P < 0.001 which is considered as statistically significant [14].

3. RESULTS

3.1 Qualitative Phytochemical Screening

The presence of alkaloids, carbohydrates, glycosides, proteins and amino acids, phenols, triterpenoids, saponins and flavonoids were observed in methanolic extract of *O. stamineus* leaves (Table 1).

3.2 Effect of Forced Swimming Endurance Stress Test on Blood Cell Count

RBC, WBC and DLC count studies were conducted in forced swimming endurance stress

in standard (*Withania somnifera*), methanolic extract of *Orthosiphon stamineus*, treated groups. From the results, it was found that standard (*Withania somnifera*) have significantly increased in RBC, WBC and DLC count. The reduction of RBC, WBC and DLC count during stress has been increased with standard drug, low dose and high dose of methanolic extract. Significant increase was observed in high dose of methanolic extract of *Orthosiphon stamineus* which is almost comparable to standard drug. Results were tabulated in (Table 2).

Table 1. Qualitative phytochemical screening of *Orthosiphon stamineus* leaves extract

S. no.	Test	Methanol extract
1.	Alkaloids	+
2.	Carbohydrates	+
3.	Glycosides	+
4.	Proteins and amino acids	+
5.	Steroids	-
6.	Fixed oils and fats	-
7.	Phenols	+
8.	Tannins	-
9.	Triterpenoids	+
10.	Saponins	+
11.	Gum and mucilage	-
12.	Flavonoids	+

*(+) = Present; (-) = Absent

Student't' test indicates that there was a significant increase in blood cell count in standard and methanolic extract.

3.3 Effects of Forced Swimming Endurance Stress Test on Biochemical Parameters

Biochemical parameters like glucose, cholesterol, triglycerides, BUN and ACTH was estimated in forced swimming endurance stress test in rats after treatment with standard (*Withania somnifera*) and methanolic extract of *Orthosiphon stamineus*. It was found that a significant reduction in glucose, cholesterol, triglycerides and BUN level were observed but increase in ACTH estimation level in methanolic extract of *Orthosiphon stamineus*.

Results were tabulated in (Table 3). Student't' test indicates a significant activity with both the extracts.

Table 2. Effect of methanolic extract of *Orthosiphon stamineus* on blood cell count in forced swimming endurance stress rats

Groups	RBC (ml/L)	WBC (ml/L)	Neutrophils (ml/L)	Lymphocytes (ml/L)	Monocytes (ml/L)	Eosinophils (ml/L)	Basophils (ml/L)
Normal control	9.32±0.02	8.5±0.3	3.5±0.14	4.68±0.09	0.51±0.02	0.2±0.02	0.1±0.02
Stress control	6.87±0.02	3.69±0.23	1.58±0.09	2.23±0.1	0.22±0.01	0.12±0.01	0.05±0.01
<i>Withania somnifera</i> (Standard 100 mg/kg)	8.43***±0.32	7.38***±0.61	2.96***±0.04	3.55***±0.38	0.41**±0.02	0.18**±0.01	0.08**±0.01
Methanolic extract of <i>O. stamineus</i> (200 mg/kg)	7.25**±0.08	6.42***±0.21	2.09***±0.02	2.78**±0.09	0.15*±0.01	0.12±0.01	0.02±0.01
Methanolic extract of <i>O. stamineus</i> (400 mg/kg)	7.94***±0.32	7.06***±0.06	2.38***±0.1	3.01***±0.02	0.4**±0.02	0.15*±0.01	0.07*±0.01

*P < 0.05, **P < 0.01, ***P < 0.001 *Withania somnifera* VS Stress Control; 2. *P < 0.05, **P < 0.01, ***P < 0.001 extract treated groups VS Stress Control; 3. Values mean ± S.E.M., 4. n=4

Table 3. Effect of methanolic extract of *Orthosiphon stamineus* on biochemical parameters in forced swimming endurance stress rats

Groups	Glucose (mmol/L)	Cholesterol (mmol/L)	Triglycerides (mmol/L)	BUN (mmo/L)	ACTH (ng/L)
Normal control	6.9±0.38	1.75±0.05	1.37±0.01	6.12±0.09	452.5±875
Stress control	8.96±1.5	2.7±0.12	1.31±0	6.85±0.21	292.75±42.75
<i>Withania somnifera</i> (Standard 100 mg/kg)	7.1**±0.14	2.02***±0.01	0.55***±0.06	5.62***±0.23	496***±16.66
Methanolic extract of <i>O. stamineus</i> (200 mg/kg)	7.79*±2.59	1.62***±0.04	0.82**±0.13	6.4±0.7	398.25*±15.75
Methanolic extract of <i>O. stamineus</i> (400 mg/kg)	7.52**±0.64	1.97**±0.21	0.78**±0.29	5.85**±0.49	373.25***±47.5

*P < 0.05, **P < 0.01, ***P < 0.001 *Withania somnifera* VS Stress Control; 2. *P < 0.05, **P < 0.01, ***P < 0.001 extract treated groups VS Stress Control; 3. Values mean ± S.E.M., 4. n=4

Table 4. Effect of methanolic extract of *Orthosiphon stamineus* on Blood cell count and biochemical parameters in chronic cold restraint stress rats

Groups	RBC (ml/L)	WBC (ml/L)	Glucose (mmol/L)	Cholesterol (mmol/L)	Triglycerides (mmol/L)	BUN (mmol/L)	ACTH (ng/L)
Normal control	9.55± 0.16	8.65± 0.15	7.58± 0.21	1.88± 0.01	1.38± 0	6.66± 0.3	462± 14
Stress control	6.99± 0.79	6.41± 0.37	10.98± 0.23	2.32± 0.05	0.3± 0	7.7± 0.5	292± 14
<i>Withania somnifera</i> (Standard 100 mg/kg)	8.65**± 0.57	7.96***±0.05	8.68***± 0.21	1.65***±0.11	1.22***±0.02	6.61**± 0.08	475.25***±1032.75
Methanolic extract of <i>O. stamineus</i> (200 mg/kg)	7.74± 1.15	6.44± 0.69	6.2***± 1.06	2.3± 1.69	0.66± 0.89	7.2± 0.52	372***± 114
Methanolic extract of <i>O. stamineus</i> (400 mg/kg)	8.46**± 0.95	7.94***±0.36	7.77***± 4.25	1.77***±0.03	1.68***±0.44	6.49**± 0.93	481.25***± 644.75

*P < 0.05, **P < 0.01, ***P < 0.001 *Withania somnifera* VS Stress Control; 2. *P < 0.05, **P < 0.01, ***P < 0.001 extract treated groups VS Stress Control; 3. Values mean ± S.E.M., 4. n=4

3.4 Effect of Chronic Cold Restraint Stress on Blood Cell Count

It was found that methanolic extract of high dose have significantly increased RBC and WBC count when compared to low dose which is almost comparable with standard drug. Results were tabulated in (Table 4).

Student's 't' test indicates there is a significant increase in levels of RBC and WBC count when compared to stress control animals.

3.5 Effect of Chronic Cold Restraint Stress on Biochemical Parameters

The 2nd phase of the experimental study was the effect of methanolic extract of *Orthosiphon stamineus* in chronic cold restraint stress induced rats.

From the study, the methanolic extract exhibited significant activity by reducing enhanced blood glucose, cholesterol and increase in triglycerides level in high dose of methanolic extract. Whereas, there is significant reduction of BUN level and increasing ACTH level was observed in high dose of methanolic extract. More effect was observed in high dose of methanolic extract of *Orthosiphon stamineus* than low dose of methanolic extract of *Orthosiphon stamineus*, which is almost comparable with standard drug.

Results were tabulated in (Table 4). Student's 't' test indicates a significant activity with both the extracts.

4. DISCUSSION

Adaptogen is a term used to describe agents that increase the non-specific resistance of organisms against a variety of stressors. A recent review is taking place in this field and problems associated in the evaluation of Adaptogens. The current study was conducted to verify the adaptogenic effect of *Orthosiphon stamineus* leaves extract of the plant. Generally, stress will alter various bio-chemical parameters and blood cell count.

Hyperglycaemic response was observed during stress, stress raises serum cholesterol is possibly associated to the enhanced activity of hypothalamo-hypophysial axis resulting increased release of catecholamine's and corticosteroids. This may perhaps lead to

increase of blood cholesterol level since, epinephrine is known to mobilize lipids from adipose tissue.

The effect of stress on serum triglycerides has been revealed to be variable. This can be recommended for the change in the levels of serum triglycerides is possibly mediated via adrenal medullary secretions and through activation of sympathetic nervous system.

There will be protein mobilization by glucocorticoids leads to increase in urea levels. There is decrease in the blood cell count due to excessive release of corticosteroids. In forced swimming endurance stress, there is increase in swimming endurance time with both low and high dose of extracts.

In case of forced swimming endurance stress and chronic cold restraint stress there is imbalance in levels of biochemical parameters. The level of significant reduction was more in forced swimming endurance stress than chronic cold restraint stress. There is decrease in the blood cell count in both the stress conditions but in swimming stress it is more significant when compared to cold stress.

Stress induces adrenomedullary response in human being, whereas in turns adrenaline stimulates β_2 receptors on the pituitary gland triggering greater release of adrenocorticotrophic hormone (ACTH). ACTH can stimulate the adrenal medulla as well as cortex.

Phytochemical profiles in *Orthosiphon stamineus* indicate the presence of alkaloids, carbohydrates, glycosides, proteins and amino acids, phenols, triterpenoids, saponins and flavonoids are the constituents of the methanolic extract of *Orthosiphon stamineus* leaves.

Existence of glycosides, flavonoids, triterpenoids, saponins will confirm the adaptogenic activity as it is compared with the standard drug *Withania somnifera* where it contains glycosides, sterols and flavonoids.

5. CONCLUSION

Result of the present studies clearly indicates a significant. Adaptogenic (anti-stress) activity of methanol extract administered at a dose of 200 mg/kg and 400 mg/kg in both forced swimming endurance stress and chronic cold restraint stress type of experimental rats.

Alkaloids, carbohydrates, glycosides, proteins and amino acids, phenols, triterpenoids, saponins and flavonoids are the constituents of the methanolic leaf extracts of *Orthosiphon stamineus*.

It is concluded that adaptogenic activity of *Orthosiphon stamineus* (400 mg/kg) is comparable to that of standard *Withania somnifera* (100 mg/kg). The adaptogenic activity of methanol extract can be due to existence of glycosides, flavonoids, triterpenoids and saponins those were identified in preliminary phytochemical screening which can exhibits the anti-stress activity.

Further studies are needed for isolation and characterization of phytochemical constituents of *Orthosiphon stamineus* leaves extract that may lead to development of adaptogenic activity that can be used in the control of different types of stress.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85- 23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee" (Reference No. KPJUC/CRI/BPS/EC/2016/15).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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