

A Study to evaluate the efficacy and safety of SanAshwa in the management of stress and anxiety in healthy adult volunteers

Clinical Research

Dr. Harisha. S

Director, ICBio Clinical Research Pvt. Ltd, # 16, ICBio Tower, Chikkabetahalli, Yelahanka Main Road, Vidyanarayapura, Bangalore - 560 097, INDIA

Mr. Deva Jain

Sandhu Products Inc, 6052 Industrial Way, suite # H, Livermore, CA 94551

ABSTRACT

Background

Stress is your body's way of responding to any kind of demand or threat. When you sense danger—whether it's real or imagined—the body's defenses kick into high gear in a rapid, automatic process known as the “fight-or-flight” reaction, or the stress response.

Anxiety is an emotion characterized by an unpleasant state of inner turmoil, often accompanied by nervous behavior, such as pacing back and forth, somatic complaints, and rumination. Anxiety is a feeling of uneasiness and worry, usually generalized and unfocused as an overreaction to a situation that is only subjectively seen as menacing. It is often accompanied by muscular tension, restlessness, fatigue and problems in concentration.

Objectives:

Efficacy and safety of the SanAshwa in the management of stress and anxiety in healthy adult volunteers.

Methods: Seventy individuals who were facing routine work stresses along with anxiety are enrolled in the study. Stress & Anxiety symptoms were measured with the General Anxiety Disorder -7 (GAD-7), Stress sub-scale of Depression Anxiety and Stress Scale-21 (DASS-21), 7-item sub-scale measuring symptoms of stress, Patient Health Questionnaire-9 (PHQ-9).

Results: SanAshwa was found to be effective in lowering the Cortisol Levels, Stress scores, Anxiety scores and Depression scores.

Conclusion: SanAshwa was found efficacious for improvement & management of stress & anxiety in healthy adult subjects who were facing routine work stresses along with anxiety

KEYWORDS:

Introduction:

Stress is a feeling of emotional or physical tension. It can come from any event or thought that makes you feel frustrated, angry, or nervous. Stress is your body's reaction to a challenge or demand. In short bursts, stress can be positive, such as when it helps you avoid danger or meet a deadline. But when stress lasts for a long time, it may harm your health. Stress is a normal feeling. There are two main types of stress:

Acute stress. This is short-term stress that goes away quickly. You feel it when you slam on the brakes, have a fight with your partner, or ski down a steep slope. It helps you manage dangerous situations. It also occurs when you do something new or exciting. All people have acute stress at one time or another.

Chronic stress. This is stress that lasts for a longer period of time. You may have chronic stress if you have money problems, an unhappy marriage, or trouble at work. Any type of stress that goes on for weeks or months is chronic stress. You can become so used to chronic stress that you don't realize it is a problem. If you don't find ways to manage stress, it may lead to health problems.

ANXIETY:-

Anxiety is the body's natural response to danger, an automatic alarm that goes off when you feel threatened, under pressure, or are facing a stressful situation. Anxiety is more than just a feeling. As a product of the body's fight-or-flight response, anxiety involves a wide range of physical symptoms. Because of the numerous physical symptoms, anxiety sufferers often mistake their disorder for a medical illness.

Types of anxiety disorders

There are six major types of anxiety disorders, each with their own distinct symptom profile: generalized anxiety disorder, anxiety attacks (panic disorder), obsessive-compulsive disorder, phobia, social anxiety disorder, and post-traumatic stress disorder. Generalized anxiety disorder (GAD) is a common anxiety disorder that causes uncontrollable worrying. Sometimes people worry about bad things happening to them or loved ones, and at other times the person may not be able to identify any source of worry.

Panic disorder is a condition that causes moments of extreme fear, a pounding heart, and shortness of breath, commonly known as panic

attacks.

Post-traumatic stress disorder (PTSD) is a condition that causes flashbacks or anxiety as the result of a traumatic experience.

Social phobia is a condition that causes intense feelings of anxiety in situations that involve interacting with others.

Obsessive-compulsive disorder is a condition that causes repetitive thoughts and the compulsion to complete certain ritual actions.

Common physical symptoms of anxiety include: Pounding heart, Sweating, Stomach upset or dizziness, frequent urination or diarrhea, Shortness of breath, Tremors and twitches, Muscle tension, Headaches, Fatigue, Insomnia

Sanashwa:

SanAshwa is widely used in management of stress and anxiety.

DESCRIPTION

SanAshwa: - Each capsule contains 440 mg of proprietary blend containing Ashwagandha root powder and extract, Holy basil leaf extract, Black pepper fruit extract and zinc

Excipients - Each capsule contains 25 mg of microcrystalline cellulose and magnesium stearate

Pharmaceutical form: Capsule

Objective:

Primary Objective:-

To assess the efficacy of the herbal medicine in the management of stress and anxiety in healthy adult volunteers.

Secondary Objective:

To evaluate the safety of the herbal medicine in the management of stress and anxiety in healthy adult volunteers

Inclusion criteria:

The subjects were included based on the following criteria

- Male or female, age 18 -50 years
- Healthy volunteers who are willing to give informed consent
- Healthy volunteers who are able to comply with the study requirements

- anxiety and depression score equal or below 12 and above 4
- Subjects with WHO-5 wellbeing index <15 or PSS scores >14
- Standard safety biology
- Subjects who are facing routine work stresses along with anxiety

Exclusion criteria:

The subjects who had following criteria were excluded for the study

- Pregnancy
- Any current ongoing medical illness
- HAD A results above 12 and below 4
- HAD D results above 12
- Neurologic or psychiatric pathology
- Consumption of psychotropic
- High level of caffeine consumption
- Any important chronic pathology
- Drugs which impairs concentration, anxiety and stress
- Subjects who are having positive serology

Ethics committee approval:

All study related documents Protocol, Case Report Form, Dairy card, Investigator Brochure and Informed Consent Documents (English and Kannada Versions). Written Informed Consent was obtained from the subjects before the start of the trial and after due approval from IEC/IRB. Ethics Committee notifications as per the GCP guidelines issued by Central Drugs Standard Control Organization and Ethical guidelines for biomedical research on human subjects issued by Indian council of Medical Research has been followed during the Conduct of the Study (Sri Venkateshwara Hospital Ethics Committee and Approved on 22 Sep 2016)

Study outcomes

Primary outcomes

- Evaluation of the changes in the Change in Stress sub-scale of Depression Anxiety and Stress Scale-21 (DASS-21) from Screening to EOT
- Evaluation of the changes in the 7-item sub-scale measuring symptoms of stress.
- Evaluation of the changes in the Patient Health Questionnaire-9 (PHQ-9) from Screening and EOT
- Evaluation of the changes in the Generalized Anxiety Disorder-7 (GAD-7)
- Evaluation of changes in the cortisol levels from Screening to EOT

Secondary outcomes

- The safety and tolerability were assessed by observation and by volunteered reports from the patients. Adverse events were documented with the concomitant medications.

Statistical analysis

Data Analysis was carried out using 5% significance level and 80 % power for study using SAS. The difference within the group will be assessed using paired t-test. The difference between the groups will be assessed using independent t-test.

Results: (in brief) with difference in baseline and % age change graph

Cortisol level:-

Mean Cortisol level from the screening to EOT:

The mean, change in mean, percentage increase of cortisol level from screening to EOT in the drug-A & drug B are represented in the below tables & figures:

Table 01: Mean Cortisol level at screening and EOT

Groups	Baseline (N=35)	EOT- Day 28 (N=35)	Change mean	% change mean	P-value*
Drug A	12.34371429 ± 4.183	7.943714286 ± 5.710	4.4	35.64 %	0.0003
Drug B	11.02629 ± 4.273068	11.65857 ± 4.972356	0.63228	5.734 %	0.5764

P-value# (Drug A vs Drug B)	0.1968	0.0050			
------------------------------	--------	--------	--	--	--

Figure 01: Mean Cortisol level at screening and EOT:

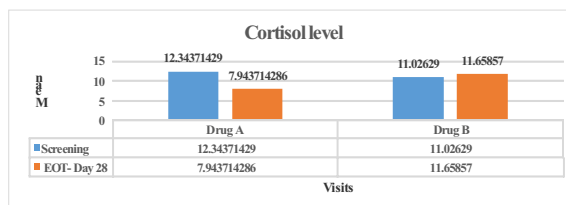
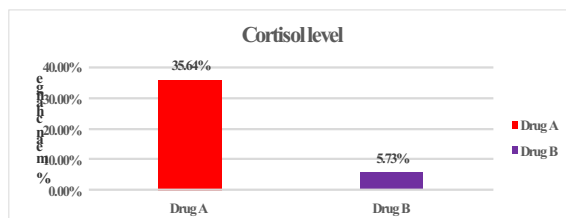


Figure 02: Percentage change in mean change of Cortisol level



Evaluation of Changes in Stress subscale of depression anxiety and stress scale level from screening to EOT by DASS-21 scale:-

The mean, change in mean, percentage change of Stress subscale of depression anxiety and stress from screening to EOT in the drug A and drug B are represented in the below tables & figures:

Table 2: Mean of Stress subscale of depression anxiety and stress from the screening to EOT:

Visits	Drug A			Drug B			-value* (Drug A vs Drug B)
	Stress	Anxiety	Depression	Stress	Anxiety	Depression	
Screening	11.71428571 ± 1.296407447	11.62857143 ± 1.059570232	10.54285714 ± 1.066684174	11.8 ± 1.255575799	11.77142857 ± 1.086974059	10.6 ± 1.11671788	0.7267
EOT	9.514285714 ± 1.788384558	9.085714286 ± 1.291862053	8.571428571 ± 1.289909123	10.48571429 ± 1.336620598	10.68571429 ± 1.231245868	9.457142857 ± 1.244821205	0.0244
Change in Mean	2.2	2.54	1.971	1.31	1.08	1.14	
Change mean	18.78 %	21.84 %	18.69 %	11.10 %	9.17 %	10.75 %	
P-value*	<.0001	<.0001	<.0001	0.0003	0.0006	0.0006	

Figure 3: Mean of Stress subscale of depression anxiety and stress from the screening to EOT

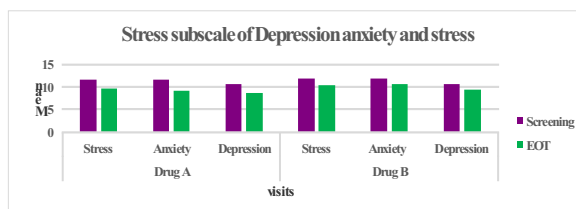
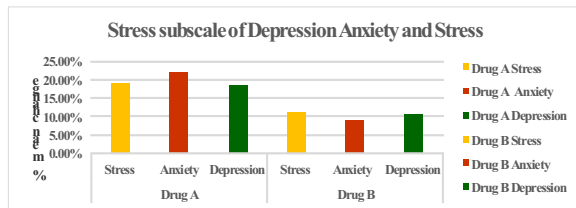
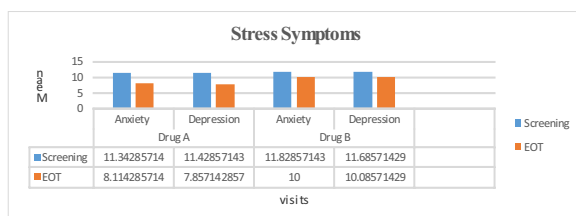
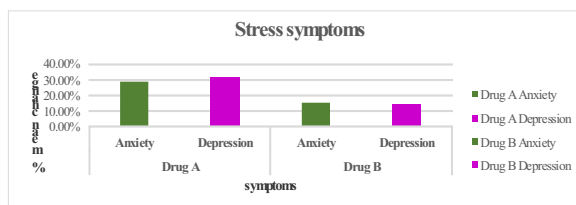


Figure 4: Percentage Change in Mean of Stress subscale of depression anxiety and stress from the screening to EOT**Evaluation of Changes in 7 item sub scale measuring symptoms of stress from screening to EOT:-**

The mean, change in mean, percentage change of Stress symptoms from screening to EOT in the drug A and drug B are represented in the below tables & figures:

Table 3: Mean of symptoms of stress from screening to EOT:

Visits	Drug A		Drug B		P-value# (Drug A vs Drug B)
	Anxiety	Depression	Anxiety	Depression	
Screening	11.34285714 ± 1.083101677	11.42857143 ± 1.195228609	11.82857143 ± 1.042782316	11.68571429 ± 1.131667915	0.2144
EOT	8.114285714 ± 1.450586668	7.857142857 ± 1.665265517	10 ± 1.084652289	10.08571429 ± 1.067471685	<.0001
Change Mean	3.228	3.57	1.82	1.6	
Change Mean	28.46 %	31.26 %	15.39 %	13.69 %	
P-value*	<.0001	<.0001	<.0001	<.0001	

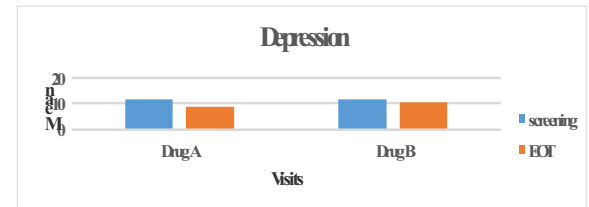
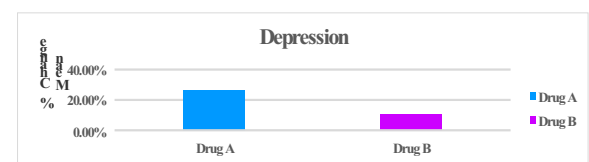
Figure 5: Mean of symptoms of stress from screening to EOT:-**Figure 6: % Change in Mean of symptoms of stress from the screening to EOT****Evaluation of Changes in Depression by Patient health Questionnaire -9 from screening to EOT:-**

The mean, change in mean, percentage change in Depression from screening to EOT in the drug A and drug B are represented in the below tables & figures:

Table 4: Mean of symptoms of Depression from screening to EOT:

Visits	Drug A	Drug B	P-value# (Drug A vs Drug B)
	Depression	Depression	
Screening	11.8 ± 0.867721831	11.88571429 ± 1.050810012	0.7149

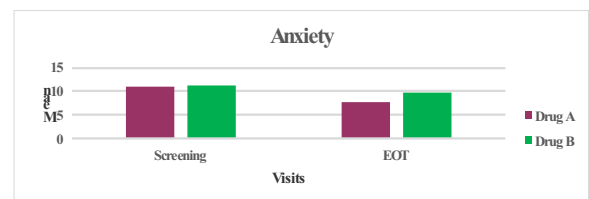
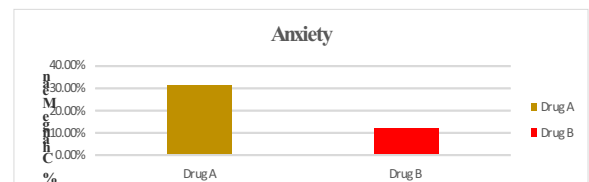
Visits	Drug A	Drug B	P-value# (Drug A vs Drug B)
	Depression	Depression	
Screening	11.8 ± 0.867721831	11.88571429 ± 1.050810012	0.7149

Figure 7: Mean of symptoms of Depression from screening to EOT:-**Figure 8: Percentage Change in Mean of Depression from the screening to EOT****Evaluation of Changes in Anxiety in the Generalized Anxiety disorder – 7 from screening to EOT:-**

The mean, change in mean, percentage change in Anxiety from screening to EOT in the drug A and drug B are represented in the below tables & figures:

Table 5: Mean of Anxiety from screening to EOT:

Visits	Drug A	Drug B	P-value# (Drug A vs Drug B)
	Anxiety	Anxiety	
Screening	11.08571429 ± 1.094677728	11.2 ± 1.430754634	0.7859
EOT	7.628571429 ± 1.516298013	9.828571429 ± 1.200140048	<.0001
Change mean	3.46	1.38	
% Change Mean	31.22 %	12.32 %	
P-value*	<.0001	0.0002	

Figure 9: Mean of Anxiety from screening to EOT:-**Figure 10: Percentage Change in Mean of Anxiety from the screening to EOT**

Results:

The total number of subjects analyzed in the study is 70, of which 35 subjects were randomly assigned to the Drug A group and 35 subjects were randomly assigned to the Drug B group. The subjects were called for screening visit and were given the Informed consent and screening procedures were started. Once the subjects were screen passed, eventually the subjects were randomized in to the group A (drug), group B (placebo). The blind was broken after Day 40 when as per the protocol the trial ended.

All individuals, who were included in this study, were analyzed in this report.

The data obtained from the two groups was analyzed statistically using paired t test as well as unpaired t test. The data was compared between the Active Groups (Group A) and Placebo Group (Group B) for the parameters. Entire statistical analysis was performed as per the procedures mentioned in the study protocol. Descriptive statistics containing N (no. of observations), mean, standard deviation (SD), minimum and maximum were evaluated for all the parameters. Normality check of data was performed using Kolmogorov-Smirnov test statistic in which only Cortisol Level Estimation test parameters at Screening and EOT were found to follow normal distribution with p-values greater than 0.05, whereas rest of all other parameters i.e., Stress Scores as per DASS-21, Anxiety Scores as per DASS-21, Depression Scores as per DASS-21, Total Scores as per PHQ-9, Total Scores as per GAD-7, Anxiety Scores as per Items Subscale Measuring Symptoms Of Stress and Depression Scores as per Items Subscale Measuring Symptoms Of Stress were found to be non-normal in nature with p-values very much less than 0.05.

Separate analyses were performed for Drug (A) and Drug (B), respectively. In which comparisons between screening and EOT values were made.

T-Test was used to calculate difference in Cortisol Levels from Baseline to EOT for Drug (A) and Drug (B), separately. The results output showed that p-value obtained for Baseline vs EOT for Drug (A) was found to be 0.0003, whereas the p-value obtained for Baseline vs EOT for Drug (B) was found to be 0.5764. This clearly depicts that a significant change has been observed from Baseline to EOT values for Drug (A) whereas Drug (B) showed no significant change from Baseline to EOT values.

This clearly indicates that Drug (A) is effective enough to control and decrease Cortisol levels whereas Drug (B) has no control on Cortisol level.

Mann Whitney U-Test (Wilcoxon Rank Sum Test) was used to calculate difference in Stress Scores as per DASS-21, Anxiety Scores as per DASS-21, Depression Scores as per DASS-21, Total Scores as per PHQ-9, Total Scores as per GAD-7, Anxiety Scores as per Items Subscale Measuring Symptoms Of Stress and Depression Scores as per Items Subscale Measuring Symptoms Of Stress from Baseline to EOT for Drug (A) and Drug (B), separately.

The analyses results showed that p-value obtained for Stress Scores as per DASS-21 for Drug (A) was found to be <.0001 and for Drug (B) was found to be 0.0003, which shows that both Drug (A) and Drug (B) showed significant change in Baseline to EOT values for Stress Scores as per DASS-21. Also, as per Table-10 percentage change in stress scores from Baseline to EOT is higher for Drug (A) in comparison to Drug (B), so this shows that Drug (A) is more effective in comparison to Drug (B) in order to decrease stress.

The p-value obtained for Anxiety Scores as per DASS-21 for Drug (A) was found to be <.0001 and for Drug (B) was found to be 0.0006, which shows that both Drug (A) and Drug (B) showed significant change in Baseline to EOT values for Anxiety Scores as per DASS-21. Also, as per Table-10 percentage change in anxiety scores from Baseline to EOT is higher for Drug (A) in comparison to Drug (B), so this shows that Drug (A) is more effective in comparison to Drug (B) in order to decrease anxiety.

The p-value obtained for Depression Scores as per DASS-21 for Drug (A) was found to be <.0001 and for Drug (B) was found to be 0.0006, which shows that both Drug (A) and Drug (B) showed significant change in Baseline to EOT values for Depression Scores as per DASS-

21. Also, as per Table-10 percentage change in Depression scores from Baseline to EOT is higher for Drug (A) in comparison to Drug (B), so this shows that Drug (A) is more effective in comparison to Drug (B) in order to decrease Depression.

The p-values obtained for Total Scores as per PHQ-9 for Drug (A) and Drug (B) were found to be <.0001, which shows that both Drug (A) and Drug (B) showed similar significant change in Baseline to EOT values for Total Scores as per PHQ-9. Also, as per Table-16 percentage change in Depression scores from Baseline to EOT is quite higher for Drug (A) in comparison to Drug (B), so this shows that Drug (A) is much more effective in comparison to Drug (B) in order to decrease Depression.

The p-value obtained for Total Scores as per GAD-7 for Drug (A) was found to be <.0001 and for Drug (B) was found to be 0.0002, which shows that both Drug (A) and Drug (B) showed significant change in Baseline to EOT values for Total Scores as per GAD-7. Also, as per Table-19 percentage change in Anxiety scores from Baseline to EOT is quite higher for Drug (A) in comparison to Drug (B), so this shows that Drug (A) is much more effective in comparison to Drug (B) in order to decrease Anxiety.

The p-values obtained for Anxiety Scores as per Items Subscale Measuring Symptoms Of Stress for Drug (A) and Drug (B) were found to be <.0001, which shows that both Drug (A) and Drug (B) showed significant change in Baseline to EOT values for Anxiety Scores as per Items Subscale Measuring Symptoms Of Stress. Also, as per Table-13 percentage change in Anxiety scores from Baseline to EOT is quite higher for Drug (A) in comparison to Drug (B), so this shows that Drug (A) is much more effective in comparison to Drug (B) in order to decrease Anxiety.

The p-values obtained for Depression Scores as per Items Subscale Measuring Symptoms Of Stress for Drug (A) and Drug (B) were found to be <.0001, which shows that both Drug (A) and Drug (B) showed significant change in Baseline to EOT values for Depression Scores as per Items Subscale Measuring Symptoms Of Stress. Also, as per Table-13 percentage change in Depression scores from Baseline to EOT is quite higher for Drug (A) in comparison to Drug (B), so this shows that Drug (A) is much more effective in comparison to Drug (B) in order to decrease Depression.

Efficacy Analysis:

A separate set of analyses were performed to check the efficacy of Drug (A) in comparison to Drug (B) for Screening and EOT values separately.

T-Test was used to compare the efficacy between Drug (A) and Drug (B) for Screening and EOT values of Cortisol Levels, separately.

Mann Whitney U-Test (Wilcoxon Rank Sum Test) was used to check the efficacy of Drug (A) in comparison to Drug (B) for Screening and EOT values separately in Stress Scores as per DASS-21, Anxiety Scores as per DASS-21, Depression Scores as per DASS-21, Total Scores as per PHQ-9, Total Scores as per GAD-7, Anxiety Scores as per Items Subscale Measuring Symptoms Of Stress and Depression Scores as per Items Subscale Measuring Symptoms Of Stress, separately.

Results obtained from comparison of Drug (A) to Drug (B) for Cortisol Levels at Screening showed a p-value of 0.1968, whereas the p-value for comparison of Drug (A) to Drug (B) for Cortisol Levels at EOT was found to be 0.0050. This shows that there was no significant change between Drug (A) and Drug (B) for Cortisol Levels at Screening, whereas a significant difference was observed between Drug (A) and Drug (B) for Cortisol Levels at EOT. So this shows that Drug (A) has shown better performance than Drug (B).

Results obtained from comparison of Drug (A) to Drug (B) for Stress Scores as per DASS-21 at Screening showed a p-value of 0.7267, whereas the p-value for comparison of Drug (A) to Drug (B) for Stress Scores as per DASS-21 at EOT was found to be 0.0244. This shows that there was no significant change between Drug (A) and Drug (B) for Stress Scores as per DASS-21 at Screening, whereas a significant difference was observed between Drug (A) and Drug (B) for Stress Scores as per DASS-21 at EOT. So this shows that Drug (A) has shown better performance than Drug (B).

Results obtained from comparison of Drug (A) to Drug (B) for Anxiety Scores as per DASS-21 at Screening showed a p-value of 0.7049, whereas the p-value for comparison of Drug (A) to Drug (B) for Anxiety Scores as per DASS-21 at EOT was found to be $<.0001$. This shows that there was no significant change between Drug (A) and Drug (B) for Anxiety Scores as per DASS-21 at Screening, whereas a significant difference was observed between Drug (A) and Drug (B) for Anxiety Scores as per DASS-21 at EOT. So this shows that Drug (A) has shown better performance than Drug (B).

Results obtained from comparison of Drug (A) to Drug (B) for Depression Scores as per DASS-21 at Screening showed a p-value of 0.8505, whereas the p-value for comparison of Drug (A) to Drug (B) for Depression Scores as per DASS-21 at EOT was found to be 0.0124. This shows that there was no significant change between Drug (A) and Drug (B) for Depression Scores as per DASS-21 at Screening, whereas a significant difference was observed between Drug (A) and Drug (B) for Depression Scores as per DASS-21 at EOT. So this shows that Drug (A) has shown better performance than Drug (B).

Results obtained from comparison of Drug (A) to Drug (B) for Total Scores as per PHQ-9 at Screening showed a p-value of 0.7149, whereas the p-value for comparison of Drug (A) to Drug (B) for Total Scores as per PHQ-9 at EOT was found to be $<.0001$. This shows that there was no significant change between Drug (A) and Drug (B) for Total Scores as per PHQ-9 at Screening, whereas a significant difference was observed between Drug (A) and Drug (B) for Total Scores as per PHQ-9 at EOT. So this shows that Drug (A) has shown better performance than Drug (B).

Results obtained from comparison of Drug (A) to Drug (B) for Total Scores as per GAD-7 at Screening showed a p-value of 0.7879, whereas the p-value for comparison of Drug (A) to Drug (B) for Total Scores as per GAD-7 at EOT was found to be $<.0001$. This shows that there was no significant change between Drug (A) and Drug (B) for Total Scores as per GAD-7 at Screening, whereas a significant difference was observed between Drug (A) and Drug (B) for Total Scores as per PHQ-9 at EOT. So this shows that Drug (A) has shown better performance than Drug (B).

Results obtained from comparison of Drug (A) to Drug (B) for Anxiety Scores as per Items Subscale Measuring Symptoms Of Stress at Screening showed a p-value of 0.2144, whereas the p-value for comparison of Drug (A) to Drug (B) for Anxiety Scores as per Items Subscale Measuring Symptoms Of Stress at EOT was found to be $<.0001$. This shows that there was no significant change between Drug (A) and Drug (B) for Anxiety Scores as per Items Subscale Measuring Symptoms of Stress at Screening, whereas a significant difference was observed between Drug (A) and Drug (B) for Anxiety Scores as per Items Subscale Measuring Symptoms of Stress at EOT. So this shows that Drug (A) has shown better performance than Drug (B).

Results obtained from comparison of Drug (A) to Drug (B) for Depression Scores as per Items Subscale Measuring Symptoms Of Stress at Screening showed a p-value of 0.5972, whereas the p-value for comparison of Drug (A) to Drug (B) for Depression Scores as per Items Subscale Measuring Symptoms of Stress at EOT. So this shows that Drug (A) has shown better performance than Drug (B).

Symptoms of Stress at EOT was found to be $<.0001$. This shows that there was no significant change between Drug (A) and Drug (B) for Depression Scores as per Items Subscale Measuring Symptoms of Stress at Screening, whereas a significant difference was observed between Drug (A) and Drug (B) for Depression Scores as per Items Subscale Measuring Symptoms

Conclusion:

As per the study outcomes no adverse events were observed during the clinical trial and this concludes that investigational product is safe enough to use.

Also, the results obtained from Intra-group Statistical analyses and Efficacy analyses of Drug (A) and Drug (B), as discussed above showed that Drug (A) was found to be effective in lowering the Cortisol Levels, Stress scores, Anxiety scores and Depression scores in comparison to Drug (B).

So, this proves that Drug (A) is more safe, efficient and superior in comparison to Drug (B) for management of stress and anxiety in

healthy adult subjects who were facing routine work stresses along with anxiety.

References:

1. http://cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf
2. <http://www.wma.net/en/60about/70history/10leaders/10assemblies/>
3. <http://www.wma.net/en/30publications/10policies/b3/>
4. <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf>
5. <http://www.sandhuproductions.com/Ashwagandha-Capsules>
6. <https://www.nlm.nih.gov/medlineplus/ency/article/003211.htm>
7. <http://www.helpguide.org/articles/anxiety/anxiety-attacks-and-anxiety-disorders.htm>
8. <http://www.healthline.com/health/stress-and-anxiety#Causes3>
9. <http://www.webmd.com/vitamins-supplements/ingredientmono-1101-holy%20basil.aspx?activeingredientid=1101>
10. <http://www.medicinehunter.com/holy-basil/>
11. <http://www.superlife.com/black-pepper-benefits/>
12. <http://www.webmd.com/vitamins-supplements/ingredientmono-800-black%20pepper%20and%20white%20pepper.aspx?activeingredientid=800&>
13. <http://www.royj.com/open-access/a-review-on-pharmacological-profile-of-withania-somnifera-ashwagandha.php?aid=33844>
14. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3252722/>
15. http://www.japsonline.com/admin/php/uploads/364_pdf.pdf
16. <http://en.mr-ginseng.com/ashwagandha/>
17. <http://www.fedmaps.org/fedmaps-files/therapeutic-uses-of-ashwagandha.pdf>
18. <https://www.drugs.com/npp/ashwagandha.html>
19. <https://www.drugs.com/npp/holy-basil.html>
20. <http://medicinalplants.us/pharmacology-of-black-pepper>
21. http://www.gaiaherbs.com/uploads/1596_HPR_HolyBasil_ResearchPaper-1371567034.pdf
22. <http://www.omicsgroup.org/journals/a-review-on-therapeutic-potential-of-piper-nigrum-l-black-pepper-the-king-of-spices-2167-0412.1000161.pdf>
23. https://www.biogreenscience.com/file/clinical/SCIENTIFIC_STUDIES_KSM-66_LAST.pdf
24. <https://www.psychologytoday.com/blog/inner-source/201401/ashwagandha-anxiety>
25. http://www.iamj.in/posts/images/upload/707_712.pdf
26. <http://patient.info/in/doctor/patient-health-questionnaire-phq-9>
27. <https://www.depression-anxiety-stress-test.org/take-the-test.html>
28. <http://patient.info/in/doctor/generalised-anxiety-disorder-assessment-g>