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A Prospective, randomized double-blind, placebo controlled study of safety and efficacy of HFSM-02 in reducing stress and anxiety in subjects with chronic medical condition and perceived stress.

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ABSTRACT:

Objective: Stress is a feeling of emotional or physical tension. It has now become a part of modern lifestyle. At some point in life, everyone must have encountered with some degrees of stress. It has negative impact of life and certain complications associated which includes increased risk of cardiovascular disease, elevating certain medical conditions like asthma, diabetes, hypertension, etc. Considering the increasing prevalence of stress and anxiety through multiple factors, there is a great need to find a solution to the existing problem. The current research depicts the safety and efficacy of HFSM-02 in reducing stress and anxiety in subjects with chronic medical condition and perceived stress.

Material and methods: 120 subjects were enrolled in the study. Subjects were undergoing clinical examination. Vitals were recorded. Blood samples were collected for biochemical tests like change in serum cortisol levels. Subjective questionnaire scores evaluation were performed like POMS-2, and GHQ-28, questionnaire. Changes in symptoms severity were noted like disturbed sleep, and day time mood swings.

Results: Reduction in stress hormone cortisol in healthy individuals, subjects with cardiovascular diseases (CVD) and diabetes mellitus (DM) was found to be 33.34%, 41.6% and 52.64% respectively. The reduction in DASS-21 and POMS-2 signifies the reduced stress levels.

Conclusion: This explains that HFSM-02 can significantly reduce the stress hormone levels in healthy as well as moderately stressed subjects with diabetes and cardiovascular confounders.

Key words: Diabetes, POMS-2, Stress, Stress symptoms

INTRODUCTION:

Stress is now part of modern lifestyle and also cause health related issues. Physiologist may describe the meaning of "stress" in terms of "fight or flight response" as a series of involuntary physiological and biochemical changes that prepare you to deal with threats of danger. **[1]** Selye (1956) gave a physiological response based definition of stress. These body reminders provide a chance to handle the stress accordingly. **[2]** Many of the researchers have referred the involvement of cognitive, emotional and behavioral factors. **[3]**

Continue episodes of stress can affect several body system working like suppression of immune system, disturbed digestive system and reproductive systems, increase the risk of heart attack and stroke, and speed up the aging process. It can even rewire the brain, leaving person more vulnerable to anxiety, depression, and other mental health problems. Over time, constant strain can also lead to development of chronic medical conditions.

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Many literatures survey demonstrate herbal medicine have key role in management of several neuro-conditions like depression, anxiety and insomnia, involving re-uptake of monoamines, affecting neuro-receptor signal transportation activity, alter neuronal communication or hypothalamic-pituitary adrenal axis (HPA) etc. Which are way safer than the conventional SSRI and tranquilizers etc. [4]

Therefore, the herbal and ayurvedic treatments are preferred over synthetic drugs for a range of disorders related to stress. Ayurvedic therapy has shown very promising role in neurological conditions. The accessibility, negligible incidence of side effects and non-habit forming nature of plant products offer considerable advantages. [5]

Considering increasing prevalence of the stress and anxiety through multiple factors like environmental stress, psychological (emotional) stress and biological stress, the Siddhayu Ayurvedic Research Fdn. Pvt. Ltd. has designed HFSM-02 in reducing stress and anxiety. The current research depicts the safety and efficacy of HFSM-02 in reducing stress and anxiety in subjects with chronic medical condition and perceived stress.

MATERIAL AND METHODS:

Materials: HFSM-02 formulation in capsule form.

Methods:

After getting approval from the ethics committee, the study was registered on CTRI website. The CTRI registration number is CTRI/2020/08/027076 [Registered on: 10/08/2020] - Trial Registered Prospectively. Patients were enrolled in the study only after registration of study on CTRI website.

The primary objectives of the study were to evaluate efficacy of HFSM-02 in subjects suffering from stress and anxiety by assessing the serum cortisol levels. The subjects were analyzed on the basis of depression and anxiety Stress scale 21 (DASS-21), graded symptom scale for irritation, poor concentration and weak memory and Profile of mood states (POMS-2), assessment of Stress related disturbed sleep cycle index and general health questionnaire – 28 (GHQ-28) for each subject.

The secondary objectives of the study were assessment of daytime fatigue using Fatigue Severity Scale (FSS). Evaluation of Symptoms gradation at work place- daytime mood, ability to function at work, concentration and memory, estimation of safety parameters like CBC, LFT, KFT, lipid profile, urine routine, fasting blood sugar, PP blood sugar, ECG. Global assessment for overall improvement by the investigator and by subject at the end of the study treatment was to be evaluated. The degree of drug compliance, tolerability of study drugs, vitals (radial pulse, blood pressure, respiratory rate, and axial temperature), adverse events/adverse drug reactions were to be assessed

Inclusion Criteria:

Healthy subjects: Subjects of age between 18 and 60 years and free of psychiatric conditions other than stress were included in the study. The subjects having a score less than 15 on the World Health Organization–five (WHO-5) well-being index and a score of at least 14 on the perceived stress scale (PSS) and were capable to give informed consent and follow study format were considered for the study.

CHD subjects: CHD subject showing resting BP < 160/100 mm Hg with a known case of CHD with or without dyslipidemia, atherosclerotic, ischemic changes etc., were included in the study. Subjects with known case of CHD with certain psychological stress related complaints mainly irritation, anxiety etc., were included in the study. Subjects currently on medication on a regular basis for CHD were considered.

Diabetic subjects: Prediagnosed diabetes type 2 subjects with HbA1c NMT 7.5 with a known case of diabetes type 2 along with certain psychological stress related complaints mainly

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irritation, anxiety etc., were included in the study. Subjects currently on any medication on a regular basis for diabetes type 2 were considered.

Exclusion Criteria:

Subjects suffering from any chronic physical illness and currently taking any herbal preparations were excluded from the study. The subjects who had received heart transplant, were on labile ECG changes prior to testing, and were currently using a pacemaker were not considered for the study. Subjects with the resting BP > 160/100 mm Hg and those who were unable to comply with assessment procedures were excluded. The ones who were primary diagnosed of schizophrenia, dementia, current delirium, or other psychotic disorders were not considered fit for to be included in the study. Subjects actively under ongoing psychiatric treatment, subjects pregnant or lactating, subjects with substance dependence were excluded. Subjects that found unfit from the view point of Investigator were excluded from the study.

Study procedure:

After ethics committee's approval, clinical study was registered on CTRI website. Male and female subjects of age tween 18 to 60 years (both inclusive) attending the study site(s) were screened for eligibility criteria. Those matching with inclusion criteria were recruited for the study and study groups were allocated 30 subjects in each group as- Arm 1 contained healthy individual and were treated with test drug, Arm 2 contained healthy individuals and received placebo, Arm 3 received contained subjects with coronary heart disease and received test drug as adjuvant to existing medication and Arm 4 contained subjects with diabetes type 2 and received test drug as adjuvant to existing medication.

On screening visit, a written informed consent was obtained from subjects for their participation in the study. Subject's demographic details were recorded. Subjects were undergoing clinical examination. Subject's medical, surgical and treatment histories were recorded. Subject's current medication/'s if any were noted in the case record from (CRF). Subject's vitals were recorded. Subject's blood samples were collected for laboratory testing.

During screening visit and the entire study duration subjects were advised to refrain from antioxidant agents, vitamins, anti-inflammatory drugs, hormones, nutraceuticals, ayurvedic, siddha, Unani, herbal /homeopathic medicines for the treatment of stress. Subjects were called at respective study sites for follow up visits after every month up to 2 months after the baseline visit. On every follow up visit, Subjects were undergoing clinical examination. Subject's vitals were recorded. All the subjective questionnaire scores were recorded in CRF. Subjects were critically examined for adverse events. All details were recorded in the CRF along with the rescue medication if present. Subject's record for the questionnaires related to stress were recorded. On last follow up visit (i.e. Day 60) following activities were done-

Subjects were undergoing clinical examination. Subject's vitals were recorded. Blood samples were collected for biochemical tests. All the subjective questionnaire scores were filled.

STATISTICS

Sample size consideration

Sample size calculation is derived taking considerations of primary and secondary outcomes by a qualified statistician. The software used for calculation of sample size is SPSS version 10.0

RESULTS

Demographic details

There were total 120 subjects i.e. 30 in each i.e. Healthy Individuals group (Arm1), Healthy Individuals Group Placebo (Arm2), Subjects with Coronary Heart Disease (Arm 3) and

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Subjects with Diabetes type 2 (Arm4) were considered as completers and their analysis data is presented.

In treatment group (Healthy individuals), out of 30 completed subjects, 15 (50.0%) were males, while 15 (50.0%) were females. The mean age of subjects was 42.27+11.92 years.

In Placebo group (Healthy individuals), out of 30 completed subjects, 13 (43.3%) were males, while 17 (56.7%) were females. The mean age of subjects was 40.40 + 13.61 years. The age range for subjects was 21 to 65 years.

In CVD group (Cardiovascular disease), out of 30 completed subjects, 15 (50.0%) were males, while 15 (50.0%) were females. The mean age of subjects was 51.37+ 9.18 years.

In CVD group (Cardiovascular disease), out of 30 completed subjects, 21 (70%) were suffering from hypertension and 9 (30%) were suffering from CHF (Chronic heart failure).

In DM group (Diabetes mellitus), out of 30 completed subjects, 15 (50.0%) were males, while 15 (50.0%) were females. The mean age of subjects was 49.28+ 8.10 years. If compared between the groups, the difference was statistically insignificant.

Changes in serum cortisol levels (nmol/L):

In treatment group the cortisol levels were reduced from 10.81 to 7.20 nmol/L which is statistically significant (p=0.0001). In placebo treated group the cortisol levels were reduced from 10.60 to 10.19 nmol/L which is statistically not significant (p=0.4817).

When compared between groups, treatment group demonstrated significant reduction in elevated cortisol levels than placebo group from baseline to end of the study, difference was statistically significant (p=0.0001).

In CDV test group the serum cortisol level was 19.06 nmol/L on day 0, and 11.11 nmol/L at the end of the study which is statistically not significant (p=0.0003) in within group analysis.

In DM test group serum cortisol level was 19.05 on day 0, and 9.00 nmol/L at the end of the study which is statistically significant (p=0.0001) in within group analysis demonstrated in Table no.1

Table 1: Changes in serum cortisol levels (nmol/L)

	Baseline	**Day 60**	**P value (Within Group)**
CDV Test Group	19.06 ± 12.09	11.11 ± 4.97	0.0003
DM Test Group	19.05 ± 12.54	9.00 ± 2.26	0.0001
Treatment	10.81 ± 2.37	7.20 ± 1.57	<0.0001
Placebo	10.60 ± 3.21	10.19 ± 1.32	0.4817
P value (Treatment vs Placebo)	0.7705	<0.0001	

Changes in DASS-21 score:

Treatment group the DASS-21 score were 33.40 on day 0, 24.20 on day 30 and 21.60 at the end of the study which is statistically significant (p=0.0001) in within group analysis. In placebo treated group DASS-21 Score were 34.67 on day 0, 30.40 on day 30 and 31.73 at the end of the study which is statistically significant (p=0.0001) in within group analysis

When compared between groups, Treatment group demonstrated significant reduction in DASS-21 Score than placebo group from baseline to end of the study the difference was statistically significant (p=0.0001) on day 30 and day 60 demonstrated in graph no. 1.

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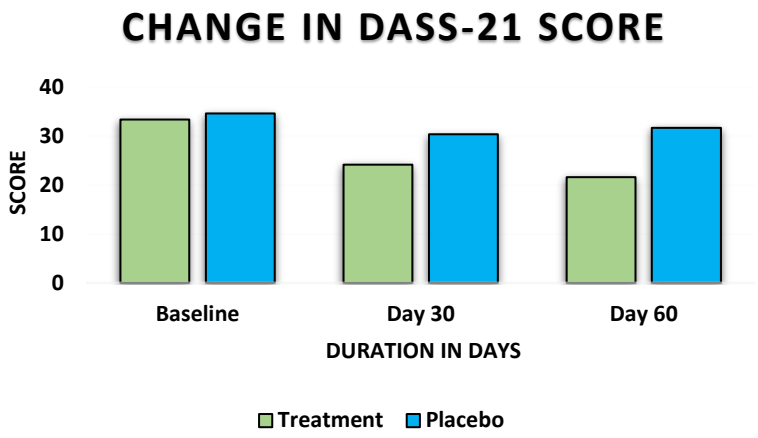
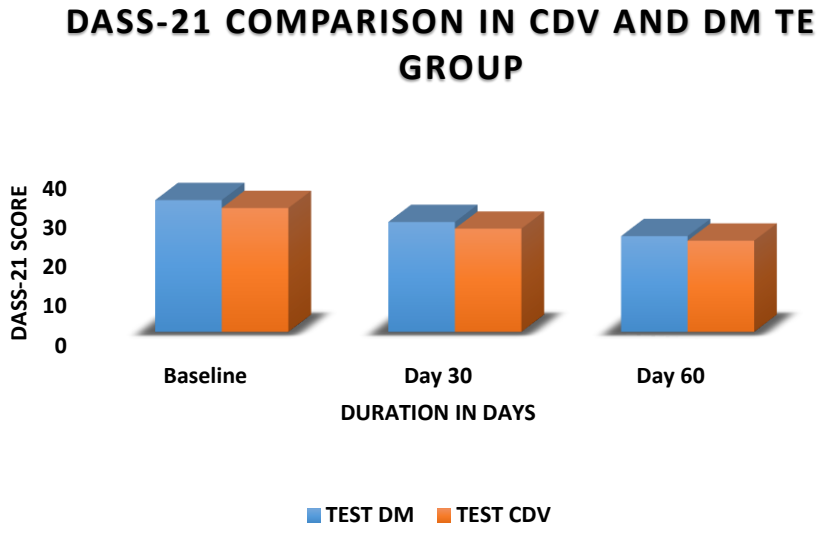


Graph 2: Change in DASS Score

Within group analysis by paired t-test, between group analysis by unpaired t-test, Significant at P=0.05

In CDV test group the DASS-21 score were 33.33 on day 0, 27.79 on day 30 and 24.23 at the end of the study which is statistically significant (p=0.0001) in within group analysis. In DM test group DASS-21 score were 31.33 on day 0, 26.10 on day 30 and 23.07 at the end of the study which is statistically significant (p=0.0001) in within group analysis demonstrated in graph no. 2.



Graph 2: Change in DASS score in CDV and DM test group

Changes in POMS-2 score:

In treatment group the POMS-2 score were 40.20 at baseline, and 23.90 at the end of the study which is statistically significant (p=0.0001) in within group analysis. In placebo treated group POMS-2 score were 40.13 at baseline and 34.17 at the end of the study which is statistically not significant (p=0.0693) in within group analysis

When compared between groups, treatment group demonstrated significant reduction in POMS-2 score than placebo group from baseline to end of the study the difference was statistically significant (p=0.0001) on day 60 demonstrated in graph no. 3.

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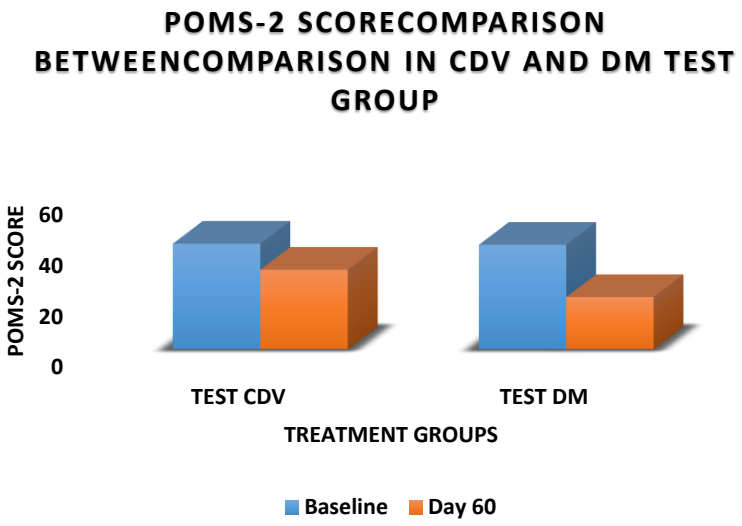
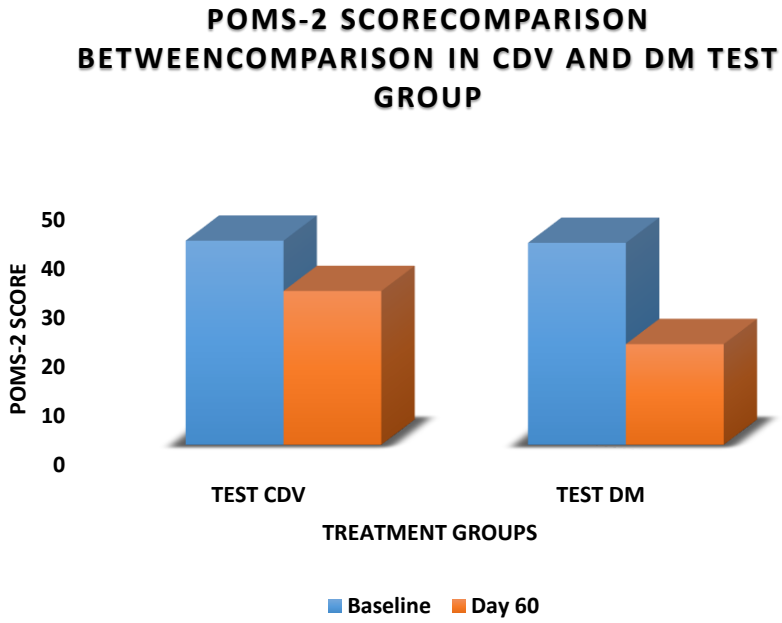


Graph 3: Change in POMS-2 score

In CDV test group the POMS-2 score were 41.50 at baseline, and 31.27 at the end of the study which is statistically significant (p=0.0001) in within group analysis. In DM test group POMS-2 Score were 41.07 at baseline, and 20.47 at the end of the study which is statistically significant (p=0.0001) in within group analysis demonstrated in graph no.4.



Graph 4: Change in POMS-2 Score in CDV and DM test group

Changes in GHQ-28 score:

In treatment group the GHQ-28 Score were 55.40 at baseline, and 72.68 at the end of the study which is statistically significant (p=0.0001) in within group analysis. In placebo treated group GHQ-28 Score were 57.23 at baseline and 79.60 at the end of the study which is statistically significant (p=0.0001) in within group analysis

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When compared between groups, treatment group demonstrated significant change in GHQ-28 score than placebo group from baseline to end of the study the difference was statistically significant (p=0.0001) on day 60.
In CDV test group the GHQ-28 score were 27.57 at baseline, and 28.57 at the end of the study which is statistically not significant (p=0.427) in within group analysis. In DM test group GHQ-28 score were 25.80 at baseline, and 25.50 at the end of the study which is statistically not significant (p=0.9082) in within group analysis.

Changes in severity of symptoms:

Changes in disturbed Sleep and daytime mood swing:

In the present study, there was difference of 26.67% subjects between group presenting 0 score on day 30 and the same trend was continued on day 60, and the difference of 43.33% subjects presenting score 0 between groups.
There was statistically significant difference (p=0.000052) between severity of disturbed sleep between both groups at the end of the study' i.e. Treatment and placebo groups. This reflects that more number of subjects were shifted from presenting score 6-10 to 1-5 and eventually to no symptom due to the test treatment.
At baseline, in CDV group, 10% subjects showing 0 score. On day 30, In CDV test group, 33.33% subjects showing 0 score and On day 60, In CDV test group, 50% subjects showing 0 score.
This reflects that more number of subjects were shifted from presenting score 6-10 to 1-5 and eventually to no symptom due to the test treatment.
At baseline, in DM test group, 26.66% subjects showing 0 score. On day 30, In DM test group, 33.33% subjects showing 0 score and On day 60, In DM test group, 50% subjects showing 0 score. This reflects that more number of subjects were shifted from presenting score 6-10 to 1-5 and eventually to no symptom due to the test treatment.
In the present study, there was difference of 6.67% subjects between group presenting 0 score on day 30 and the same trend was continued on day 60, and the difference of 40% subjects presenting score 0 between groups.
There was statistically significant difference (p=0.003) between severity of day time mood swing between both groups at the end of the study' i.e. treatment and placebo groups. This reflects that more number of subjects were shifted from presenting score severe to moderate, mild and eventually to no symptom due to the test treatment.
At baseline, in CDV group, there was difference of 30% subjects presenting 0 score between day 30 and day 60.
Reflects that more number of subjects were shifted from presenting score severe to moderate, mild and eventually to no symptom due to the test treatment.
At baseline, in DM group, there was difference of 6.67% subjects presenting 0 score between day 30 and day 60. reflects that more number of subjects were shifted from presenting score severe to moderate, mild and eventually to no symptom due to the test treatment.

Changes in difficulty in concentration and memory at work score:

In the present study, there was difference of 50% subjects between group presenting 0 score on day 30 and the same trend was continued on day 60, and the difference of 50% subjects presenting score 0 between groups.
There was statistically significant difference (p=0.0001) between severity of difficulty in concentration and memory at work between both groups at the end of the study.
This reflects that more number of subjects were shifted from presenting score severe to moderate, mild and eventually to no symptom due to the test treatment.

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At baseline, in CDV group, there was difference of 16.66% subjects presenting 0 score between day 30 and day 60.
Reflects that more number of subjects were shifted from presenting score severe to moderate, mild and eventually to no symptom due to the test treatment.
At baseline, in DM group, there was difference of 30% subjects presenting 0 score between day 30 and day 60. reflects that more number of subjects were shifted from presenting score severe to moderate, mild and eventually to no symptom due to the test treatment.

Changes in fatigue severity score:
In healthy treatment group the fatigue severity score was reduced from 47.03 to 25.47 and in placebo treated group from 47.00 to 42.70. There was significant decrease in fatigue severity score with the treatment arm compared to placebo.
In CVD DM group there was significant reduction in fatigue severity score.

Safety parameters:

Biochemical estimations:
All the safety parameters like CBC, LFT, KFT, lipid profile, urine routine, fasting blood sugar, PP blood sugar, ECG were assessed. All parameters readings were found normal which state that the test treatment is safe.
Tolerability of study drugs:
All the subjects (100%) from the test group reported excellent tolerability to given intervention.
Profile of adverse events:

Out of 120, 18 (15%) subjects reported a total of 5 adverse events during the study period. These adverse events included fever, menstrual pain, hyperacidity, digestion related problem and headache. All these adverse events were mild in severity. These adverse events were resolved completely after rescue medication was given. Study treatment was not stopped during these adverse events. All these adverse events were not related to the study drug.

DISCUSSION:

Diseases linked to stress and inflammation includes cardiovascular dysfunctions, diabetes, mental illnesses such as depression and anxiety disorders. Such disease conditions may in turn develop chronic stress, which lead to overstimulation and break down of the neuro-immune axis, thus causing neuroendocrine/immune imbalances that establish a state of chronic low-grade inflammation, a possible prelude to complications of the existing comorbidity. It is a great need to reduce the stress in healthy as well as subjects with chronic illnesses like CVD and DM. The present study offers an opportunity to incorporate a natural, safe and effective alternative to incorporate HFSM-02 as a preventive supplement by healthy individuals as well as adjuvant in patients with CVD and DM to improve stress response.

Following are the broad outcomes of the present study of HFSM-02 in healthy as well as moderately stressed subjects like CVD and DM.

In the present study when compared between groups, treatment group demonstrated significant reduction in elevated cortisol levels than placebo group in healthy individuals from baseline to end of the study. There is 33.34%, 41.6% and 52.64% reduction in stress hormone cortisol in healthy individuals, subjects with cardiovascular diseases (CVD) and diabetes mellitus (DM) respectively. It indicates possible role of HFSM-02 to be used along with the conventional medication to reduce the stress related complications in CVD and DM.

DM and cortisol- The hypothalamic-pituitary-adrenal (HPA) axis secretion in patients with type 2 diabetes has been extensively investigated and found leading to the elevation of ACTH, and cortisol levels. Glucocorticoid secretion has been suggested to be a possible link between

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insulin resistance and metabolic syndrome. [6]

CDV and cortisol-there are ample evidences that the elevated blood pressure stimulated increases in cortisol secretion which is predominant in patients with CVD. The hemodynamic changes in CVD patients leads to ACTH stimulated cortisol secretion. [7]

In CDV test group and DM test group the serum cortisol level was significantly reduced from baseline to end of study. This indicates that HFSM-02 is able to provide potential anti-stress and adaptogenic activity to combat the chronic stress with underlying cause of the comorbidity either cardiovascular or diabetes origin.

Depression and anxiety are states of mind which are often confounder with stress; it is inevitable to look into the state of mind when the stress is getting modulated. DASS-21 is a well-established self-reported instrument for measuring depression, anxiety, and stress. [8] Total DASS-21 scores for depression and anxiety were significantly reduced after treatment with HFSM-02 in healthy as well as subjects with CVD and DM. Decreased DASS-21 score is an indicative of HFSM-02 being useful in subjects to combat with the chronic stress.

POMS is a self-reported assessment of mood capturing transient and fluctuating feelings providing indications of potential mood disturbance. [9]
In the present study, after treatment with HFSM-02 to healthy individuals and subjects with CVD and DM subjects representing severe to moderate severity of day time mood swings shifted to no mood swings at the end of 60 days that is in hand with improved quality of sleep.

Treatment group demonstrated significant reduction in POMS-2 score than placebo group from baseline to end of the study the difference was statistically significant ($p=0.0001$) on day 60. There was 40.55, 24.82 and 50.15% reduction in POMS-2 score from baseline to end of study in healthy, CVD and DM subjects. This indicates reduction in mood fluctuations. It is evident from reduced POMS-2 score that treatment with HFSM-02 can enhance mood and thus vitality in healthy as well as moderately stressed subjects like CVD and DM.

GHQ-28 questionnaire is a scale of measuring quality of life which has a characteristic scale structure, which allows it to measure four health dimensions: somatic symptoms, anxiety and insomnia, social dysfunctions and symptoms of depression. [10]

In the present study it is palpable fact that the quality of life score of subjects with CVD and DM was around 50% less at baseline indicating in general poor quality of life of subjects with comorbidity. HFSM-02 treatment has improved the QOL score by 32.1, 3 and 1% in healthy, CVD and DM subjects. HFSM-02 has significantly improved QOL in healthy individuals but not in subjects with CVD and DM.

Stress exposure disrupts sleep, resulting in difficulty falling and staying asleep. Individuals with highly reactive sleep systems experience drastic deterioration of sleep when stressed, whereas those with low sleep reactivity proceed largely unperturbed during stress. Disturbed sleep further correlates with deceased work efficiency, fatigue and feeling less energetic a deficient. [11]

The significant effect of HFSM-02 in management of stress can be seen after 7 days of treatment. HFSM-02 significantly improved symptoms associated with stress such as fatigue, problems in daytime mood, ability to function at work, concentration and memory.

This is very common complaint of not only subjects with comorbidity but of healthy individuals as well. From the present study it is evident that treatment with HFSM-02 to healthy individuals and subjects with CVD and DM, there is improved work life efficiency through more subjects experiencing no impact on concentration and memory at work. Subjects were very satisfied with the benefit of treatment.

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As a result of safety parameters HFSM-02 characterized as safe and effective in promoting emotional and mental wellbeing of subjects. All the subjects (100%) from the test group reported excellent tolerability to given intervention. There were 15 % of subjects report adverse events. When compared to placebo 50% less subjects experienced hyperacidity and digestion related problems.

CONCLUSION:

Treatment with HFSM-02 has induced emotional and mental wellbeing. It produced reduced irritation and anxiety in diabetic, hypertensive and patients with preexisting cardiac disease. This explains that HFSM-02 can significantly reduce the stress hormone levels in healthy as well as moderately stressed subjects with diabetes and cardiovascular confounders. It can be concluded from the present study that there is possible role of HFSM-02 to be used along with the conventional medication to reduce the stress related complications in CVD and DM.

HFSM-02 treatment demonstrated improvement in sleep quality evident by in healthy individuals and subjects with CVD and DM indicated by subjects showing severe to moderate severity of sleep disturbances shifted to no sleep disturbance at the end of 60 days.

There were no significant adverse events and changes in safety biochemical parameters after treatment with either placebo or HFSM-02. Overall, it can be concluded from the present study that treatment with HFSM-02 is safe and effective in healthy subjects compared to placebo. HFSM-02 is safe and effective as an adjuvant in subjects with CVD and DM.

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