Randomized, Double blind and Placebo controlled Clinical evaluation to determine safety and efficacy of i-CHARGE liquid, an Ayurvedic health promoter drink in the management of stress induced fatigue

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Abstract: *Herbal medicine is being used widely without any apparent recorded adverse effects and has the potential to be of immense benefit. Plant based traditional medicine systems are playing a vital role for health care in both developing and developed countries. Ayurveda, the traditional Indian holistic medicine, uses plant derived products for managing diseases, is not merely a system of medicine. Rather, it is a way of life otherwise called wellness. Even with great advancements in treatment and control of diseases and disorders, western medicine has significant deficiencies such as dose-limiting toxicity and drug resistance. Moreover, the enormous search for novel compounds is escalating, in which Ayurveda with its huge active compound repository can lend a hand to find new potential leads. Currently, global population is widely accepting the Ayurvedic medicine as the plant based treatments can rescue the patients from adverse side effects of western medicine. Chronic fatigue syndrome (CFS) is a disorder characterized by sudden onset of severe unexplained fatigue, lasting 6 months or more. Associated symptoms include impairment of neurocognitive function, non-refreshing sleep, headache, arthralgias, post exertional malaise, muscle aches, and recurrent sore throat. The aetiology and pathology of chronic fatigue syndrome is still unknown, but is generally known to be heterogeneous and with numerous causes.[1,2] . i-Charge is a unique and innovative polyherbal formulation from Indusviva Health Sciences Pvt. Ltd., Bangalore which is delivered in liquid form with a carbonated fizz effect and a lashing mouth-watering taste with enchanting aroma. The present clinical study has demonstrated the safety and effectiveness of i-Charge in the management of Stress induced fatigue.*

Key Words: *Herbal Medicine, Ayurveda, Wellness, Chronic fatigue Syndrome (CFS), i-Charge.*

1. INTRODUCTION:

The body & mind react to any stress factor wherein brain and nervous system became intensely active during stress and may lead to altered metabolism. Hormones such as adrenaline are released into system along with glucose from Liver. In Modern era, there are various challenges to health like stress leading to anxiety, depression, insomnia and related disorders. Persistent stress can lead to altered autonomic nervous drive which is root cause of stress related ailments.[3] Stress is basic elements of various human diseases and mental illness. Stress is a term that refers to the sum of the physical, mental, and emotional strains or tensions on a person. Stress is the wear and tear our mind and body experiences as we attempt to cope with our continually changing environment. Stress is also called as anxiety, tension etc depending on the circumstances. Psychosocial stressor is defined as "any life event or life change that may be associated temporally with the onset, occurrence, or exacerbation of a mental disorder.[4] Feelings of stress in humans result from interactions between persons and their environment that are perceived as straining or exceeding their adaptive capacities and threatening their well-being. The element of perception indicates that human stress responses reflect differences in personality as well as differences in physical strength or health.

A stressor is defined as a stimulus or event that provokes a stress response in an organism. Stressors can be categorized as acute or chronic, and as external or internal to the organism.[5] One significant source of stress in modern life is the cumulative effect of various toxic waste products in the environment. Our personality, behaviour, and lifestyle all have important influences on our stress level. Much stress occurs through emotions such as aggression, impatience, anger, anxiety, and fear, all of which kindle the body ‘s stress responses. Eating an unhealthy diet, smoking, drinking, and taking drugs can also contribute further to physical strain. Stress may be generated through work, at home, within relationships, as a result of internal emotional conflict, through environment, diet, ill-health, and financial insecurity as well as through major life events such as marriage death, divorce etc.

The initial stage of arousal remains the same whether we are faced with a major or minor. But under extreme, prolonged, or persistent pressure the body continues to manufacture extra quantities of stress chemicals, triggering further processes to maintain energy. If arousal continues, the adrenal glands manufacture anti-inflammatory chemicals that simultaneously speed tissue repair while depressing the body’s immune defence system. If all these

changes continue, the body goes on trying to adapt under increasing strain and pressure. Eventually it breaks down. Exhaustion, variety of illnesses and even death may be the outcome of uninterrupted, excessive stress.[6,7]

Charaka Samhita, describes eight essential psychological factors that are negatively affected in various ways in all psychiatric disorders. The psychopathological condition is a function of these factors, which are *Manas* (mind), *Buddhi, Smriti* (memory), *Sajna jnana* (orientation and responsiveness), *Bhakti* (devotion), *Shila* (habits), *Cheshta* (psychomotor activity) and *Achara* (conduct). Compared to other major ayurvedic texts like *Sushruta Samhita*, and *Ashtanga Hrdayam*, *Charaka Samhita* gives more emphasis to the view of life as a self-aware field of pure consciousness and natural intelligence where the knower and the known are one. Ayurveda is very effective for stress management and to encourage body and soul to achieve composure of the mind.

Among the 8 branches of Ayurveda, *Rasayana chikitsa* plays a pivotal role in stress management and is usually corelated with Rejuvenation therapy. It basically boosts the immune system and helps to maintain good health or to establish impaired or lost physical or mental health. It provides a long disease-free life to the person who undergoes this therapy.[8]

Chronic fatigue syndrome (CFS) is essentially a very debilitating disease that can cause persistent fatigue leading to deterioration of productive activity of the sufferer along with loss of quality of life, mental peace and happiness. It can pose a very serious threat to health. Fatigue, even persistent fatigue, can be a common symptom of many medical conditions, but CFS is remarkably different from these conditions in many aspects. The most important being the severity of persistent fatigue with a sudden onset that is precipitated but not relieved by rest and the absence of any other fatigue producing medical condition. This CFS has been recognized as an independent clinical entity. Prolonged and disabling fatigue is present in 10%– 25% of patients presenting to general practitioners.[9-15]

Fatigue syndromes lie along a continuum of severity from ubiquitous transient and mild states to the more severe and prolonged fatigue disorders, including CFS.[16-17]

As with many other problems in clinical medicine (such as blood pressure and body weight), the challenge is to identify the point at which the problem becomes clinically significant. In relation to fatigue states, it is important to focus on those in whom the disorder is associated with ongoing disability and significant social or economic cost.[18]

The pathophysiological basis of CFS is unclear. The leading hypotheses put forward over the past decade include:

- A unique pattern of infection with a recognised or novel pathogen
- Altered central nervous system (CNS) function resulting from an abnormal immune response against a common antigen
- A neuroendocrine disturbance
- A neuropsychiatric disorder with clinical and neurobiological aspects suggesting a link to depressive disorders
- CFS is distinguished from similar fatigue-related illnesses not only by carefully characterising the fatigue itself, but also by evaluating associated symptoms and signs. People with CFS also report:
- Unrefreshing sleep
- Myalgia: arthralgia
- Loss of concentration
- Memory impairment
- Irritable mood
- Post exertional malaise

Although these symptoms are common in people with CFS, they are not specific and may occur in a range of other medical and neuropsychiatric disorders. In adults presenting for medical assessment with fatigue states the most common alternative diagnosis to consider is major depression. Other commonly detected disorders are sleep apnoea, hypothyroidism, anaemia, coeliac disease, chronic hepatitis, panic disorder, generalised anxiety, and somatoform disorders.

i-Charge has numerous effects on the body. It gives you instant energy and also provides long lasting energy up to 6-8 hours, it improves alertness, memory, stress and chronic fatigue. Well known for its stimulatory properties, infuses the user with instant energy and activeness while providing immunity against routine lethargy, aches and muscular pains. It is a natural rejuvenator, Non-habit forming with no risk of addiction even when used for longer periods. i-Charge also has a unique holistic combination of evidence based traditional formulations of *Ashvagandharishta*, *Balarishta* and *Drakshasava*. In addition to this, i-Charge is Caffeine free and sugar free. This exceptional combination is best known for its Adaptogenic benefits for calming nerves and easing agitation while it effectively increases physical and psychological stress threshold and rejuvenates the whole body.

2. AIM:

Randomized, double blind, placebo controlled, parallel group study of i-Charge, Ayurvedic health promoter formulation in the management of stress induced fatigue and wellbeing.

3. MATERIALS AND METHODS:

Local ethical committee approval was obtained before initiation of the study. Those who opted for treatment were informed of voluntary nature of trial and written consent was obtained from the parent or guardian. They were free from withdrawal of the study.

3.1 INFORMED CONSENT PROCESS:

All subjects who were willing to participate in the study were given detailed description about the investigational product, nature and duration of the study. Also, subject's responsibilities after entering, the study were explained. Subjects were pre-screened by the investigators for the inclusion criteria. Only subjects who met the requirements of this section, signed an informed consent form (by the parent/guardian), subjects or parents and guardian who were willing to follow instructions given by the investigator and have an updated medical history on file with the investigator were entered in the study. A written informed consent by subject using an 'informed consent form' was obtained from each study subject. The subjects of each study subject were informed about the study verbally as well as using a patient information sheet, in an easy-to understand language.

3.2 INCLUSION CRITERIA:

- Male & female of age 18 to 60 years old
- Subjects having symptoms of quick drained energy, lethargy, accepting to return to the centre for the planned visits
- Four or more of the following symptoms that last 6 months or longer: – Impaired memory or concentration – Post exertional malaise, where physical or mental exertions bring on "extreme, prolonged exhaustion and sickness"
- Unrefreshing sleep
- Muscle pain (myalgia)
- Pain in multiple joints (arthralgia)
- Headaches of a new kind or greater severity
- Sore throat, frequent or recurring
- Tender lymph nodes (cervical or axillary) accepting to follow the investigator's instructions during the entire study period accepting to not change their habits regarding: food, physical activity, agreeing to not receive any drug able to change the skin characteristics during the entire duration of the study.

3.3 EXCLUSION CRITERIA:

- Pregnant and lactating mother
- Patients with features of other co-morbidity features like stroke, heart disease, insulin dependent Diabetes mellitus
- Cancer
- Stomach ulcers
- Asthma and psychosis
- Depressive disorders
- Patients with addiction of higher levels of alcohol and nicotine

3.4 STUDY DESIGN:

Randomized, double blind, placebo controlled, parallel group study of i-Charge, an Ayurvedic health promoter formulation in the management of stress induced fatigue and wellbeing.

A baseline history will be obtained in order to determine the patient's eligibility for enrolment in the study. The baseline assessment included personal data, a description of symptoms and details of past medical history, history of possible exacerbating factors, etc. All the patients were advised to apply the given product on the affected area for a period of 2 weeks.

The subjective improvement evaluation will be done by a predefined global grading system, which includes following gradations:

- No improvement
- Fair improvement
- Remarkable improvement
- Very good improvement
- Excellent improvement

250 ml of i-charge to be given twice a day, shaken properly for group A, and placebo twice day for group B. Every day the subjects recorded the actual time when the product is consumed.

3.5 NOTE OF ADVERSE EVENT (AE):

An adverse event is the development of an undesirable medical condition - e.g. symptoms or abnormal results of an investigation - or the deterioration of a pre-existing medical condition (not relevant in this study). AE's were be collected by means of a standard question: "Have you had any health problems since the previous visit?"

AE's were recorded at every visit. Spontaneously reported AE's and/or observed AE's and the subject's response to this question were recorded on the AE form with information about seriousness, action taken, date of onset and recovery, maximum intensity and outcome.

The subjects were asked to assess the intensity of the reported Adverse Event according to the following scale: Mild = awareness of sign or symptom, but easily tolerated

Moderate = discomfort sufficient to cause interference with normal activities Severe = incapacitating, with inability to perform normal activities.

A Serious Adverse Event is an adverse event occurring during any phase of the study and at any dose of the investigational product or placebo, which fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalization
- Results in persistent or significant disability or incapacity.

Relation of adverse events to study medication was predefined as 'Unrelated' (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), 'Possible' (follows a known response pattern to the suspected drug, but could have been produced by the subject's clinical state or other modes of therapy administered to the subject), and 'Probable' (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the subject's clinical state).

A diary will be filled in at home during the entire study after intake of liquid. The following variables will be recorded:

- Consumption
- Occurrence of any adverse effects.
- Intake of any incidental medication
- Exact time intake of the medicament and placebo as the case may be. The recordings are considered as a measurement of compliance.

3.6 PRIMARY ENDPOINTS:

- Tolerance (number of participants with adverse events) and subject compliance to the i-Charge liquid.
- Perception of palatability and easiness.
- Reduction in fatigueless assessed as per the Pines Burnt scale.
- Questionnaire with good psychosomatic scale.

3.7 SECONDARY ENDPOINTS:

1. Short-term safety as assessed by incidence of adverse events, and compliance to the drug therapy.

3.8 STATISTICS:

3.8.1 EVALUATION OF SAFETY PARAMETERS

Table 1. EVALUATION OF i-CHARGE ON SAFETY AND TOLERANCE PARAMETERS

PARAMETERS	**Day 1**	**Day 90**
Erythema	**0**	**0**
Edema	**0**	**0**
Vomiting	**0**	**0**
Pruritus and Urticaria	**0**	**0**
Burning micturition	**0**	**0**
Hypopigmentation	**0**	**0**
Hyperpigmentation	**0**	**0**

TABLE 2. CHARACTERISTICS OF THE TREATMENT AND PLACEBO GROUPS AT THE START OF THE STUDY LEVEL OF COMPLIANCE WITH MEDICATION REGIME DURING THE STUDY PERIOD

Details	Treatment group	Placebo group	t/x2	P
Number of women	27 (90%)	27 (90%)	0.00	1.00
Age	41.0	42.1	0.52	0.60
On sick leave/average	33.33	33.33	0.00	1.00
Number of Psychosomatic agents	7	9	0.34	0.56
Compliance/tab left	18.8	11.7	1.82	0.07

3.8.2 EVALUATION OF EFFICACY PARAMETERS

TABLE 3. RESULTS IN STUDY OF QUALITY OF LIFE (QOL) – PARAMETERS IN TREATMENT AND PLACEBO GROUPS

Parameters	Treatment group (n=29)				Placebo group (n=29)			
	Pre-treatment		Post treatment		Pre-treatment		Post treatment	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pines Burnout scale	4.27	0.54	4.01	0.58	4.33	0.56	4.26	0.51
Physical health	40.94	12.56	43.64	11.74	45.58	10.65	44.83	11.44
Mental health	27.30	11.24	32.79	12.28	23.10	9.43	30.99	9.14
MADRS	19.17	7.66	15.66	7.93	21.72	6.58	17.40	8.28

4. RESULTS:

The safety and tolerability of i-Charge are shown in Table.1. i-Charge is seen to be safe and tolerable. None of the subjects complained about erythema, oedema, vomiting, pruritic, urticaria, burning micturition, hypopigmentation and hyperpigmentation. I-Charge was observed to be safe from baseline till the end of the study.

Characteristics of treatment in both trial and placebo groups are described in Table.2 with the level of compliance and the medication regime during the study period. It is observed that women subjects constituted 90% in both Treatment and Placebo groups. The average age in Treatment and Placebo groups were 42 and 41 respectively. 33.33 subjects in treatment and placebo groups were in sick leave. 7 subjects in treatment group and 9 subjects in placebo group were under psychosomatic medications.

Results pertaining to Quality of Life (QOL) in treatment and placebo groups are discussed in Table.3

- **Treatment group**: Pines Burnout scale had a mean value of 4.27 with SD 0.54 in the pre-treatment phase. Post the treatment schedule, it was observed that scale had a mean value of 4.01 with SD 0.58. (p>0.001)
- **Placebo group**: Pines Burnout scale had a mean value of 4.33 with SD 0.56 in the pre-treatment phase. Post the treatment schedule, it was observed that scale had a mean value of 4.26 with SD 0.51. (p>0.001)
- **Treatment group**: Physical health with a mean value of 40.94 with SD 12.56 during pre- treatment increased to a mean value of 43.64 and SD 11.74 post treatment. (p>0.001)
- **Placebo group**: Physical health with a mean value of 45.58 with SD 10.65 during pre- treatment increased to a mean value of 44.83 and SD 11.44 post treatment. (p>0.001)
- **Treatment group**: Mental health with a mean value of 27.30 with SD 11.24 during pre-treatment increased to 32.79 and SD 12.28 post treatment. (p>0.001)
- **Placebo group**: Mental health with a mean value of 23.10 with SD 9.43 during pre-treatment increased to 30.99 and SD 9.14 post treatment. (p>0.001)
- **Treatment group**: Montgomery–Åsberg Depression Rating Scale (MADRS) with a mean value of 19.17 and SD 7.66 pre-treatment reduced to a mean value of 15.66 with SD 7.93 post treatment. (p>0.001)
- **Placebo group**: Montgomery–Åsberg Depression Rating Scale (MADRS) with a mean value of 21.72 and SD 6.58 pre-treatment reduced to a mean value of 17.40 with SD 8.28 post treatment. (p>0.001)

For all the parameters, the results indicate marked improvement in physical health and energy, mental health and reduction in stress, fatigue, depression in most subjects on i-Charge treatment for a period of two weeks. No

clinically significant adverse reactions were either reported or observed, during the entire study period and overall compliance to the safety and efficacy was excellent.

5. DISCUSSION:

Chronic fatigue syndrome (CFS) is a complex and serious illness that is often misunderstood. Experts have noted that the terminology "chronic fatigue syndrome" can trivialize this illness and stigmatize persons who experience its symptoms. However, the fatigue in this illness is striking and quite distinct from the common fatigue everyone experiences. A variety of other names have been used, including myalgic encephalomyelitis (ME), ME/CFS, chronic fatigue immune dysfunction, and most recently, systemic exertion intolerance disease.[19,20,21]

At this time, there are no treatments (pharmacologic) that have been proven effective in large randomized trials and replicated by other investigators in other groups of patients with ME/CFS. Recommendations are based on expert clinical opinion and the standard clinical approach to symptom management. Sleep disruption and pain are the symptoms usually addressed first, and consultation with sleep or pain management specialists are usually followed.[22]
i-Charge is a unique well researched Ayurvedic health promoter drink which extends adaptogenic, cognition enhancing, stress and fatigue relieving and energy providing properties. Overall, it rejuvenates the body with its aroma and taste.

5.1 INGREDIENTS OF I-CHARGE

TABLE4. COMPOSITION OF i-CHARGE

Form	Sanskrit name	Botanical Name	Part used	Quantity	Reference/Page No
	Asvagandhyadirista	*NA*	NA	40.00 mg	AFI/I/ 1:6
Liquids	*Balarishta*	*NA*	NA	16.50 mg	AFI/I/1:24
	Draskhasava	*NA*	NA	12.48 mg	AFI/II/1.1
	Zandu	*Tagetes erecta*	Flower	0.107 mg	BPN/822
	Jal	NA	NA	QS	API/VI/242

i-Charge is powered by the essence of Ayurveda which is proved by time essence including *Ashwagandharishta*, *Balarishta*, and *Drakshasava* with goodness of natural flavors.

Ashwagandhadyarista as the name specifies nurture ourselves in improving our alertness, diminishing anxiety, improving stamina to fight against various occupational body pain, improving digestive power by catalyzing the liver function.[23]

Balarishta is an anther power packed time tested formulation that is enriched with Bala (*Sida cordifolia*), a known ingredient that extend nootropic, and neuro stimulating essences that is believed in strengthening of nerves, muscles and bones.[24]

Drakshasava rich in raisins and other nutrients along with other synergistic ingredients, and known for its use in respiratory diseases and intestinal disorders. *Drakshasava* is one of the rare Ayurvedic medicine which improves strength and also helps in intestinal cleansing. It is useful in relieving gastritis and hyperacidity. It is also used in the treatment of skin diseases of *Pitta* origin. Traditional uses like tuberculosis, weight loss, throat infection / throat disorders and cleanses intestines.[25]

I-CHARGE INCREASES ALERTNESS: i-CHARGE is a synergistic combination of 100 % natural traditional Ayurvedic formulations like *Ashvagandhadyarishta*, *Balarishta*, and *Draksasava* helps improve alertness. It supports the natural ability of the healthy brain and nervous system to readily store, retain and recall information. Enhances memory and cognition. It exhibits significant physiological effects on the peripheral and central nervous system and helps reduce the feeling of anxiety and other psychological distress. Helpful in relieving depression related issues like aching muscles, lethargy, "fuzzy" thinking and mental fatigue. Mild stimulatory properties of i-CHARGE infuse the user with activeness and a sense of well-being and optimism. It is a natural choice for mood enhancement which provides a relaxed feeling.
I-CHARGE RELIEVES STRESS AND FATIGUE: *Ashvagandha* and *Bala* are the exceptional ingredients form traditional Ayurveda which are proven to reduce stress, increase stamina against occupational bodily pains, exert neuro stimulating effects that strengthen muscles and bones. This combination is believed to provide exclusive antioxidant and adaptogenic benefits known for increasing physical and psychological threshold.
I-CHARGE PROVIDES SUSTAINED ENERGY WHILE IT IMPROVES PHYSICAL AND MENTAL HEALTH: i-CHARGE is an innovative time-tested formula for providing long lasting sustainable energy. i-

CHARGE is a perfect combination of ingredients with low glycemic index which are broken down slowly, trickling glucose into your system over time, providing immediate, optimum and stable energy levels throughout the day. A unique combination of time tested poly herbal Ayurvedic formulations known for its antioxidant benefits helps regulate energy metabolism. Healthy stimulatory properties of i-Charge infuse the user with energy and activeness while providing immunity against routine lethargy, aches and pains and keeping the person rejuvenated throughout the day.

i-CHARGE is "Sugar free". It is a perfect combination traditional Ayurvedic formulations which possess natural sugars from the ingredients that does not contribute to metabolic impairment in the body. i-CHARGE has low calorie sweeteners like which possess very low glycemic index which are devoid of all adverse health effects. They not only impart sweetness to the product but they are also best suitable for all age groups.

In addition to all these, i-CHARGE is "Caffeine free". Power packed with natural energy boosters like *Ashvagandhadyarishta* and *Balarishta*, i-CHARGE supports optimum energy production and energy retention throughout the day. This is non-habit forming with no risk of addiction even when used for long periods without producing adverse effects.

6. CONCLUSION:

The Clinical trial clearly demonstrates the safety and efficacy of i-Charge. Chronic fatigue syndrome (CFS) and stress is always a burden to patients of all age groups. CFS remains to be an area of continual research and i-Charge as a polyherbal Ayurvedic health promoter drink has shown significant results in the overall holistic management of stress related conditions. I-Charge helps overcome symptoms of tiredness and fatigue in patients while it enhances the productivity as compared to placebo. Overall compliance to the study was good. No adverse effects were either reported or observed during the clinical study. It is safe without any adverse effects for short-term and long-term use.

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