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Screening of Antistress Properties of Herbal Extracts and Adaptogenic Agents - A Review

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ABSTRACT

Stress is a daily phenomenon faced by every human, normal functioning of every individual is dependent on optimum levels of stress; it is very vital that stress is kept under control and normal functioning is not hampered due to excess of stress. Adaptogens are such herbal agents, which help the body to overcome excess stress even in chronic cases. Many marketed formulations claim to possess antistress actions, but still many herbs which have claims to be general tonics as well as wonder drugs need to be investigated and their claims be authenticated. In recent era there is a great thrust on screening of herbal extracts and formulations for Adaptogenic action. In this article efforts have been taken to list as well as discuss various models and parameters used for antistress activity. The motto is to discuss the models, to bring them under one title, which would surely prove to be some help to the researchers.

KEY WORDS: Adaptogens, Antistress, Physical endurance

INTRODUCTION

According to the Oxford dictionary, stress means pressure or tension. Stress can be defined as an injury or threat to our physical and mental well being, loss or a perception of loss, or challenge that we fear which is partly or totally beyond our control. Stress, according to late Dr. Hans Selye (1) an early guru on stress, is the non-specific response of the body to any demand made upon it. Stress is the body's physical, mental or chemical reaction when we get excited or confused or we otherwise feel unsafe or threatened. If daily demands are easy and well balanced an individual is fine. It is when one decides that pressure is unreasonable or the situation is upsetting, that the potential for damage occurs. That's when one feels stressed. Stress reactions begin in our minds. As long as humans have been around there has been stress. Perhaps, it's been known by different things or labeled as tension, over work, or strain but it has definitely been there. Cave men and women knew stress well. When danger lurked, their adrenalin flowed, their hearts went into pitter/patter high drive, their breathing got faster, they perspired more, and they were in a state of physical arousal and readiness to go into battle or make haste when needed. If it weren't for stress - we humans would not have survived the process of evolution. Had we had not the sense and the ability to run away or act spontaneously we'd have been an easy prey for a fierce and hungry beast. This reaction is called the FIGHT and FLIGHT syndrome.

Over and above the basic functions of day to day living, biochemical chain reactions or stress reactions could be labeled as bad when the body over reacts to demands made on it. It means one experiences certain acute physical symptoms when one faces things that trigger a state of alert in our system. Our body goes into the 'high gear mode'. This means the heart beats faster, breathing rate increases, sweating is more, muscles tense, and various chemical reactions take place in the brain. We should also recognize that we need certain amount of stress to get us motivated to

achieve. But it is the chronic, bad stress that overburdens our resources that we usually mean when we say 'STRESS'.

A large proportion of all illness (perhaps 70-80%) is believed to occur because of stress - because the level is too high, and/or too long-term. High-stress modern living is probably the main factor causing chronic disease. Fortunately Mother Nature has an answer to this challenge - a unique class of herbal products called "adaptogens". Adaptogens have the most broad-spectrum healing properties of any herbal medicines, but their unique value is that they specifically relieve stress.

STRESS

Indications of stress (2)

Frequent headache, jaw clenching, grinding teeth, tremors, neck/back ache, dizziness, frequent cold, rashes, itching, heart burn, stomach pain, low sexual desire, excess worry, anxiety, depression, insomnia, poor concentration, forgetfulness, constant fatigue. When we experience stress serotonin level in the brain is reduced. Chronic stress can lead to anxiety, general irritability and crankiness. Stress is also leading contributor to death. There are different kinds of stress. They are;

Acute stress (3)

Acute stress is the most common form of stress. It comes from demands and the pressures of the recent past and anticipated demands and the pressure of the near future. Acute stress is thrilling and exciting in all doses, but too much is exhausting. Fortunately, acute stress symptoms are recognized by most people. It is a laundry list of what has gone awry in their lives: the loss of an important contract, a deadline they are rushing to meet, their child's occasional problems at school and so on, because it is short term, acute stress doesn't have enough time to do extensive damage associated with long term stress. The most common symptoms are:

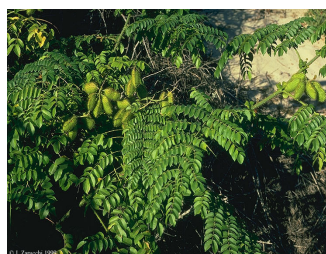
Emotional distress- some combination of anger and

Plant	Model
Baccopa Moneirea 13	Immobilization stress
Boerhaavia diffusa 15, 28	Anoxia induced stress Cold restraint, Adjuvant Induced Stress
Butea monosperma 16	Cold restraint
Butea frondosa	
Caesalpinia bonduc 30	Cold stress model and Swim endurance model
Chlorophytum borivilianum 17	Cold stress model
Eleutherococcus sibiricus (siberian ginseng) 18	--
Ginkgo biloba 20	Cold immobilization stress
Ocimum sanctum 21, 40	Swim endurance model Noise stress
Panax ginseng 20, 29	Immobilization stress Writhing test Swim endurance model
Sida cordifolia, linn 36	Gravitational stress Anoxia stress tolerance test Heat induced stress
Tinospora cordifolia 23	--
Trichopus zeylanicus gaerten 37	Adjuvant Induced Stress immobilization stress
Tribulus Terrestris 26	
Withania somnifera 25	Swim endurance model

Figure 1: Plants reported to possess anti-stress effects



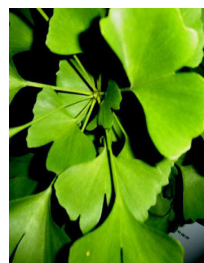
Bacopa monniera



Caesalpinia bonduc



Sida cordifolia



Ginkgo biloba



Ocimum sanctum



Panax ginseng



Withania somnifera



Tribulus terrestris

irritability, anxiety and depression are the three stress emotions; Muscular problems including headache, back pain, jaw pain and muscular tension that lead to pulled muscles, tendon and ligament problems; problems such as heart burn, acidity, flatulence, diarrhea, constipation and irritable bowel syndrome; transient over arousal leads to elevation in blood pressure, rapid heart beat, sweaty palms, heart palpitations, dizziness, migraine headache, cold hand or feet, shortness of breath and chest pain. Acute stress can cope up in anyone's life, and it is highly treatable and

manageable.

Episodic acute stress

There are those, however, who suffer acute stress frequently, whose lives are so disordered that they are studies of chaos and crisis. They are always in rush, but always late. If something can go wrong, it does. They take on too much, have too much iron in the fire, and can't organize the slew of self-inflicted demands and pressure clamoring for their attention. They seem perpetual in the clutches of acute stress. It is common for people with acute stress reaction to

be over aroused, short tempered, irritable, anxious and tense.

Chronic stress

While acute stress can be thrilling and exciting, chronic stress is not. This is the grinding stress that wears people away day after day, year after year. Chronic stress destroys bodies, minds, and lives. It works havoc through long term attrition. It is the stress of poverty, of dysfunctional families, of being trapped in an unhappy marriage in a despised job and career. A general definition would be that a state of stress exists when there is discrepancy between the perceived demand on an organism and its perceived ability to cope. In the pathophysiology of stress the emphasis is on physical problems, referred to as psychosomatic disorder. These include,

- Gastric ulcer
- General digestive problems
- Raised blood pressure (hypertension)
- Eczema
- Some forms of asthma
- Allergic conditions

If the fight or flight response is successful, the Sympathetic Nervous System (SNS) activity reduces and the system returns to normal level. However, if the response is unsuccessful, the SNS will not return to base line but will remain chronically elevated. Hence heart rate will remain higher than normal, this is a state of physiological stress. Under these conditions there are long term effects on the Hypothalamic-Pituitary-Adrenocortical (HPA) system.

Hypothalamic - Pituitary - Adrenocortical (HPA) system (2, 3, 4)

We have two adrenal glands which has cortex and medulla. The adrenal cortex is controlled by the pituitary gland via the release of pituitary hormone called ACTH (adreno corticotrophic hormone). Release of ACTH causes the adrenal cortex to secrete corticosteroids in to blood stream. In turn the pituitary gland is controlled by the hypothalamus which releases ACTH - releasing factor (ACTH-RF).

Much of our interest in the HPA system concerns the release of corticosteroid from the adrenal cortex. One class of corticosteroids is important in the study of stress. These are the glucocorticoids. The glucocorticoids include: Cortisone, hydrocortisone, corticosterone.

They facilitate the conversion of stored fat and protein into usable energy and suppress the body's immune system. So for example, the long term effect of cortisone release would be to leave the body vulnerable to infections. But these hormones also play a vital role in non-stressful conditions.

The hypothalamus releases the hormone called corticotrophin-releasing-hormone (CRH) which travels directly to the pituitary gland where it causes the release of adreno-corticotrophic hormone (ACTH) in the blood stream. Once in the blood, ACTH travels to the adrenal cortex where it affects the release of corticosteroids.

Corticosteroid receptors are found at number of brain sites such as hypothalamus and hippocampus. When there is high

percentage of corticosteroids in the blood stream they bind to these receptors and cause a reduction in ACTH release. Hence this system is a negative feed back system.

Stress progression can be characterized into three phases:

- 1) **Alarm phase** - When some new stress factor strikes the organism it causes a sudden release of internal stress-hormones - corticosteroids and cathecholamines. If the stress is very intense it can damage the regulatory systems of the organism permanently and at once
- 2) **Adaptation phase** - If the stress factor continues (for example, in sport it might be heavy athletic training) our body learns to tolerate the stressful stimulus - "adapt" - and increases its resistance to the stress factor. The "adaptation phase" is usually a safe period.
- 3) Finally, the **exhaustion phase** appears, when the organism fails to fight stress any more and simply gives up. In this "exhaustion phase", disease symptoms rapidly appear and get worse.

Diseases associated with stress may appear in the first "alarm phase", but they mainly appear in the third "exhaustion phase" when the organism cannot fight stress any more. This third phase usually develops after a period of months or years.

ADAPTOGENS (5, 29, 30)

Adaptogens are the plant derived biologically active substances which appear to induce a state of non specific increase of resistance of the organism to diverse aversive assaults which threaten internal homeostasis which improve physical endurance for doing work even in adverse circumstances and in difficult environmental conditions. These agents are basically preventive rather than curative in action and appear to function best when the resistance of the body is diminished, as seen in the case of prolonged illness, chronic stress and old age. They increase tolerance to change in environmental conditions and resistance to noxious stimuli such as exposure to cold, heat, pain, general stress, infectious organisms. Such agents have been claimed to arrest ageing process and age induced deterioration in physical and mental performance.

The main effects of adaptogens are an increased availability of energy during the day, a reduction of stress feelings, increased endurance, greater mental alertness, and deep and restful sleep. Also, adaptogens significantly accelerate the recovery process after illness. Here in an example of a person who was ill for many years, and became weaker and weaker, despite trying a variety of medicines and supplements. He went through so much mental and physical trauma that he felt he was going to die. Doctors could not diagnose his illness, but eventually found out it was an autoimmune disorder, with too many symptoms to name. One day he discovered *adaptogens* and, after some trial and error, he found they worked better than anything else he had tried; and they increased the effectiveness of other supplements as well.

According to modern science adaptogens are natural plant products that increase the body's ability to cope with internal and external stress factors, and normalize the functions of the organism. They help maintain the stable internal

environment inside the organism known as homeostasis. An important characteristic is that they are safe, possessing few known side-effects.

Hans Selye and Stress (1, 6)

Dr. Selye, a Canadian professor and leading pioneer in stress research, is internationally acknowledged as 'the father of stress.' Prior to his death in 1982, Dr. Selye had written more than 1700 scholarly papers and 39 books on stress, and he is still by far the world's most frequently cited author on the topic.

Among the most memorable of Selye's work was his General Adaptation Syndrome (GAS). The GAS involves three progressive stages; The first stage, the alarm reaction, is characterized by surprise and anxiety when exposed to a new situation. During this stage the body reacts by producing epinephrine and norepinephrine the 'flight or fight' hormones. Additionally, the adrenal cortex is stimulated to produce additional hydrocortisone and related hormones.

The second stage, resistance, is characterized by adaptation, whereby the body learns to efficiently cope with the stressor. Ideally, this adaptive stage continues until the stressful situation is resolved, leading to a rapid return to the resting state.

Unfortunately, our capacity for adaptation is limited and highly individualized (i.e. what is stimulating to one person may be devastating to another). Just as a chain breaks at its weakest link, so too can exhaustion of our adaptive capacity result in stress-induced disease. In the presence of long-term exposure to the same stressor, we enter the third stage of GAS, exhaustion. Exhaustion is characterized by a depletion of energy reserves and loss of adaptational ability, leading to fatigue or other symptoms or diseases.

This third stage is sometimes referred to as the adrenal maladaptation, or hyperadaptosis. Adrenal dysfunction may be manifest by

- (1) An excess or inadequacy of cortisone, DHEA, ACTH and/or CRF
- (2) Relative imbalances of these hormones and releasing factors
- (3) Loss of sensitivity of the hypothalamus and pituitary to the normal inhibiting effects of these hormones.

Dr. Nikolai Lazarev and stress (6,7)

One of the first Soviet scientists to embrace Selye's ideas was Dr. Nikolai Lazarev, a pioneer in the then-emerging fields of toxicology and preventive medicine.

Shortly after graduating from medical school in 1928, Lazarev started working on ways to prevent the damaging effects of new industrial chemicals on humans. Lazarev and his scientific team identified over 400 previously unknown chemical compounds in the new factories, and studied the effects of these toxic industrial byproducts on humans.

In 1932, Lazarev discovered that different industrial chemicals, even in mild concentrations and small dosages, can cause similar alarm reactions, and that if exposure is prolonged, the body will adapt by altering its physiological response (resistance). This adaptive reaction tends to gradually disturb homeostasis, which is damaging to health.

Brekhman's Contribution

Being a long distance runner, Brekhman chose stamina as an index of vitality. One cold morning in April 1948, 100 soldiers set out to run a 3-kilometer race. Prior to the race, half of them had been given an extract of ginseng, while the others received a placebo. Soldiers given the ginseng extract finished the race an average of 53 seconds ahead of the placebo group. These results were beyond Brekhman's wildest expectations. For the first time he and his team had scientifically proven the effectiveness of this ancient Chinese herb.

Stress and stress-related disorders are a significant cause of disease in modern man, contributing to perhaps 75% of all illnesses. Western medicine has developed multiple approaches to coping with stress, including pharmaceutical drugs, exercise, and relaxation techniques like meditation. While these methods can provide some benefits, results are mixed and often unsatisfactory. In the East, researchers have also struggled to find solutions to stress-related problems. In Russia, after years of scientific investigation, scientists developed a unique approach to stress reduction and the prevention of stress-related symptoms.

Natural adaptogens (8,9, 10, 11, 12).

Let us now discuss about some plants which have been proved to possess antistress activity and possess adaptogenic properties. There have been many plants (Figure 1) of foreign origin but many plants found in India too are proved to be adaptogenic in nature.

Evaluation of Anti-Stress / Adaptogenic Properties (27-41)

Many researchers have screened various plant extracts for Adaptogenic activity using various models. The animals are exposed to stress and the alteration in the biochemical as well as physical well being is observed. It is difficult at times to observe any positive changes and anabolic actions in stress induced animals; hence it becomes difficult to ascertain whether the drug possesses any anti stress action. If we consider the definition of adaptogens it solves this problem and any drug or extract or formulation which can help the body in overcoming the biochemical changes due to imbalance in natural homeostasis and which help the body to function normally in adverse conditions are surely potent Adaptogens. Meanwhile some efforts have been done to modify the current models to create severe stressful conditions, which have been successful in screening of adaptogenic activity (27).

Here our aim is to get an overview of various Animal models which can be used to screen adaptogenic properties of various polyherbal extracts.

1. Anoxia stress tolerance test
2. Swimming endurance test in rats and mice.
3. Acute Swim Stress and hormonal changes in rats
4. Subacute Cold Stress
5. Cold restraint stress in rats
6. Gravitational stress
7. Heat induced stress
8. Adjuvant induced trauma in rats
9. Writhing test
10. Immobilization stress
11. Stress Induced By Anaemic Hypoxia In Rabbits

12. Vibration stress
13. Noise induced stress

1. Anoxia stress Tolerance Test in mice (28)

Albino mice of either sex are taken for experimentation. Hermetic vessel of 1 litre air capacity is used to induce anoxia stress. Each animal is kept in the hermetic vessel and the time to show the first sign of convulsion is noted, and are immediately removed from the vessel and resuscitated if needed. This is carried out daily for a period of 21 days. At the end of each week i.e. 1st, 2nd and 3rd weeks of drug treatment, the animals are exposed to the anoxic stress and anoxic tolerance time is noted. Here the anoxic tolerance time proved to be an efficient parameter in concluding the adaptogenic action of the plant extract. This method is a moderate stress induction method and as such anoxia induced stress does not significantly alter the physiological parameters leading to acute judgment. Though mental trauma due to anoxia is a significant stressor.

2. Swimming Endurance Test in Rats Mice (10, 28, 29, 30)

Rats of either sex (200-250g) or Swiss albino mice (15-20 g) of either sex are used for swim endurance. The rats are subjected to swimming stress by keeping them in cylindrical vessel filled with water to a height of 25cm and total swimming time of each rat is noted. Extracts are given to rats, once daily for period of 7 days. On 8th day the rats were allowed to swim till complete exhaustion and the endpoint is taken when the animal starts drowning. The mean swimming time for each group is calculated. Then animals are killed and blood is collected by cardiac puncture to estimate biochemical parameters like serum glucose, triglycerides, cholesterol(16), BUN and blood cell count (RBC, WBC and DLC). The weights of organs such as liver, adrenals, spleen are recorded after washing with alcohol.

In case of mice After drug administration the animals are forced to swim in glass chambers 30cm X 30cm X 15cm containing water at room temperature. The mice are allowed to swim till they get exhausted and the moment they drown is considered as the endpoint where the time is noted. Normal untreated group serves as standard

Swim endurance reflects the true stamina as well as the muscle strength as well as general good health of animal. Here to conduct this test no special instruments are required neither is it more time consuming. Mice are more suited for this model and acute physical endurance can be effectively noted.

3. Acute Swim Stress and hormonal changes in rats (31)

In another method Stress is induced by forcing rats to swim in water for 2 hrs. The rats are administered the drug 30 minutes prior to stress. After that brain 5-HT and plasma corticosterone (32) are estimated using a fluorimetric method. Here the plasma corticosterone levels and serotonin levels are observed to be changed as well as increase in the ulcer index.

Evaluation of biochemical parameters especially corticosterone and serotonin are clear cut indicators of stress as well as ability of a drug to prevent any changes in alteration of these hormones proves its efficacy as an adaptogenic agent.

5. Subacute Cold Stress (33) - To induce stress the experimental animals are allowed to swim freely in cold water, maintained at 10° C till the point of exhaustion. It is the stage at which the animals will no longer be able to stay at surface and it starts sinking. At this point the animals are taken out. The same procedure is repeated once in a day for 10 continuous days and animals are sacrificed on the eleventh day by exsanguinations under light ether anesthesia. Parameters evaluated: Total WBC count, eosinophils, basophils. Phagocytic index and avidity index is also estimated.

This model is one of the most commonly used one and exposure to severe conditions leads to a significant imbalance in the hormonal levels as well as leads to pathogenic conditions which is observed due to altered WBC count and even imbalance in the lipid profile suggests that exposure to cold is a potent stressor. Only the drawback observed here is animals if not kept individually tend to crowd in a corner and counter the cold.

6. Cold Restraint Stress in Rats (28, 30, 34)

Rats are subjected to cold stress by exposing them to 4 ± 1°, daily for 2hrs/4hrs for a period of 10 days. Animals are sacrificed at the end of the study period and blood is collected for estimation of various biochemical parameters such as Serum cortisol (35), blood glucose levels, total leukocyte count, differential count as well as lipid profile. Similarly the weights of organs i.e. liver, spleen and adrenal glands are also recorded.

In some cases the animals are exposed to cold stress for a span of 7 day only which also creates GAS disturbances and is efficient model to screen extracts for adaptogenic properties. This model is a combination of cold which leads to physical stress as well as immobilization stress which is additional physical stress as well as mental trauma. This model has proved efficient in altering the normal homeostasis of the body and drugs which are effective in countering these changes should prove to be potent adaptogens.

7. Gravitational Stress in rats (36)

Albino rats (130-150 g) of either sex are subjected to stress. All the animals are made to hang head down position from a horizontal bar daily 2 hours for a period of 8 days. After which the animals are sacrificed and parameters considered are determination of blood cell counts like RBC and DLC. Some of the blood collected is centrifuged at 5000 rpm for 10 mins for separation of plasma for estimation of biochemical parameters like glucose, cholesterol, triglycerides, urea nitrogen (BUN).

Gravitational stress is easy to handle and no instruments are required. Even the time consumed is less though this model does not produce significant or critical stress conditions it has been used widely in various studies. Hanging of an animal upside down may even at times lead to minor accidents as wearing or tearing of the tail portion. If the animals are near any solid support they are able to take its support or even in some cases it has been observed that these animals tend to climb back in U turn and thus easily counter the stress.

Though ethically it seems improper to hang animals for such investigations it is not mandatory to follow this model only, but some how or other animals have to be exposed to some or other stressor otherwise the activity itself can never be proved. Hence for the noble purpose of research and betterment of mankind such investigations need to be carried out.

8. Heat Induced Stress (36)

Albino rats (130-150 g) of either sex are subjected to stress. All the animals are subjected to heat stress by exposing them to a controlled temperature of 40 ± 2 daily for a period of 8 days. After which the animals are sacrificed and parameters considered are determination of blood cell counts like RBC and DLC. Some of the blood collected is centrifuged at 5000 rpm for 10 mins for separation of plasma for estimation of biochemical parameters like glucose, cholesterol, triglycerides, urea nitrogen (BUN).

This method of stress induction is not uniform and animals are certain cases die due to dehydration and lack of fluid balance.

9. Adjuvant Induced Stress (37)

Suppressed immune response is also a parameter which is considered to be a signal of stress and hence the ability of a drug to stimulate the suppressed immune response itself is a adaptogenic property, here in this study normal animals are subjected to immuno suppressing agents and effect of drug in rejuvenating these suppressed parameters is observed. The parameters which are studied to assess the anti stress activity are viz. Adjuvant induced trauma in rats and RBC induced trauma in mice. Antigen (SRBC) induced humoral immune response in normal and immuno-suppressed mice, Chemical (GalN) and physical (immobilization) stress induced hepatic function in rats. These are efficient models leading to the conclusion whether a drug possesses immuno-modulating (stimulating) properties.

10. Writhing Test (29)

Muscular cramps and writhing is also a parameter, which can be evaluated as a stress factor. Swiss white mice are treated with drugs / extracts for 21 days, one group of animals is untreated/treated with vehicle, which acts as normal. At the end of 21st day; all the animals are administered with 0.1 ml of 6% glacial acetic acid by intraperitoneal route. Number of writhes and time of onset of writhes is observed in all the groups. The ability of the drug to suppress the no of writhes is considered as an efficient adaptogenic parameter

The number of writhes produced indicates the acute stress condition. Pain is a major stressor and exposure to acute pain of a certain period leads to pathological condition. The drugs, which effectively control the writhes and reduce their intervals, are able to help the body to overcome the pain as well as the trauma caused.

In certain cases the drug may act as an analgesic thus reducing the pain and the writhes. Here it is more important to see that the drug has been able to reduce the stress due to acute pain and help the body to overcome it. Though this test is not a conclusive one to substantiate the adaptogenic claims of any drug, it can be used in combination with any other two

models which will help in overcoming the analgesic action of the drug.

11. Immobilization stress (38)

Stress is also caused due to immobilization and which leads to imbalance in normal biochemical parameters, here Rats are kept for 4 hours daily for 7 days in ventilated small tightly fit plastic boxes. Where rats are unable to move this causes physical as well as emotional stress due to irritation developed due to immobility.

Stress due to immobilization is potent stressor and can lead to mental trauma as well as muscle fatigue. It has the ability to create imbalance in the normal functioning of the body. It is easy to conduct and monitor but while handling animals due to irritation animals tend to become more aggressive.

12. Stress Induced By Anaemic Hypoxia In Rabbits (39)

Blood samples are taken for estimation of haemoglobin, blood glucose and plasma malondialdehyde of both the groups of rabbits at beginning of the study (day 1) and after one month (day 30) of maintenance on respective diets. Rabbits of both groups are subjected to the following operative procedure and oxidative stress after 30 days.

After overnight fasting, rabbits are administered with intravenous injection of urethane (1.5 gm/kg body weight). Tracheotomy is performed and femoral vein is cannulated for taking blood samples for assessment of haemoglobin. Glucose and plasma MDA levels. One hour after anesthesia, anemic hypoxia is induced chemically by injecting the rabbits intraperitoneally with 15 mg Sodium nitrite (NaNO_2) / 100 gm body weight. Sodium nitrite used for induction of anemic hypoxia led to formation of methaemoglobin and free radicals. Blood samples are taken 40 minutes after oxidative stress for estimation of hemoglobin and glucose for assessment of stress and plasma MDA is done to assess oxidative damage induced by stress.

Here oxidative stress due to free radical action leads to direct tissue damage and severe pathogenic conditions are observed in some cases. It is quite complicated to induce this type of stress. To maintain post-operative healthy conditions in animals is another difficult task and constant monitoring is essential.

13. Noise Stress (40)

Stress is produced by exposing rats to 30 min noise (100 dB) in case of acute stress which led to significant elevation of the corticosterone level in plasma, in chronic case exposure (4 hr daily for 30 days) to noise with same intensity reduced the hormonal level significantly.

Noise stress is more of emotional stress rather than physical stress, experimentation is easy and in many cases it has proved to be efficient in causing imbalance in corticosterone as well as HPA hormones. Chronic exposure though might lead to adaptation and in some scenarios even hearing ability may be damaged.

14. Flickering Light Stress (41)

The acute effects of flickering light of 80 Lux intensity for thirty minutes duration, on plasma corticosterone, total serum cholesterol, serum triglycerides, serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) levels are studied in albino rats.

Statistically significant increase is observed in the corticosterone, cholesterol, SGOT and SGPT, while a marked reduction is seen in the serum triglyceride level, indicating that the flickering light is a potent stressor to these animals causing alterations in the biochemical parameters studied. This may lead to physical as well as mental trauma and has proved to be an potent stressor only too much exposure may lead to visual impairment.

CONCLUSION

Stress is a major factor that constitutes every individuals daily life. Stress in optimum quantum acts as stimulator to achieve the best, but when it exceeds, it surely causes imbalance in the biochemical parameters as well as leads to suppression in physical endurance as well as mental capability for logical thinking and also suppress immunity leading to pathological conditions and hampering the normal functioning of the body. Adaptogenic agents either molecules or polyherbal formulations or extracts have time and again proved efficient in preventing the disturbances in normal homeostasis as well as changes in biochemical balance of the body. In today's era of fast-track life, normal individuals are subjected to innumerable stressful situations, thus the need to develop herbal formulations having antistress-adaptogenic properties is very much essential. Many plants are known stress relievers and many such more plants need to be investigated for these actions. Many researchers who have carried out work to prove adaptogenic action of drugs have used either of the animal models mentioned above, but it's difficult to follow only one model and in many a cases repeated results can not be produced. Various animal models which have proved efficient in proving antistress properties of extracts and formulations would be of more help when used as a set of models at a time for screening adaptogenic activity, as it would prove the adaptogenic potential of any drug/extract under maximum stress conditions and even a comparative data can be generated. It is imperative for researchers to use as much possible animal models at a time to generate more reliable results to prove the claims. Maximum efforts should be put in to develop new antistress formulations/products considering the 21st century living and working conditions.

REFERENCES

1. H. Seyle. The Evolution of Stress Concept. Am. Sci. **61**: 692-699 (1973).
2. A.C. Guyton, *Textbook of Medicinal Physiology*, (Philadelpia, Harcourt, Brace, Jovanovich, Inc, 1991) pp. 679.
3. G.J. Tortora, Grabowski, *Principals of Anatomy & Physiology*, 9th edition, (New York, Harper Collins College Publishers, New York, 2000), pp. 599 .
4. J.W. Kathleen, Wilson, Ross & Wilson, *Anatomy and Physiology*, 8th edition, (Churchill Livingstone Elsevier, Spain, 1996)pp 215-36 .
5. S. Bhattacharya, K. Bhattacharya, A. Bhattacharya, A. Chakraborty. Adaptogenic activity of Sistine, a Poly Herbal formulation of Ayurvedic Rasayanas, *Indian J Exp Biol* **38**: 119-128 (2000).
6. Ben Tabachnik, Ward Dean. Adaptogens: Natural Protection for Stress Maladaptation and Recovery. *Nov*: **21** (2002) available at <http://www.vrp.com/articles>
7. Rick Allen, DC Natural Remedies - Part 2: Adaptogens - Herbs for Additional Energy Better health leads to better dancing." *Oct* (1999). available at <http://www.cascadewellnessclinic.com/>
8. S. K. Bhattacharya, A. V. Muruganandam. Adaptogenic activity of *Withania somnifera*: an experimental study using a rat model of chronic stress. *Pharmacol Biochem Behav*. **75**(3): 547-55 (2003).
9. N. N. Rege, U. M. Thatte, S.A. Dahanukar. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. *Phytother Res*. **13**(4): 275-91 (1999).
10. K.P. Bhargava, N. Singh. Anti-Stress activity of *Ocimum sanctum*. *Indian J Med Res*. **73**: 443-51 (1981).

11. R.H. Singh Et.al. Studies on the psychotropic effect of Indian indigenous drug Ashwagandha. *J.Res. Ind Med Yoga homoco*.**14**: 49-59 (1979).
12. A.A. Mungatiwar, A.M. Nair, K.K. Kamal. Adaptogenic activity of aqueous extract of the roots of *Boerhaavia diffusa*. Linn. *Indian Drugs*. **34** (4): 184-189 (1997).
13. D. Rai, G. Bhatia, G. Palit , R. Pal, S. Singh, H.K. Singh. Adaptogenic effect of *Bacopa monniera* (Brahmi). *Pharmacol Biochem Behav*. **75**(4): 823-30 (2003).
14. S. S. Kalkunte, A.P. Singh, F.C. Chaves, T. J. Gianfagna, V.S. Pundir, A.K. Jaiswal, N. Vorsa, S. Sharma. Antidepressant and antistress activity of GC-MS characterized lipophilic extracts of Ginkgo biloba leaves. *Phytother Res*. **21**(11): 1061-1065 (2007).
15. A. A. Mungantiwar, A. M. Nair, U. A. Shinde, V. J. Dikshit, M. N. Saraf, V. S. Thakur and K. B. Sainis. Studies on the immunomodulatory effects of *Boerhaavia diffusa* alkaloidal fraction. *J Ethnopharmacol*. **65** (2): 125-131(1999).
16. I. Soman, S. A. Mengi, S. B. Kasture. Effect of leaves of *Butea frondosa* on stress, anxiety, and cognition in rats. *Pharmacol Biochem Behav*. **79** (1): 11-16 (2004).
17. R. D. Kenjale, R K Shah & S S Sathaye. Anti-stress and anti-oxidant effects of roots of *Chlorophytum borivilianum*. *Indian J Exp Biol*. **45**: 980-983 (2007).
18. Davydov M.; Krikorian A.D. *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. *J Ethnopharmacol* . **72** (3): 345-393 (2000).
19. Naila Sheikh, Ausaf Ahmad, Kiran Babu Siripurapu, Vijaya Kumar Kuchibhotla, Satyawan Singh and Gautam Palit. Effect of *Bacopa monniera* on stress induced changes in plasma corticosterone and brain monoamines in rats. *J Ethnopharmacol* **111** (3) : 671-676 (2007).
20. Deepak Rai, Gitika Bhatia, Tuhinadri Sen and Gautam Palit. Anti-stress Effects of *Ginkgo biloba* and *Panax ginseng*: a Comparative Study. *J Pharmacol Sci* . **93**(4) 458-464 (2003).
21. Tapan K. Maity , Subhash C. Mandal , B. P. Saha , M. Pal. Effect of *Ocimum sanctum* roots extract on swimming performance in mice. *Phytother Res* . **14**(2): 120 – 121 (2000).
22. Yerevan S. Yacoubian. STRESS CONTROL using NATURAL ADAPTOGENS <http://www.naturalelixir.com/stresscontrol.html>.
23. D. N. K. Sarma, R. L. Khosa, J. P. N. Chansauria, M. Sahai. Antistress Activity of *Tinospora cordifolia* and *Centella asiatica* Extracts. *Phytother Res*. **10**, (2) : 181 – 183 (1998).
24. R. Archana and A. Namasivayam. Antistressor effect of *Withania somnifera*. *J Ethnopharmacol*. **64**(1): 91-93. (1998).
25. P. Kaur; S. Mathur; M. Sharma; M. Tiwari; K. K. Srivastava; R Chandra, A Biologically active constituent of *Withania somnifera* (Ashwagandha) with anti-stress activity. *Indian J Clinical Biochem*. **16** (2): 195-8 (2001).
26. H. Shivakumar, Talha Javed, T. Prakash, R. Nagendra Rao, B. H. M. Jayakumar Swamy, A. Veerana Goud. Adaptogenic activity of ethanolic extract of *Tribulus terrestris* L. *J. Nat. Remedies*. **6** (1): (2006).
27. V. Ramachandran Et.al. New Experimental models for evaluation of adaptogens. *J.Ethno Pharmacol*. **29**: 275-81(1990).
28. B. Krupavaram, N. Venakat Rao, K. Nandakumar , T.S. Gowda, M. D. Shalam, S. Shatakumar. Study on Adaptogenic Activity of Root Extracts of *Boerhaavia diffusa* (Linn). *Indian Drugs*. **44**(4): 264-270 (2007).
29. S. R. Nimbakar , V.P. Patki, M.P. Patki. Pharmacological evaluation of anti-stress & androgenic activity of polyherbal formulation "A.P. -3000" – containing Panax ginseng. *Indian Drugs*. **38**(1): 27 -39 (2001).
30. D.M. Kannur, V.I. Hukkeri, K.S. Akki. Adaptogenic Activity of *Caesalpinia bonduc* Seed Extracts in Rats *J Ethano Pharmacol*.**108**: 327-331(2006).
31. S.B. Kasture et al. Antistress Activity of *Butea monosperma*. *Indian J Pharmacology*. **21**(2): 153-155 (1999).
32. S.M Barlow, A.K. Knight, F.M. Sullivan. Plasma corticosterone responses to stress following chronic Oral administration of Diazepam in the rat. *J Pharm & Pharmacol*. **31**: 23-26 (1979).
33. G Sudarshan, Suthanthirarajan. Certain Immunological parameters in Subacute Cold Stress. *Indian, J Physiol. Pharmacol*. **34**(1): 57-60 (1990).
34. S.K. Bhattacharya, Ghosal S. Experimental evaluation of anti stress activity of Zee stress. *Indian J Indg Med*. **2**: 1-8 (1994).
35. T.K. Sur, Bhattacharya D. The effect of Panax ginseng & diazepam on brain & hypothalamic 5-hydroxytryptamine during stress. *Indian J Pharmacol*. **29**: 318-321 (1997).
36. B. Amarnath, S.M.S. Kumar, N.V Rao. Evaluation of Adaptogenic Activity with root extracts of *Sida cordifolia*, linn. *Indian Drugs*. **43**(1): 25-30 (2006).
37. B. Singh, B. K. Chandan, N. Sharma, S. Singh, A. Khajuri, D. K. Gupta O. P. Suri. Adaptogenic Activity of Glyco-Peptido-Lipid Fraction from Alcoholic Extract of *Trichopus zeylanicus* Gaerten. *Phytomedicine*. **12**(6-7): 468-81 (2005).
38. Sunil Dutt Shukla, Sushma Jain, Kanika Sharma, Maheep Bhatnagar. Effects Of Semecarpus anaecardium Linn On Neuron Cell Bodies On Hippocampal Sub Regions Of The Stressed Female Rats. *Indian Drugs*. **37**(8): 379 -82 (2000).
39. Jyoti Sethi, Sushma Sood, Shashi Seth and Anjana Talwar. Protective Effect Of Tulsi (*Ocimum sanctum*) On Lipid Peroxidation in Stress Induced by Anaemic Hypoxia in Rabbits. *Indian J Physiol.Pharmacol*. **7**(1): **115-19** (2003).
40. Dwivedi.S. Effect of *Ocimum sanctum* Linn on noise induced changes in plasma corticosterone level. *Indian J Physiol Pharmacol*. **41** (4): 429-430 (1997).
41. R. Lalitha, Suthanthi Rajan, Namasivayam. Effect of flickering light stress on certain biochemical parameters in rats. *Indian J Physiol. Pharmacol* . **32**(3): 182-186 (1988).